



**Health Evidence Review
Commission's
Value-based Benefits Subcommittee**

August 8, 2013

**Meridian Park Hospital
Community Health Education Center, Room 117B&C
19300 SW 65th Avenue, Tualatin, OR 97062**

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
August 8, 2013
8:30am - 12:30pm
Meridian Park Hospital
Community Health Education Center, Room 117B&C
19300 SW 65th Avenue, Tualatin, OR 97062
A working lunch will be served at approximately 12:00 PM
All times are approximate

- I. Call to Order, Roll Call, Approval of Minutes – Lisa Dodson 8:30 AM**
- II. Staff report –Ariel Smits, Darren Coffman 8:35 AM**
 - A. Biennial review
- III. Coverage Guidances for Prioritized List– HERC Staff 8:45 AM**
 - A. *Previously discussed*
 - A. Chronic otitis media in children
 - B. *New*
 - A. Treatment of ADHD in Children
- IV. New Discussion Items – Ariel Smits/Paige Hatcher 9:15 AM**
 - A. Implantable intraocular steroids
 - B. Conditions arising in the perinatal period
 - C. Fluoride varnish
 - D. Surveillance MRI in multiple sclerosis
- V. Guidelines – Ariel Smits/Paige Hatcher 10:15 AM**
 - A. Guideline for treatment of cancer near the end of life
 - B. Advanced Imaging for Back Pain Guideline—guideline note D4 correction
 - C. Health and Behavior Assessment/Intervention codes guideline
 - D. Cystocele repair (GN 50)
 - E. Cervical fusion and smoking
 - F. Guideline for adenotonsillectomy for children with OSA
 - G. Disorders of Spine with Neurologic Impairment
- VI. ICD-10 Issues – Ariel Smits/Paige Hatcher 12:00 PM**
 - B. Perinatal gastrointestinal conditions
 - C. Frenulotomy for tongue tie
- VII. Straight Forward Items/Consent agenda – Ariel Smits 12:15 PM**
 - A. August straightforward issues table
 - B. V55 series
 - C. Changes to Genetic Testing Guideline for new NCCN recommendations
 - D. Complications involving vascular grafts
 - E. Epilepsy
 - F. ICD-10 straightforward/consent agenda
 - i. Coding specifications
 - ii. Spastic dysphonia

VIII. Public Comment

12:25 PM

IX. Adjournment – Lisa Dodson

12:30 PM

**Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on (5/9/13)**

For specific coding recommendations and guideline wording, please see the text of the (5/9/13) VbBS minutes.

CODE MOVEMENT

- Cervical brachial syndrome was moved from a funded to a non-funded line
- Certain chronic pelvic inflammatory conditions were added to a non-funded line
- The procedure code for therapeutic apheresis was added to several funded lines and removed from the Ancillary File
- The procedure code for corneal pachymetry was added to several funded lines
- The procedure codes for intra-aortic balloon device insertion and removal were limited to two funded lines and a new guideline adopted
- Acupuncture procedure codes were added to the funded knee arthritis line
- Several procedure codes regarding splenectomy were added to a covered line for internal injuries
- Several procedure codes for surgical treatment of fecal incontinence were added to an unfunded line starting with the October 1, 2014 ICD-10 Prioritized List
- Nerve block procedure codes were added to a number of funded and unfunded lines and removed from the Ancillary File
- Various straightforward coding changes were made
- Several diagnostic codes for fetal death were added to the funded pregnancy line

ITEMS CONSIDERED BUT NO CHANGES MADE

- A new guideline for adenotonsillectomy for obstructive sleep apnea in children was considered; HERC staff will work with experts to revise
- There was no change made to the current noncoverage of PET scans for breast cancer

GUIDELINE CHANGES

- A new guideline was adopted to define when certain pelvic inflammatory conditions are included on the upper, funded line and when on the lower, non-funded line
- A new guideline was adopted to limit coverage of intra-aortic balloon device on the acute myocardial infarction line to patients with cardiogenic shock
- The acupuncture guideline was modified to include knee arthritis
- A new guideline was adopted restricting which patients qualify for lung volume reduction surgery
- A new guideline was added to clarify which treatments for fecal incontinence are included on the funded and which on the unfunded line for the ICD-10 Prioritized List effective October 1, 2014
- Guideline note 28 had modifications to make the wording clearer
- Modifications were made to the hyperbaric oxygen guideline and the addition of this guideline to the List was affirmed
- A new diagnostic guideline was adopted on the diagnosis of obstructive sleep apnea in adults
- A new guideline was adopted on continuous glucose monitoring in diabetics
- The guidelines on cochlear implants, guideline notes 31 and 49, were modified to clarify coverage intent for bilateral cochlear implants and define levels of hearing loss
- The diagnostic guideline on neuroimaging for headache was modified for clarity

- The guideline on induction of labor was modified to define when elective induction would be covered and other indications and contraindications to induction
- A new guideline on self-monitoring of blood glucose in type 2 diabetics was adopted
- A new diagnostic guideline on screening for asymptomatic carotid artery stenosis was adopted
- A new guideline on carotid endarterectomy for carotid stenosis was adopted

DRAFT

VALUE-BASED BENEFITS SUBCOMMITTEE
Wilsonville Training Center, Room 112
Wilsonville, Oregon 97070
May 9, 2013
8:30 AM – 12:30 PM

Members Present: Lisa Dodson, MD, Chair; Kevin Olson, MD, Vice-chair; James Tyack, DMD; David Pollack MD; Irene Croswell RPh (by phone until 11:30 AM); Laura Ocker, LAc; Susan Williams, MD (left at 12:30 PM).

Members Absent: Mark Gibson

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich

Also Attending: Denise Taray, Wally Shaffer MD, DMAP; Jesse Little, Actuarial Services Unit; Paige Hatcher, MD, OHSU Preventive Medicine; Duncan Neilson, MD, Legacy Health; BJ Carnor, NWPEN; Mike Willett, Phizer; Joanne Rogovoy, March of Dimes; Kathy Kirk, Oregon Pain Management Commission; Cheryl Moore, ODE/AADE; Jason Parks, ACCAN; Ben Marx, LAc, OCOM; Ryan Milley, OCOM; Bill Struyk, Johnson and Johnson; Shane Jackson, Autism Society of Oregon; Mary Stumph, Lilly Oncology

Roll Call/Minutes Approval/Staff Report

The meeting was called to order at 8:30 am and roll was called. Minutes from the 3/14/13 VbBS meeting were reviewed. Ocker noted one technical correction regarding the affiliation of Ben Marx, who provided testimony at the March meeting. The amended minutes were approved. Note: HERC staff later noted that the date of presentation to the HERC at the top of the March minutes had the wrong date and this was corrected.

ACTION: HERC staff will post the approved minutes on the website as soon as possible.

Smits reported on the HERC progress on the ICD-10 Prioritized List.

Coffman shared issues with using healthy life years in the prioritization methodology. Putting more weight on treatments for children that provide many years of benefit is in conflict with the Affordable Care Act (ACA). Changing the language in the prioritization methodology to reflect the “magnitude” of the benefit (as discussed at the HERC meeting) will address this problem.

Coffman also announced that Chris Kirk has resigned from the VbBS due to a job change. The VbBS is currently actively recruiting for Dr. Kirk’s position.

NEW DISCUSSION

➤ **Topic:** Cervicobrachial syndrome

Discussion: Smits presented a summary document with recommended changes for the placement of cervicobrachial syndrome. There were questions about whether the ICD-9

code for cervicobrachial syndrome was also used for cervical radiculopathy (no, 723.4 is the correct code) or thoracic outlet syndrome (no, 353.0 is the correct code).

Actions:

- 1) Move 723.3 (cervicobrachial syndrome) from line 441 PERIPHERAL NERVE ENTRAPMENT to line 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

➤ **Topic:** Chronic pelvic inflammatory conditions

Discussion: Smits presented a summary document with recommended changes for the placement of chronic pelvic inflammatory conditions. There was discussion about what treatments might be covered for chronic pelvic pain. The answer was diagnostic work up, and currently medications. This coverage is similar to most other chronic pain conditions on the Prioritized List. Smits noted that abscesses of the pelvic organs would be covered on the upper line. Health plans could choose to priorauthorize treatments like hysterectomy and may deny them for chronic pelvic pain once moved to the unfunded line.

Actions:

- 1) Add 614.2, 614.4, 614.5, 614.8, 614.9, 615.9 to line 552 PELVIC PAIN SYNDROME, DYSPAREUNIA and keep on line 56 ACUTE PELVIC INFLAMMATORY DISEASE
- 2) Move 614.7 and 615.1 from line 56 to line 552
- 3) Change the name of line 552 to CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA
- 4) A new guideline was adopted for line 56 and 552 as shown in Appendix A

➤ **Topic:** Therapeutic apheresis

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) Add CPT 36514-36516 (therapeutic apheresis) to lines 100, 117, 136, 138, 140, 142, 150, 151, 157, 183, 199, 223, 225, 249, 308, 338, 366, 479
- 2) Advise DMAP to remove 36515 and 36516 from the Ancillary List

➤ **Topic:** Corneal pachymetry

Discussion: Smits reviewed the summary document. Dodson requested clarification that this procedure could not be paired with refractive diagnoses to be used prior to laser refractive surgery. This diagnosis is not located on one of the lines suggested for placement and therefore should not be paired.

Actions:

- 1) Corneal pachymetry (CPT 76514) was added to lines 149 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE, 258 PRIMARY ANGLE-CLOSURE GLAUCOMA, 282 ACUTE, SUBACUTE, CHRONIC AND OTHER TYPES OF IRIDOCYCLITIS, 308 COMPLICATIONS OF A PROCEDURE ALWAYS

REQUIRING TREATMENT, 337 CORNEAL OPACITY AND OTHER DISORDERS OF CORNEA and 362 RUBEOSIS IRIDIS

➤ **Topic:** Intra-aortic balloon devices

Discussion: Smits reviewed the summary document. Hatcher gave additional evidence indicating that there was good data for use of intra-aortic balloon devices as a bridge to definitive treatment such as CABG, LVAD placement, etc. The group decided to limit the placement of this procedure to lines 76 (with a guideline) and 108.

Actions:

- 1) CPT 33967 was removed from line 195 CHRONIC ISCHEMIC HEART DISEASE
- 2) CPT 33968 was added to line 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION and 108 HEART FAILURE and DMAP was advised to remove from the Excluded List
- 3) CPT 33970 and 33971 were removed from line 195 and added to line 108
- 4) CPT 33973 and 33974 were added to line 108 and removed from lines 109, 192, 105, 237, 274, 304, 354, 376, and 385
- 5) A new guideline was adopted for line 76 as shown in Appendix A

PREVIOUS DISCUSSION ITEMS

➤ **Topic:** Acupuncture for knee osteoarthritis

Discussion: Smits reviewed the summary document. Ben Marx, LAc and Ryan Milley from OCOM gave testimony and Smits read written testimony from Deborah Ackerman from OCOM. There was testimony and discussion about how finding a true sham control for acupuncture is extremely difficult, and most experts recommend focusing on comparing acupuncture to wait list controls or usual care controls. There was discussion about the statistics used in the Vickers 2012 study. The treatment effect was considered “medium” but appeared to be less than the improvement seen with viscosupplementation for knee arthritis. It was pointed out that the Cochrane review (Mannheimer 2011) did not show any benefit to acupuncture when added to exercise as a treatment. The risks of alternative procedures (NSAIDs, narcotics, injections, surgery) were discussed. The effect size of NSAIDs on knee arthritis was pointed out to be less than that shown for acupuncture.

MOTION: To approve the addition of acupuncture to line 489 and the changes to the acupuncture guideline as presented. CARRIES 5-1.

Actions:

- 1) Add acupuncture (CPT 97810-4) to line 489 OSTEOARTHRITIS AND ALLIED DISORDERS
- 2) The acupuncture guideline was modified as shown in Appendix B

➤ **Topic:** Obstructive sleep apnea (OSA) in children

Discussion: Smits reviewed the summary document. Dr. Holger Link from OHSU Sleep Medicine gave verbal testimony.

There was discussion about whether the guideline should apply to children 12 and younger, 18 and younger, or some other age group. Dr. Link raised concerns about using 12 and younger, as some older children are physiologically more like children and other more like adults. Dodson asked whether puberty should be used as a cut-off. Dr. Link felt that age 16 might be a better cut off, as most children are done growing by this age.

There was discussion about when a formal sleep study should be required. Dr. Link felt that the physician should have leeway as to when a sleep study should be done. He was concerned about the significant regional differences in coverage of sleep studies in Oregon. Dodson raised the issues that sleep studies are difficult to obtain in many areas of Oregon. Link felt that any child with big tonsils with the right symptoms should not have to have a mandatory sleep study, that the expertise of the treating providers should be sufficient. However, if the exam does not support large tonsils, or if the history is unclear, or if the child is younger than age 2 or have complicating medical conditions (Down's etc.), then the child should have a sleep study even if it required travel. Dr. Link felt that the sleep questionnaires were useful in predicting neurological outcome/improvements in daytime function after adenotonsillectomy, although not helpful in diagnosing OSA.

There was discussion about what should constitute a positive sleep study. The OHP medical directors are requesting specific guidelines for what makes a positive study, such as a specific apnea-hypopnea index AHI cut off. Link felt that a positive study should depend on daytime symptoms. An AHI between 2-5 should require daytime symptoms, while an AHI >5 would be considered positive with or without daytime symptoms, and an AHI <2 should be considered negative. Dr. Link felt that the types of events seen during the sleep study should also be considered in determining whether the study should be considered positive. Some types of events are more serious than others. He felt that it was important to define what events should be considered. Link noted that his sleep lab is required to score sleep studies based on national criteria, and requiring specific changes to how to read the studies would result in them having to be read twice and would be burdensome.

The decision was that the general direction of the guideline was correct. HERC staff was directed to work with primary care providers, ENT providers, and sleep specialists to help to clarify 1) the age cut-off for the guideline (12 and younger, 18 and younger, or other), 2) whether children younger than age 2 should be included in the high risk group and have required sleep studies prior to adenotonsillectomy, and 3) how to define a positive sleep study.

Actions:

- 1) HERC staff to work with providers to revise the proposed adenotonsillectomy for OSA guideline and bring back to a future VBBS meeting

➤ **Topic:** Coverage guidance - Diagnosis of sleep apnea in adults

Discussion: Livingston presented the issue summary on applying the Coverage Guidance - Diagnosis of Sleep Apnea in Adults. She discussed proposed modifications from the VbBS language based on feedback from the OHP CCO Medical Directors. Shaffer clarified that across Oregon there should be access to Type 1 monitors but one of the alternatives should also be available. Questions were raised as to whether the other types of monitors provided comparable data, and what exactly were the additional non-Type IV monitors. It was clarified that this was derived from Medicare language and that all types of monitors provided relatively comparable results. Suggestions were made to cover Type 1 and at least one of the other types of monitors and to modify the language to clarify that CPAP titration should be performed at the time of the diagnostic study.

Actions:

- 1) Adopt a new diagnostic guideline on Diagnostic Testing in Sleep Apnea as shown in Appendix A

➤ **Topic:** Coverage guidance follow up - Continuous blood glucose monitoring

Discussion: Livingston presented an issue summary combining the HTAS Coverage Guidance and OHP CCO Medical Directors input. Public comment was received from Sheryl Moore, a diabetes educator, representing the Oregon Diabetes Educators Association, and American Association of Diabetes Educators. She argued that retrospective monitoring was a valuable tool for Type 2 diabetics, and also that requiring the HbA1c cutoff of greater than 8 was too limiting. Bill Stryke from Johnson & Johnson also presented testimony. There was a brief discussion about the lack of evidence demonstrating any benefit in retrospective monitors in type 2 diabetics, and the need to limit coverage in the absence of proven benefit. The guideline note was approved as presented.

MOTION: To approve the guideline note on continuous blood glucose as presented. CARRIES 6-0.

Actions:

- 1) Adopt a new guideline note on continuous blood glucose monitoring as shown in Appendix A

COVERAGE GUIDANCES FOR PRIORITIZED LIST

➤ **Topic:** Neuroimaging in headache

Discussion: Livingston presented the coverage guidance and proposed modifications to the guideline on neuroimaging in headache. There was some discussion about the language changes. There was a recommendation to add examples of dizziness, lack of coordination, numbness and tingling to the appropriate lines and to make a grammatical change.

MOTION: To approve the guideline note on neuroimaging in headache as amended. CARRIES 6-0.

Actions:

- 1) Modify DIAGNOSTIC GUIDELINE D5, NEUROIMAGING FOR HEADACHE as shown in Appendix B.

➤ **Topic:** Induction of labor

Discussion: Livingston presented an issue summary with the revised coverage guidance and a proposed modification to GUIDELINE NOTE 85, INDUCTION OF LABOR. There was minimal discussion.

MOTION: To approve the guideline note on induction of labor as presented. CARRIES 6-0.

Actions:

- 1) Modify GUIDELINE NOTE 85, INDUCTION OF LABOR as shown in Appendix B.

➤ **Topic:** PET scan for breast cancer

Discussion: Livingston presented an issue summary. Shaffer added additional background that the coverage guidance was trying to limit unnecessary PET scans, but that the HTAS members thought that PET scans are useful in some patients with breast cancer at high risk of metastases. Data for using PET scans for any types of breast cancer is not strong. There was a discussion about the different options for either adding the guideline to the breast cancer line or not. HTAS chose not to make a positive recommendation about when PET is appropriate because of a dearth of evidence. It was concluded that there is insufficient evidence to support opening up PET scans for breast cancer.

MOTION: To approve Option 1 as presented in the meeting materials. CARRIES 6-0.

Actions:

- 1) Make no change to the PET Scan Guidelines or to Line 197
- 2) Recommend to DMAP to move code G0252 from the DMAP *Ancillary Codes File* to the *DMAP Excluded File*

➤ **Topic:** Self-monitoring of blood glucose

Discussion: Livingston presented an issue summary about applying limits to supplies for the self-monitoring of blood glucose to the Prioritized List. There was a clarification that previously many codes for group visits (such as chronic disease self-management) were not opened due to payment issues related to Federally Qualified Health Centers. DMAP is actively working to solve the issues related to payment and to alternative payment methodologies around this issue specifically.

Public comment was received from Sheryl Moore, certified nurse and diabetes educator (with no declared conflicts of interest) who stated that restricting coverage was limiting an essential tool for self-monitoring of a chronic disease. Bill Struyk from Johnson & Johnson, which makes blood glucose monitoring equipment, stated that the self-monitoring is important, and also that there would be significant administrative burden incurred from the implementation of the 9 exemptions in the guideline. BJ Cavanough, from the Patient Education Network and NW Collaborative Care Network argued against the limitations, stating that it will have an impact on vulnerable patients.

There were concerns raised by subcommittee members about sending the message to patients that test strips would not be covered. There was a clarification that patients who are changing regimens would have additional strips covered. Test strips are a high cost item for OHP; this is the fourth highest code in terms of costs for durable medical equipment. Given the large cost, it would be worth having a prior authorization mechanism in place.

MOTION: To approve the guideline note on self-monitoring of blood glucose as presented. CARRIES 4-2.

Actions:

- 1) Approve code recommendations as presented
- 2) Adopt a new guideline note as shown in Appendix A

➤ **Topic: Carotid endarterectomy**

Discussion: Livingston presented an issue summary applying the approved coverage guidance to the Prioritized List. There was discussion as to whether or not a screening guideline should be added to the Prioritized List. Shaffer clarified that screening was looked into by HTAS, however, there was insufficient evidence to determine if there are high risk individuals who should receive screening. It was clarified that the USPSTF recommendation against screening in the general population applied to “adults without neurological symptoms and without a history of transient ischemic attacks (TIA) or stroke.” Given this, it was felt to be appropriate to include a screening guideline.

There was also a discussion about how studies on medical management that are outdated would overestimate the effects of surgery given the improvement in medical management.

MOTION: To approve the guideline notes on the screening for carotid artery stenosis and use of carotid endarterectomy as presented. CARRIES 6-0.

Actions:

- 1) Adopt a new diagnostic guideline as shown in Appendix A
- 2) Adopt a new guideline note as shown in Appendix A

GUIDELINES

➤ **Topic:** Lung volume reduction surgery guideline

Discussion: Smits reviewed the summary document. There was a suggestion to simply link to the CMS guideline covering lung volume reduction surgery; however, staff pointed out that the Prioritized List must reference a dated document and this could become problematic if CMS changed their guideline. The guideline was adopted as presented in the materials.

Actions:

- 1) A new guideline was adopted as shown in appendix A

➤ **Topic:** Concussion guideline

Actions:

- 1) Tabled until the August HERC meeting

➤ **Topic:** Bilateral cochlear implant guideline

Discussion: Livingston presented the issue summary. There was no discussion.

Actions:

- 1) Approve proposed changes to the cochlear implant guidelines 31 and 49 as shown in Appendix B.

➤ **Topic:** Diseases of lips

Discussion: Smits reviewed the summary document. There was no discussion.

Actions:

- 1) Add 528.5 to line 688 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
- 2) A new guideline was adopted as shown in Appendix A

➤ **Topic:** Treatment of cancer with little or no effectiveness near the end of life

Actions:

- 1) To be discussed at that afternoon's HERC meeting, see the May HERC meeting minutes for discussion and action

ICD-10 CONVERSION

➤ **Topic:** 2013 ICD-10 codes

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) The suggested placement for 2013 ICD-10 codes was accepted as shown in the meeting document

➤ **Topic:** ICD10 codes on no lines

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) CPT 38100-38102 (Splenectomy), 38115 (splenorrhaphy) and 38120 (Laparoscopic splenectomy) were added to line 84 INJURY TO INTERNAL ORGANS
- 2) Various coding changes done for the ICD-10 Prioritized List as presented in meeting materials

➤ **Topic:** ICD-10 General Surgery follow up

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) A new guideline was added to the ICD-10 Prioritized List as shown in Appendix A
- 2) The following CPT codes were added to line 551 for the ICD-10 Prioritized List: 44141, 44143, 44144, 44188, 44206, 44320, 44340, 44345, 44346, 45110, 45395

➤ **Topic:** Prioritized List changes/errata found through ICD-10 review

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) Guideline Note 14 had a line number deleted which did not contain this treatment
- 2) CPT 64400-64455, 64505-64530 were added to all lines referenced in Guideline Note 76 regarding nerve blocks
- 3) The treatment descriptions of lines 124, 137, and 549 were modified to add chemotherapy
- 4) The treatment descriptions of lines 371, 466, and 485 were modified to remove reference to radiation therapy
- 5) The title of line 387 was changed to "Central Serous Chorioretinopathy" for the October 1, 2014 ICD-10 Prioritized List

STRAIGHTFORWARD ITEMS

➤ **Topic:** March 2013 Straightforward Table

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) Add 32663 to line 204
- 2) Add 115.92 to line 106
- 3) Remove 115.92 from lines 147 and 354
- 4) Add 77421 to line 287
- 5) Add 57505 to line 144
- 6) Add 77301 to lines 340 and 356.
- 7) Add 253.8 to line 162
- 8) Add 67412 to lines 124 and 208
- 9) Add 52214 to lines 228 and 287
- 10) Do not add 52214 to line 291
- 11) Remove 54530 and 54535 from lines 104 and 261
- 12) Add 54520-54535 to line 275
- 13) Change treatment description for line 70 to MEDICAL / PSYCHOTHERAPY
- 14) Remove 99241-99245 from all lines on the Prioritized List. Advise DMAP to place 99241-99245 on the Excluded List
- 15) Remove 41512 from line 171. Keep 41512 on Excluded List
- 16) Add 56441 to lines 380 and 658
- 17) Add 62272 to line 320
- 18) Add 45114 and 45116 to line 35
- 19) Add 44130 to line 163
- 20) Add 59821 to line 394
- 21) Add 27707 to line 467

➤ **Topic:** May 2013 Straightforward Table

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) Add 62160 to lines 40 and 308
- 2) Add 61322 to line 101
- 3) Add 35516 and 35616 to line 293
- 4) Add 44147 to line 84
- 5) Add 44141-44160 to line 88
- 6) Add 37183 to line 308
- 7) Add 61885 to line 308
- 8) Add 47562 and 47563 to line 459
- 9) Add 77418 to line 277
- 10) Add 569.89 to line 503
- 11) Add 62223 to line 359
- 12) Add 47010 to line 84. Remove 47010 from line 111
- 13) Add 573.8 to lines 319, 360 and 365
- 14) Add 47010 to line 319
- 15) Add 96150-96154 to line 5
- 16) Add H0018 & H0019 to line 5
- 17) Add 66680 to line 362

➤ **Topic:** Clarification for Guideline Note 28 MOOD DISORDERS IN CHILDREN AGE EIGHTEEN AND UNDER

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) Guideline note 28 was modified as shown in Appendix B

➤ **Topic:** Hyperbaric oxygen guideline

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) The modified guideline for hyperbaric oxygen was adopted as shown in Appendix B and placement of this guideline on the Prioritized List was affirmed

➤ **Topic:** Death code placements

Discussion: Smits reviewed the summary document. There was minimal discussion.

Actions:

- 1) 656.40-656.43 were added to Line 1 Pregnancy
- 2) DMAP was advised to move V17.41 from the Ancillary File to the Diagnostic Workup File
- 3) Placement of 761.6, 768.0 and 768.1 were tabled until further review of this code series

MOTION: To approve the items included in the Guidelines, ICD-10 Conversion and Straightforward Items sections as discussed. CARRIES 6-0.

➤ **Public Comment:**

No additional public comment was received.

➤ **Issues for next meeting:**

- Follow up of Adenotonsillectomy for treatment of OSA in children
- ICD-10 Orthopedics follow up
- ICD-10 Dysfunction lines
- Sensory processing disorder
- Implantable intraocular steroids
- Advanced Imaging for Back Pain Guideline—guideline note D4
- Enzyme replacement therapy for Gaucher's disease

DRAFT

➤ **Next meeting:**

Thursday, August 8, 2013 at Meridian Park Hospital Medical Education Center.

➤ **Adjournment:**

The meeting was adjourned at 12:52 PM.

DRAFT

Appendix A

Recommended New Guidelines

New Guidelines to be added to the October 1, 2013 Prioritized List

GUIDELINE NOTE XXX CHRONIC PELVIC INFLAMMATORY CONDITIONS

Lines 56, 552

Chronic pelvic inflammatory conditions (ICD-9 614.2, 614.4, 614.5, 614.8, 614.9, 615.9) are included on the lower line only; acute conditions are included on the upper line.

GUIDELINE NOTE XXX, INTRA-AORTIC BALLOON PUMPS

Line 76

Intra-aortic balloon pumps (CPT 33967-33974) are included on this line only for use in cardiogenic shock

GUIDELINE NOTE XXX LUNG VOLUME REDUCTION SURGERY

Line 306

Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on line 306 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (ICD-9 492.0, 492.8) and all of the following:

- 1) BMI ≤ 31.1 kg/m² (men) or ≤ 32.3 kg/m² (women)
- 2) Stable with ≤ 20 mg prednisone (or equivalent) dose a day
- 3) Pulmonary function testing showing
 - a. Forced expiratory volume in one second (FEV₁) $\leq 45\%$ predicted and, if age 70 or older, FEV₁ $\geq 15\%$ predicted value
 - b. Total lung capacity (TLC) $\geq 100\%$ predicted post-bronchodilator
 - c. Residual volume (RV) $\geq 150\%$ predicted post-bronchodilator
- 4) PCO₂ ≤ 60 mm Hg (PCO₂ ≤ 55 mm Hg if 1-mile above sea level)
- 5) PO₂ ≥ 45 mm Hg on room air (PO₂ ≥ 30 mm Hg if 1-mile above sea level)
- 6) Post-rehabilitation 6-min walk of ≥ 140 m
- 7) Non-smoking for 6 months prior to surgery, as shown by cotinine level

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF $< 45\%$; dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (> 5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

GUIDELINE NOTE XXX DISEASES OF LIPS

Lines 214, 688

ICD-9 code 528.5 (Diseases of lips) is included on line 214 only for treatment of abscess or cellulitis of the lips. All other sub-diagnoses under this code are included on line 688.

Appendix A

Recommended New Guidelines

DIAGNOSTIC GUIDELINE XX DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA) IN ADULTS

Type I PSG is covered when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed attended in a sleep lab facility.

OHP clients should have access to least one of the alternatives listed below:

1. Type II or Type III sleep testing devices when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
2. Type IV sleep testing devices measuring three or more channels, one of which is airflow, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
3. Sleep testing devices measuring three or more channels that include actigraphy, oximetry, and peripheral arterial tone, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

CPAP titration should be performed as part of the diagnostic study, if possible.

GUIDELINE NOTE XXX CONTINUOUS BLOOD GLUCOSE MONITORING

Line 10

Continuous blood glucose monitoring (*CPT codes 95250-95251, HCPCS codes S1030-S1031*) with real-time or retrospective continuous glucose monitoring systems are only included on Line 10 for Type 1 diabetics for whom insulin pump management is being considered, initiated, or utilized and who also have one of the following:

- HbA1c levels greater than 8.0% (despite compliance with treatment), or
- a history of recurrent hypoglycemia.

GUIDELINE NOTE XX SELF-MONITORING OF BLOOD GLUCOSE

Line 33

For patients with Type 2 diabetes mellitus not requiring multiple daily injections of insulin, home blood glucose monitors and related diabetic supplies are covered only for those who have uncontrolled diabetes (defined as HbA1c levels greater than 8.0%), and in sufficient quantity to allow once a week testing.

Additional supplies for self-monitoring of blood glucose, up to 50 test strips for 90 days, are covered for patients with Type 2 diabetes who have additional complicating factors such as: changing treatment regimens, are newly diagnosed and receiving diabetes education, unexplained or new onset hyperglycemia or hypoglycemia, use of basal (once daily insulin), comorbid conditions affecting diabetic control, microvascular or macrovascular complications of diabetes, or use of systemic corticosteroid therapy.

A structured education and feedback program for self-monitoring of blood glucose is covered.

Appendix A

Recommended New Guidelines

For patients requiring multiple daily injections of insulin, home blood glucose monitors and related diabetic supplies are covered.

DIAGNOSTIC GUIDELINE XX SCREENING FOR CAROTID ARTERY STENOSIS

Screening for carotid artery stenosis (CPT 93880) in asymptomatic individuals is not a covered service.

GUIDELINE NOTE XXX CAROTID ENDARTERECTOMY

Line 440

Carotid endarterectomy is covered in patients with 70-99% carotid stenosis without near-occlusion.

For patients with 50 – 69% carotid stenosis who are symptomatic (recent transient ischemic attack or ischemic stroke), carotid endarterectomy is covered only for those who have failed optimal medical management.

Carotid endarterectomy is not covered for patients with any of the following:

- less than 50% carotid stenosis
- 50-69% stenosis who are asymptomatic
- near occlusion.

New Guidelines to be added to the October 1, 2014 (anticipated) ICD-10 Prioritized List

GUIDELINE NOTE XXX FECAL INCONTINENCE

Line 78, 551

ICD-10-CM code R15.9 (Full incontinence of feces) is included on Line 78 only for supportive equipment (e.g. diapers, gloves). Surgical treatment for fecal incontinence is included on Line 551 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS.

Appendix B

Recommended Modifications to Guideline Notes

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,212,435,489,562,563

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-9 codes: 643.00, 643.03, 643.10, 643.11, 643.13

Acupuncture is paired with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to 2 sessions of acupressure/acupuncture

Breech presentation

ICD-9 codes: 652.20, 652.23

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to 2 visits.

Back and pelvic pain of pregnancy

ICD-9 codes: 648.70, 648.73

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Line 212 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 15 total sessions, with documentation of meaningful improvement.

Line 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Acupuncture is included on Line 400 only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by the diagnosis codes M47.26, M47.27, M51.06, M51.07, M51.16, M51.17, M51.26, M51.27, M54.16, M54.17 with referral for up to 12 sessions.

Line 435 MIGRAINE HEADACHES

Acupuncture pairs on Line 435 for ICD-9 346, when referred, for up to 12 sessions.

Line 489 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on line 489 for treatment of osteoarthritis of the knee only, when referred, for up to 12 sessions

Line 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

Acupuncture pairs on Line 562 with the low back diagnoses (M47.816, M47.817, M47.896, M47.897, M48.36, M48.37, M51.26, M51.27, M51.36, M51.37, M51.86, M51.87, M54.5, M62.830, S33.5xxA, S33.9xxA, S39.092A, S39.82xA, S39.93xA), when referred, for up to 12 sessions. Acupuncture pairs with chronic (>90 days) neck pain diagnoses (723.1, 723.8, 723.9, 847.0), when referred, for up to 12 sessions.

Line 563 TENSION HEADACHES

Acupuncture is included on Line 563 for treatment of tension headaches, when referred, for up to 12 sessions.

Appendix B

Recommended Modifications to Guideline Notes

GUIDELINE NOTE 28, MOOD DISORDERS IN CHILDREN AGE EIGHTEEN AND UNDER

Line 212

The use of 296.90, Unspecified Episodic Mood Disorder, is appropriate only ~~when the following apply: For children 18 years old and under, in the presence of who have significant difficulty with emotional regulation that causes functional impairment~~ caused by significant difficulty with emotional regulation.

Use of 296.90 is limited to pairings with the following procedure codes:

- Assessment and Screening: 90801, 90802, H0002, H0031, H0032, T1023
- Family interventions and supports: 90846, 90847, 90849, 90887, H0038, H0045, H2021, H2022, H2027, S5151, S9125, T1005
- Individual Counseling and Therapy: 90804, 90806, 90810, 90812, H0004
- Group therapy: 90853, 90857, H2032
- Medication management: 90862
- Case Management: 90882, T1016
- Interpreter Service: T1013

GUIDELINE NOTE XXX HYPERBARIC OXYGEN

Lines 358, 399

Hyperbaric oxygen is a covered service only under the following circumstances:

- when paired with ICD-9-CM code 526.4 for osteomyelitis of the jaw only
- when paired with ICD-9-CM codes 526.89 for osteoradionecrosis of the jaw only
- when paired with ICD-9-CM codes 639.0, 670.02, and 670.04 only if the infection is a necrotizing soft-tissue infection;
- when paired with ICD-9-CM codes 730.10-730.99 only for chronic refractory osteomyelitis unresponsive to conventional medical and surgical management;
- when paired with ICD-9-CM codes 927-929 only for posttraumatic crush injury of Gustilo type III B and C;
- when paired with ICD-9-CM codes 990 only for osteoradionecrosis;
- when paired with ICD-9-CM codes 996.7 only for compromised myocutaneous flaps

GUIDELINE NOTE 31, COCHLEAR IMPLANTATION, AGE 5 AND UNDER

Line 298

Children will be considered candidates for cochlear implants if the following criteria are met:

- A) Profound sensorineural hearing loss in both ears (defined as 91dB hearing loss or greater at 500, 1000 and 2000 Hz)
- B) Child has reached the age of 1
- C) Receive little or no useful benefit from hearing aids
- D) No medical contraindications
- E) High motivation and appropriate expectations (both child, when appropriate, and family)

Appendix B

Recommended Modifications to Guideline Notes

Bilateral cochlear implants are covered. Simultaneous implantation appears to be more cost-effective than sequential implantation.

GUIDELINE NOTE 49, COCHLEAR IMPLANTS, OVER AGE 5

Line 491

Children will be considered candidates for cochlear implants if the following criteria are met:

- 1) Profound sensorineural hearing loss in both ears (defined as 91dB hearing loss or greater at 500, 1000 and 2000 Hz)
- 2) Receive little or no useful benefit from hearing aids
- 3) No medical contraindications
- 4) High motivation and appropriate expectations (both child, when appropriate, and family)

Postlinguistic adults will be considered candidates for cochlear implants if the following criteria are met:

- 1) Severe to profound sensorineural hearing loss in both ears (defined as 71dB (decibels) hearing loss or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz)
- 2) Hearing loss acquired after learning oral speech and language development (postlinguistic hearing loss)
- 3) Receive limited benefit from appropriately fit hearing aids; i.e., scores of 40% or less on sentence recognition test in the best-aided listening condition
- 4) No medical contraindications

Prelinguistic adults will be considered candidates for cochlear implants if the following criteria are met:

- 1) Profound sensorineural hearing loss in both ears (defined as 91dB (decibels) hearing loss or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz)
- 2) Hearing loss acquired before learning oral speech and language development (prelinguistic hearing loss)
- 3) Receive no benefit from hearing aids
- 4) No medical contraindications
- 5) A desire to be a part of the hearing world

Bilateral cochlear implants are covered. Simultaneous implantation appears to be more cost-effective than sequential implantation.

DIAGNOSTIC GUIDELINE D5, NEUROIMAGING FOR HEADACHE

Neuroimaging is not covered in patients with a defined tension or migraine type of headache, or a variation of their usual headache (e.g. more severe, longer in duration, or not responding to drugs).

Neuroimaging is covered for headache when a red flag* is present.

Appendix B

Recommended Modifications to Guideline Notes

*The following represent red flag conditions for underlying abnormality with headache:

- A. New onset or change in headache in patients who are aged over 50
- B. Thunderclap headache: rapid time to peak headache intensity (seconds to 5 minutes)
- C. Focal neurological symptoms (e.g. limb weakness, lack of coordination, numbness or tingling)
- D. Non-focal neurological symptoms (e.g altered mental status, dizziness)
- E. Abnormal neurological examination
- F. Headache that changes with posture
- G. Headache wakening the patient up (NB migraine is the most frequent cause of morning headache)
- H. Headache precipitated by physical exertion or valsalva maneuver (e.g. coughing, laughing, straining)
- I. Patients with risk factors for cerebral venous sinus thrombosis
- J. Jaw claudication
- K. Nuchal rigidity
- L. New onset headache in a patient with a history of human immunodeficiency virus (HIV) infection
- M. New onset headache in a patient with a history of cancer
- N. Cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), or short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA)

GUIDELINE NOTE 85, INDUCTION OF LABOR

Line 1

Induction of labor is covered for:

- Gestational age beyond 41 weeks 0 days
- Prelabor rupture of membranes, term
- Fetal demise
- Preeclampsia, term (severe or mild)
- Eclampsia
- Chorioamnionitis
- Diabetes, pre-existing and gestational
- Placental abruption
- Preeclampsia, preterm (severe or mild)
- Severe preeclampsia, preterm
- Cholestasis of pregnancy
- Preterm, prelabor rupture of membranes;
- Gastroschisis
- Twin gestation
- Maternal medical conditions (e.g., renal disease, chronic pulmonary disease, chronic hypertension, cardiac disease, antiphospholipid syndrome)
- Gestational hypertension
- Fetal compromise (e.g. isoimmunization, oligohydramnios)
- Intrauterine growth restriction/Small for gestational age, term
- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with a favorable cervix (for example, with a Bishop score ≥ 6)

Appendix B

Recommended Modifications to Guideline Notes

Induction of labor is not covered for the following:

- Macrosomia (in the absence of maternal diabetes)
- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with an unfavorable cervix (for example, a Bishop score <6)
- Elective purposes <39 weeks (without a medical or obstetrical indication)
- Intrauterine growth restriction/Small for gestational age, preterm (without other evidence of fetal compromise)

DRAFT

Section 3

Coverage Guidances

Chronic otitis media guideline note issue summary

Question: How should the guideline note 51 be modified to capture the intent of the coverage guidance?

Question source: VBBS subcommittee, HERC staff

Issue: At the March VBBS meeting, there were a number of concerns about the language of the guideline note, and greater clarification desired to clearly indicated what would be required for coverage. Staff was instructed to work with Chair Dodson and bring back a revised version for review.

Current Prioritized List status:

Line: 383
Condition: HEARING LOSS - AGE 5 OR UNDER (See Guideline Notes 64,65,76)
Treatment: MEDICAL THERAPY INCLUDING HEARING AIDS
ICD-9: 388.00,388.02-388.2,388.40-388.5,388.8,389.00-389.9,V53.2
CPT: 69424,69433,69714,69715,92590-92595,92597,98966-98969,99051,99060,99070,99078,99201-99360,99366,99374,99375,99379-99412,99429-99444,99468-99480,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,S0270-S0274

Line: 502
Condition: CHRONIC OTITIS MEDIA (See Guideline Notes 51,64,65,76)
Treatment: PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY
ICD-9: 380.50-380.53,381.10-381.89,382.1-382.3,382.9,383.1,383.20-383.31,383.9,384.20-384.9
CPT: 42830-42836,69210-69222,69310,69400-69511,69601-69650,69700,69801,69905,69910,69979,92562-92565,92571-92577,92590,92591,98966-98969,99051,99060,99070,99078,99201-99360,99366,99374,99375,99379-99412,99429-99444,99468-99480,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,S0270-S0274

Chronic otitis media is included on line 502. Currently, guideline note 51 applies to Line 502 only. The tympanostomy codes are scheduled to be removed from Line 383.

CPT codes

Code	Description	Line Placement	
69424	Ventilating tube removal requiring general anesthesia	Line	Condition
		178	ACUTE MASTOIDITIS
		308	COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
		325	CLEFT PALATE AND/OR CLEFT LIP
		405	CHOLESTEATOMA; INFECTIONS OF THE PINNA
		418	ACUTE OTITIS MEDIA
		502	CHRONIC OTITIS MEDIA
69433	Tympanostomy (requiring insertion	Line	Condition

Code	Description	Line Placement	
	of ventilating tube), local or topical anesthesia	178	ACUTE MASTOIDITIS
		325	CLEFT PALATE AND/OR CLEFT LIP
		405	CHOLESTEATOMA; INFECTIONS OF THE PINNA
		418	ACUTE OTITIS MEDIA
		502	CHRONIC OTITIS MEDIA
69436	Tympanostomy (requiring insertion of ventilating tube), general anesthesia	Same as 69433	

HERC Staff Recommendations

- 1) Adopt the modified Guideline Note 51:

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Line 383, 502

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 383. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 502.

For coverage to be considered on either Line 383 or 502, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay (should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children over 3 years who are having their second set of tubes.

2) Add tympanostomy codes (69424, 69433, 69436) to Line 383
Hearing Loss – Age 5 or Under

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN

DRAFT for VbBS Meeting Materials 8/8/13

HERC COVERAGE GUIDANCE

Children under Age 6

For children under 6 diagnosed with disruptive behavior disorders¹, including those at risk for ADHD, specific parent behavior training² is recommended for coverage as first-line therapy (*strong recommendation*).

Pharmacotherapy³ is recommended for coverage as a second line therapy (*weak recommendation*).

Provider consultation with teachers is recommended for coverage (*weak recommendation*).

Children Age 6 and Over

For children 6 and over who are diagnosed with ADHD¹, pharmacotherapy³ alone (*weak recommendation*) or pharmacotherapy³ with psychosocial/behavioral treatment (*strong recommendation*) are recommended for coverage.

Provider consultation with teachers is recommended for coverage (*weak recommendation*).

¹*Children with comorbid mental health conditions may require additional or different treatments that are not addressed in this guidance.*

²*Effective studied types of parent behavior training include: Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program. The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.*

³*Limited to medications that are FDA-approved for the condition.*

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

American Academy of Pediatrics (AAP). (2011). Supplemental information. Implementing the key action statements: An algorithm and explanation for process of care for the evaluation, diagnosis, treatment, and monitoring of ADHD in children and adolescents. *Pediatrics*, SI1-SI21. Retrieved December 5, 2012, from <http://pediatrics.aappublications.org/content/128/5/1007/suppl/DC1>

Charach, A., Dashti, B., Carson, P., Booker, L., Lim, C.G., Lillie, E., et al. (2011). *Attention deficit hyperactivity disorder: Effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Comparative effectiveness review no. 44.* (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02- 0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by inattention, overactivity, and impulsivity. While ADHD can begin before children enter

school, it is most commonly identified and treated in primary school. Boys are classified with ADHD approximately twice as frequently as girls, and primary school-age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population and are considered a “disorder” to a greater or lesser degree. Symptoms are clinically significant when they cause impaired functioning. The DSM-IV criteria include subtypes: (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, and (3) combined inattentive and hyperactive.

Although the condition now classified as ADHD was first described clinically in 1902, few treatments were available until the 1950s, when methylphenidate (brand name, Ritalin) was developed to target the condition. The use of pharmacotherapy has increased through the years, along with refinements in understanding and recognition of the condition as a disorder. The diagnosis of ADHD and prescriptions for its treatment have grown exponentially, particularly in North America. By the end of the 1960s, approximately 150,000 to 200,000 children were treated with stimulants, which represented 0.002% of the U.S. child population at that time. In contrast, the U.S. National Survey of Child Health provides a 2003 estimate of 4.4 million children who were identified at some point as having ADHD, which represents 7.8% of that population, of which 2.5 million (56%) were receiving medication. Within the United States, the estimated prevalence of adult ADHD stands at 4.4%. Prescriptions for the treatment of ADHD have increased as well, with methylphenidate prescriptions increasing from 4 million to 11 million, and prescriptions for amphetamines increasing from 1.3 million to 6 million in an eight year period of time (1991-1999).

Drugs currently FDA approved for treatment of ADHD and their maximum recommended daily dosages are listed in Table 1. In addition, a variety of antidepressants are used off-label to treat this condition.

Table 1. FDA Approved Medications for the Treatment of ADHD

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
<i>Amphetamine preparations</i>		
Mixed amphetamine salts	Adderall	40mg
	Adderall XR	30mg
Dextroamphetamine	Dexedrine, Dextrostat	40mg
	Dexedrine spanule	40 mg
Lisdexamfetamine	Vyvanse	70mg
<i>Methylphenidate preparations</i>		
Dexmethylphenidate	Focalin	20mg

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
	Focalin XR	30mg
Methylphenidate HCL	Methylin, Ritalin, Ritalin LA, Ritalin SR, Metadate CD, Metadate ER	60mg
	Daytrana	30mg
	Concerta	54mg < 13 years/ 72mg ≥ 13 years ¹
SNRIs		
Atomoxetine	Strattera	1.4mg/kg or 100mg
Other		
Guanfacine extended release	Intuniv	4mg
Clonidine extended release	Kapvay	0.4mg/day

Evidence Review

The purpose of this review is to critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior and therefore at high risk for ADHD and to similarly examine the comparative long-term effectiveness and adverse events of interventions for ADHD.

Treatment of Preschoolers with Disruptive Behavior Disorders

For the management of preschoolers with disruptive behavior disorders, including children considered to be at risk for ADHD², evidence was grouped into two broad categories of treatment: behavioral interventions and psychostimulant medication. A total of 31 studies evaluated parent behavior training, which was primarily defined as one of four manualized programs³. Nearly all studies showed positive effects, and pooled results for eight good-quality studies also found a significant improvement in

¹ From AAP 2011 reference

² The ADHD diagnosis has not been widely applied in children under age 6 because of uncertainty regarding the reliability and validity of the diagnostic criteria in this age group. Because ADHD in this age group is commonly identified in the context of other disruptive behaviors, and in children with diagnoses of Disruptive Behavior Disorders including Oppositional Defiant Disorder and Conduct Disorder, the evidence review includes studies of children less than six with Disruptive Behavior Disorders.

³ Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program

Coverage Guidance: Treatment of Attention Deficit Hyperactivity Disorder in Children

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child behavior with parent behavior training. In addition, the single good-quality study of methylphenidate finds that it appears to be effective. The strength of evidence for use of parent behavior training was judged high due to number of studies and consistency of results. The strength of evidence for methylphenidate was judged low because there is only one good-quality study.

Long-term extension (follow-up) studies for the RCTs of parent behavior training suggest that the benefits are maintained for several years, although no long-term study (lasting 12 months or more) of parent behavior training alone included untreated comparison groups, and attrition was high. A recent study examining parent behavior training with and without school-based teacher or child interventions included a no-treatment control. This study showed maintenance of benefits of parent behavior training at two years. Studies do not comment on adverse events related to parent behavior training.

Five studies examining combinations of parent behavior training and school or daycare interventions for preschool children at risk for disruptive behavior disorder and/or ADHD suggest that adding classroom teacher consultation may be important for children in low socioeconomic status (SES) communities, but not for families with educated parents who live in communities with resources, although direct comparisons of identical interventions offered to families of different SES have not yet been performed. All behavioral interventions showed benefits relative to no-treatment controls, and a dose response to the number of parent behavior training sessions attended by parents was also identified, enhancing the overall strength of evidence for effectiveness of parent behavior training.

Several small, short-term trials of psychostimulant medication use in preschoolers, primarily immediate release methylphenidate, suggest that it is efficacious and safe. In addition, the Preschool ADHD Treatment Study (PATs), a large, high quality trial funded by the National Institute of Mental Health also suggests that methylphenidate is effective for improving parent-rated child behavior in preschoolers. This multisite trial had multiple phases, beginning with 10 sessions of parent behavior training. The training was followed by an open label safety lead-in phase of a psychostimulant medication, then a titration phase, a cross-over phase and open-label maintenance phase that lasted 10 months. The PATs study offers information about both the potential benefits and limitations of stimulant medication use in very young children. Limitations include the following: preschool children experience more dose-related adverse events than older children, stimulants interfere with rates of growth, and the presence of three or more comorbid conditions and psychosocial adversity are associated with lessened effectiveness of psychostimulant medication. These findings are supported by two additional “fair” quality RCTs.

In conclusion, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate. This favors the use of parent behavior training for preschoolers at risk for ADHD due to disruptive behavior. A direct comparison has not yet been done.

Long-Term Effectiveness and Safety of Interventions in People Age 6 and Older

Pharmacologic Agents

The long-term effectiveness and safety (at least 12 months of treatment and/or follow up) of several psychostimulants (e.g., methylphenidate immediate release amphetamine, Osmotic-controlled Release Oral delivery System methylphenidate, dextroamphetamine, mixed amphetamine salts, atomoxetine, clonidine and guanfacine extended release) have all been examined prospectively in children and adolescents age 6 and over. The agents examined were all shown to be efficacious for control of inattention, overactivity, and impulsiveness for at least 12 months and up to three years, and few serious adverse events were noted, although guanfacine extended release appears to be less well tolerated than other agents examined. Global ratings of impairment also indicate continued benefit throughout the extension studies for patients still receiving medications. In general, those who remain on medication show continued benefit, and few adverse events are reported for them. With a majority of the studies funded by industry (12 of 21), there may be enhanced representations of effectiveness and safety. Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time.

Fewer children experienced adverse events with methylphenidate than with dextroamphetamine. Concerns about adverse events led to discontinuation of medications for 15% to 20% of children age 6 and over using extended release mixed amphetamine salts. Concerns about exacerbation of tics with stimulants appear to be unfounded, although the sample size remains small. Use of psychostimulants slows the rate of growth, and increases blood pressure and heart rate to a small degree. At a group level, the mean changes are clinically insignificant, although on rare occasions individuals discontinue an agent because of changes in vital signs. There are many similarities between methylphenidate immediate release and other preparations of psychostimulants, both in terms of efficacy and in the side effect profile. Therefore, many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust.

Atomoxetine is both safe and effective for ADHD symptoms over 12 to 18 months among children and for up to three years in adults. Discontinuation in children and teens appears to be higher (26%) due to ineffectiveness and lower (3%) due to adverse events than with other agents, although these are not direct comparisons. As with

psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases. There is only one study of a pharmacologic intervention over an extended time period (three years) in adults with ADHD, and that study found symptom improvement was maintained for those on atomoxetine, and discontinuation due to adverse events was somewhat higher for adults (11%) than for children (3%).

An extension study of guanfacine suggests that this agent is also effective in controlling ADHD symptoms for up to two years; however, high rates (40% to 60%) of somnolence, headache, and fatigue occur when it is used as a monotherapy, especially in the initial six to eight months of treatment. A second study examined concurrent use of psychostimulants and noted improved tolerance to these adverse effects. Changes in vital signs occur, but no clear group trends are noted. Individuals may develop clinically significant hypotension and bradycardia. Serious adverse events include syncope and clinically significant changes on electrocardiogram.

Overall, pharmacologic agents used for controlling the symptoms of inattention, overactivity, and impulsivity of ADHD show maintenance of effectiveness and safety for 12 to 24 months. Following that, attrition from use interferes with the ability to draw conclusions. Along with decreased symptoms, overall functioning is improved.

Psychosocial and Behavioral Interventions, Alone and in Combination with Medication
Investigations comparing psychosocial/behavioral interventions, alone and in combination with psychostimulant medication management, showed that both medication and combined medication/behavioral treatment (including school-based interventions) are more effective in treating ADHD and oppositional defiant disorder symptoms than psychosocial or behavioral interventions alone. Psychosocial interventions in the four included trials included intensive behavioral treatment (parent behavior training, child-focused treatment and a school-based intervention), multimodal treatment (parent behavior training, behavior management training, family therapy and child social skills training), “behavior treatment” (undefined) and EEG biofeedback.

Longer Term Outcomes

Evaluation of long-term outcomes (five or more years follow up) following interventions for ADHD is complex due to multiple patterns of services used and very few studies available, with only two RCTs of well-characterized clinical samples, both of boys ages 7 to 9 years with DSM-IV ADHD, combined subtype. The best quality data come from the Multimodal Treatment of ADHD Study, which compared 14 months of management with immediate release methylphenidate to three other interventions: psychosocial and behavioral treatment; the combination of medication management and psychosocial and behavioral treatment; and standard community care. Three years after initiation, the four intervention groups showed comparable outcomes. No clear relationship was identified between duration of medication use and psychiatric or overall functional outcomes at

three years or beyond. In contrast, a few long-term cohort studies lasting five years or more suggest that increased duration of medication was associated with improved grade retention and academic achievement. No prospective studies have been designed to investigate the question of long-term functional outcomes directly. There appear to be long-term academic benefits with medication interventions in some domains.

In conclusion, the evidence for long-term effectiveness of pharmacologic agents for improving ADHD symptoms is based on a single good study for methylphenidate and a single good study for atomoxetine. These studies followed the children for 12 or 14 months and showed benefit with few adverse effects, thereby resulting in low strength of evidence for longer term effectiveness for each of these agents. Similarly, there is a single good study showing benefits for the combination of methylphenidate and psychosocial interventions. The evidence for other pharmaceutical agents is insufficient, as is the evidence pertaining to parent behavior training and academic interventions.

[\[Evidence Source\]](#)

Evidence Summary

For children under age six, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. Classroom teacher consultations in addition to parent behavior training are beneficial to children of lower socioeconomic status. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate.

In children age six and over, there is evidence to support the long-term effectiveness of both methylphenidate and atomoxetine for improving ADHD symptoms, as well as methylphenidate combined with behavioral/psychosocial interventions. There is evidence for only the short-term effectiveness for other FDA approved medications and guanfacine, the latter of which has more frequent adverse events.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Pharmacologic treatment age <6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Pharmacotherapy is recommended for coverage as a second line therapy (<i>weak recommendation</i>)
Parent Behavior Training (PBT) age <6	net benefit without apparent harms	high	modest costs	likely moderate variability in parent preferences for treatment	Specific parent behavior training is recommended for coverage as first-line therapy (<i>strong recommendation</i>)
Behavioral/ psychosocial treatment age <6 (excluding PBT)	no evidence	insufficient	modest costs	likely moderate variability in parent preferences for treatment	<i>No recommendation</i>
Pharmacologic treatment alone and combined with behavioral/ psychosocial interventions age ≥ 6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Pharmacotherapy alone (<i>weak recommendation</i>) or pharmacotherapy with psychosocial/ behavioral treatment (<i>strong recommendation</i>) are considered first-line therapy and are recommended for coverage

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Behavioral/ psychosocial treatment alone, PBT, academic interventions age $\geq$ 6	unable to draw conclusions	insufficient	modest costs	likely moderate variability in parent preferences for treatment	Behavioral/ psychosocial treatment alone, PBT, academic interventions age $\geq$ 6 for primary ADHD are not recommended for coverage (<i>weak recommendation</i>)
School/ daycare based interventions	net benefit in those <6 of low SES, benefit in $\geq$ 6 as element of intensive behavioral treatment, no apparent harms	low	modest costs	likely minimal variability in parent preferences	School/daycare based interventions are outside the purview of this coverage guidance (<i>No recommendation</i>) Provider consultation with teachers is recommended for coverage (based on evidence of children <6 with low SES) (<i>weak recommendation</i>)

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Five quality measures were identified when searching the [National Quality Measures Clearinghouse](#). The Institute for Clinical Systems Improvement developed three measures around diagnosis and management of attention deficit hyperactivity disorder (ADHD) in primary care for school age children and adolescents: 1) Percentage of patients diagnosed with ADHD whose medical record contains documentation that the clinician discussed the need for school-based supports and educational service options for children with ADHD; 2) Percentage of patients treated with psychostimulant medication for the diagnosis of ADHD whose medical record contains documentation of a follow-up visit at least twice a year; and 3) Percentage of patients newly diagnosed with ADHD whose medical record contains documentation of DSM-IV-TR or DSM-PC criteria. These three measures have not been endorsed by the National Quality Forum (NQF).

The National Committee for Quality Assurance developed two HEDIS measures, which are both endorsed by the NQF: 1) Follow-up care for children prescribed ADHD medication (initiation phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who had one follow-up visit with a practitioner with prescribing authority during the 30-day initiation phase; and 2) Follow-up care for children prescribed ADHD medication (continuation and maintenance [C&M] phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who remained on the medication for at least 210 days and who, in addition to the visit in the initiation phase, had at least two follow-up visits with a practitioner within 270 days (9 months) after the initiation phase ended.

Oregon's Coordinated Care Organizations' quality of care objectives include the following measure: Meet or exceed the 90th percentile national Medicaid benchmarks for follow up care for children on ADHD medication.

COMMITTEE DELIBERATIONS – EVIDENCE-BASED GUIDELINE SUBCOMMITTEE

The Evidence-based Guidelines Subcommittee had extensive deliberations on the types and availability of behavioral and psychology treatments available. An additional literature search was performed to determine if additional types of interventions had evidence to support beyond the parent behavioral training, and none were found. The decision was also made to remain silent on the treatment of children over 6 with behavioral treatments alone, due to implementation considerations. Subcommittee members determined the best way to address the coordination with teachers for school-based interventions was through communication/coordination between the provider and teacher being recommended as a covered service.

COMMITTEE DELIBERATIONS – VALUE-BASED BENEFITS SUBCOMMITTEE

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A. GRADE Framework Description

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
312.9	Unspecified disturbance of conduct
314	Hyperkinetic syndrome of childhood
314.0	Attention deficit disorder of childhood
314.00	Attention deficit disorder without mention of hyperactivity
314.01	Attention deficit disorder with hyperactivity
314.1	Hyperkinesis with developmental delay
314.2	Hyperkinetic conduct disorder
314.8	Other specified manifestations of hyperkinetic syndrome
314.9	Unspecified hyperkinetic syndrome
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
90785	Interactive complexity, add-on code to be used in conjunction with codes for primary service
90791	Psychiatric diagnostic evaluation (no medical services)
90792	Psychiatric diagnostic evaluation (with medical services)
90832	Psychotherapy, 30 minutes with patient and/or family member
90834	Psychotherapy, 45 minutes with patient and/or family member
90837	Psychotherapy, 60 minutes with patient and/or family member
90839	Psychotherapy for crisis, first 60 minutes
90840	Add-on for each additional 30 minutes of psychotherapy for crisis, used in conjunction with code 90839
90845	Psychoanalysis
90846	Family psychotherapy without the patient present
90847	Family psychotherapy, conjoint psychotherapy with the patient present
90849	Multiple-family group psychotherapy
90853	Group psychotherapy (other than of a multiple-family group)
90863	Pharmacologic management, including prescription and review of medication, when performed with psychotherapy services; used only as add-on to primary psychotherapy code
98960	Education and training for patient self-management by a qualified, nonphysician health care professional using a standardized curriculum, face-to-face with the patient (could include caregiver/family) each 30 minutes; individual patient
98961	2-4 patients
98962	5-8 patients
HCPCS Codes	
H2027	Psychoeducational service, per 15 minutes
S9444	Parenting classes, non-physician provider, per session
S9482	Family stabilization services, per 15 minutes
T1027	Family training and counseling for child development, per 15 minutes

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework – ADHD Indications

Pharmacologic Treatment age <6 as 1st Line Therapy




Center for Evidence-based Policy

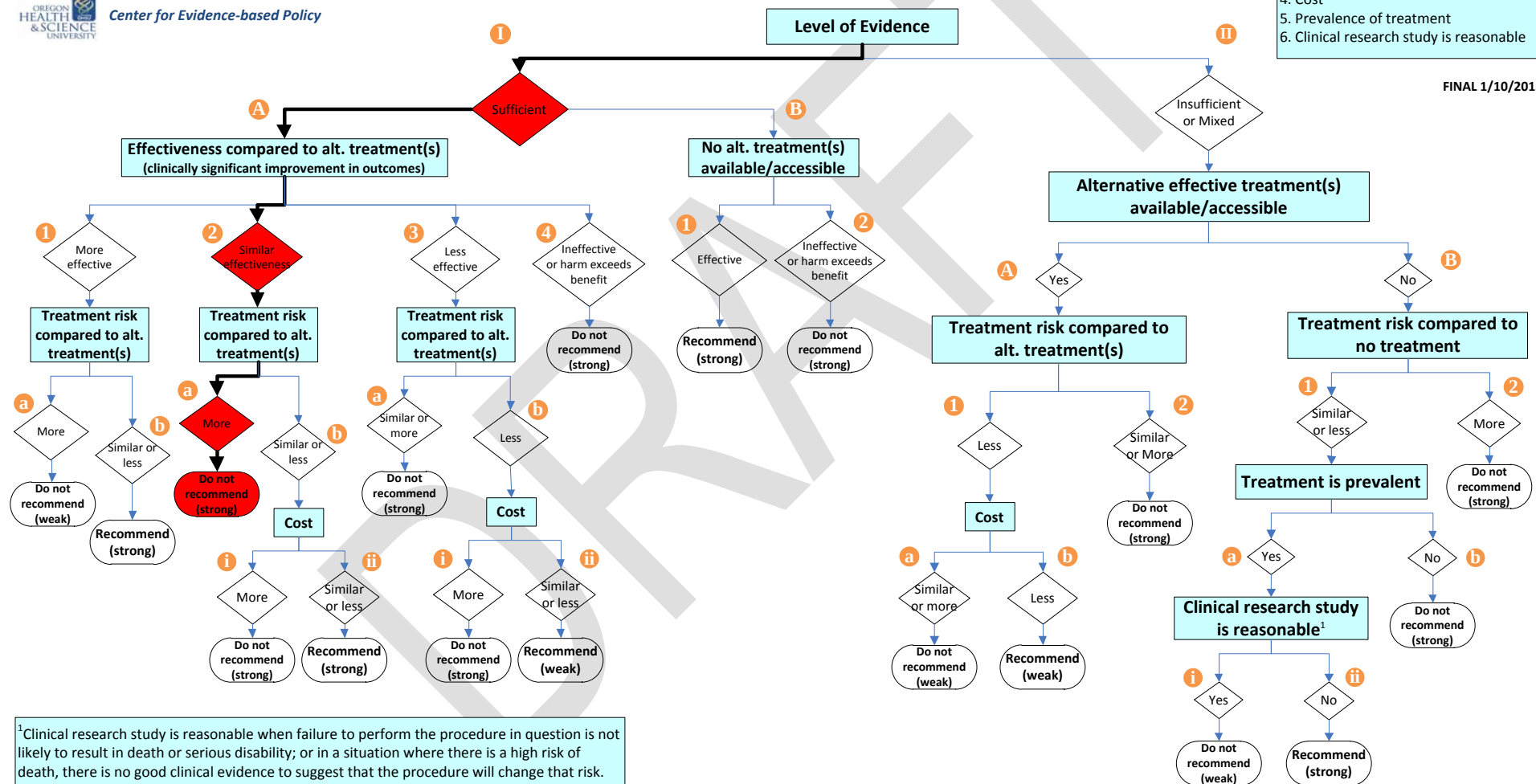
HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



Pharmacologic Treatment age <6 as 2nd Line Therapy

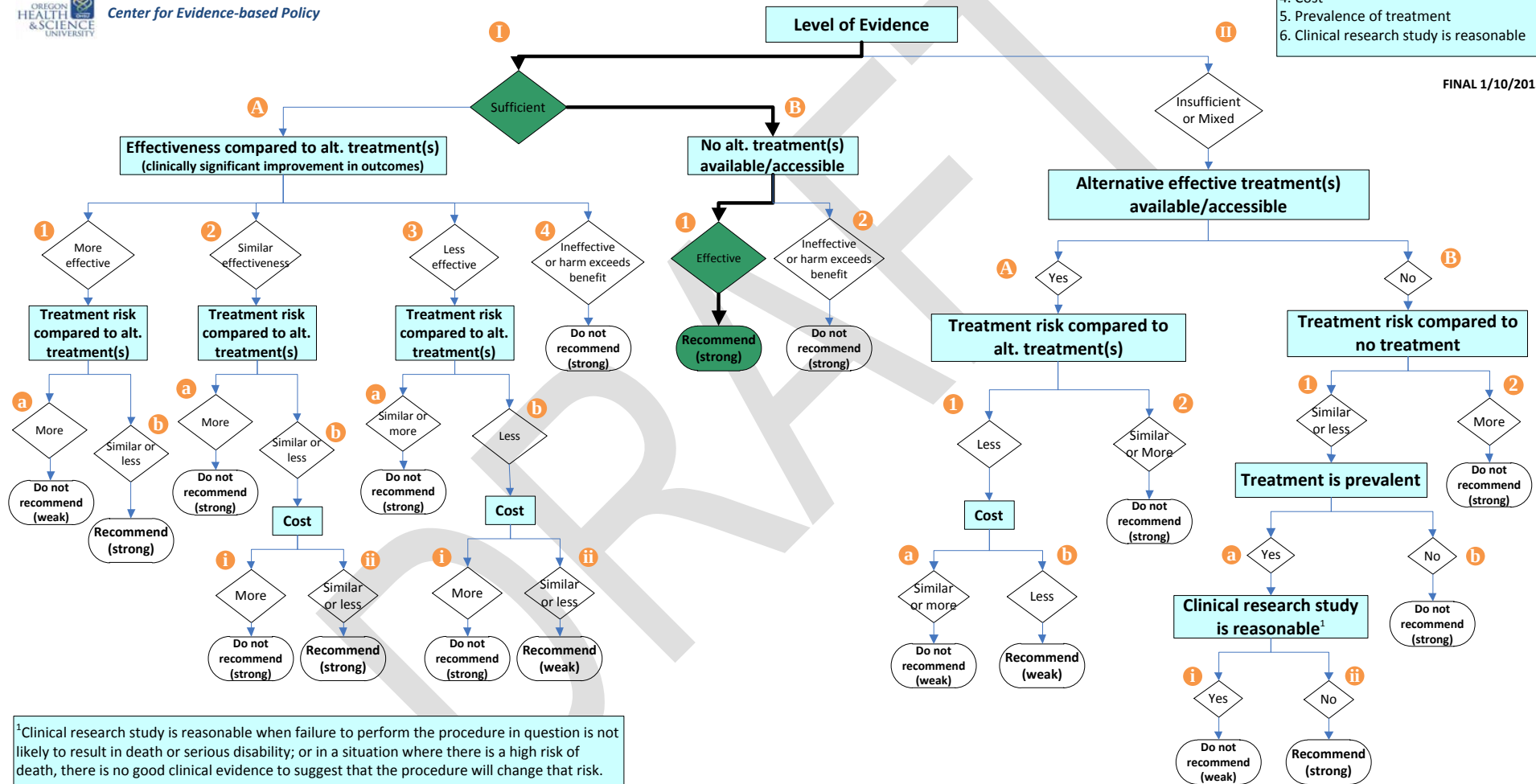
OREGON HEALTH & SCIENCE UNIVERSITY
Center for Evidence-based Policy

HERC Guidance Development Framework

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Decision Point Priorities
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2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Parent Behavior Training (PBT) or School/Daycare Interventions age <6 Compared to Pharmacologic Treatment



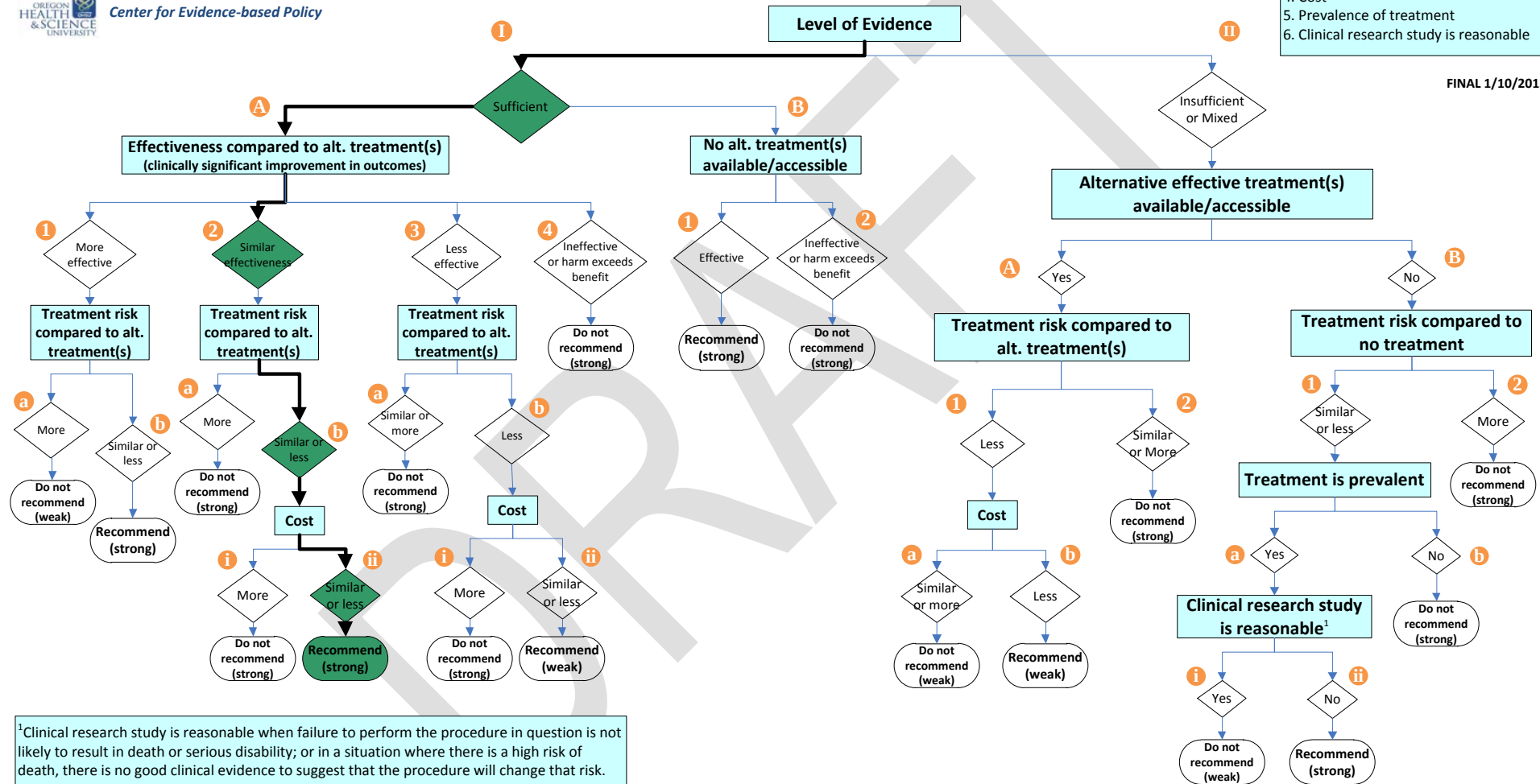
OREGON HEALTH & SCIENCE UNIVERSITY
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Pharmacologic Treatment Alone and Combined with Behavioral/Psychosocial Interventions Age ≥ 6



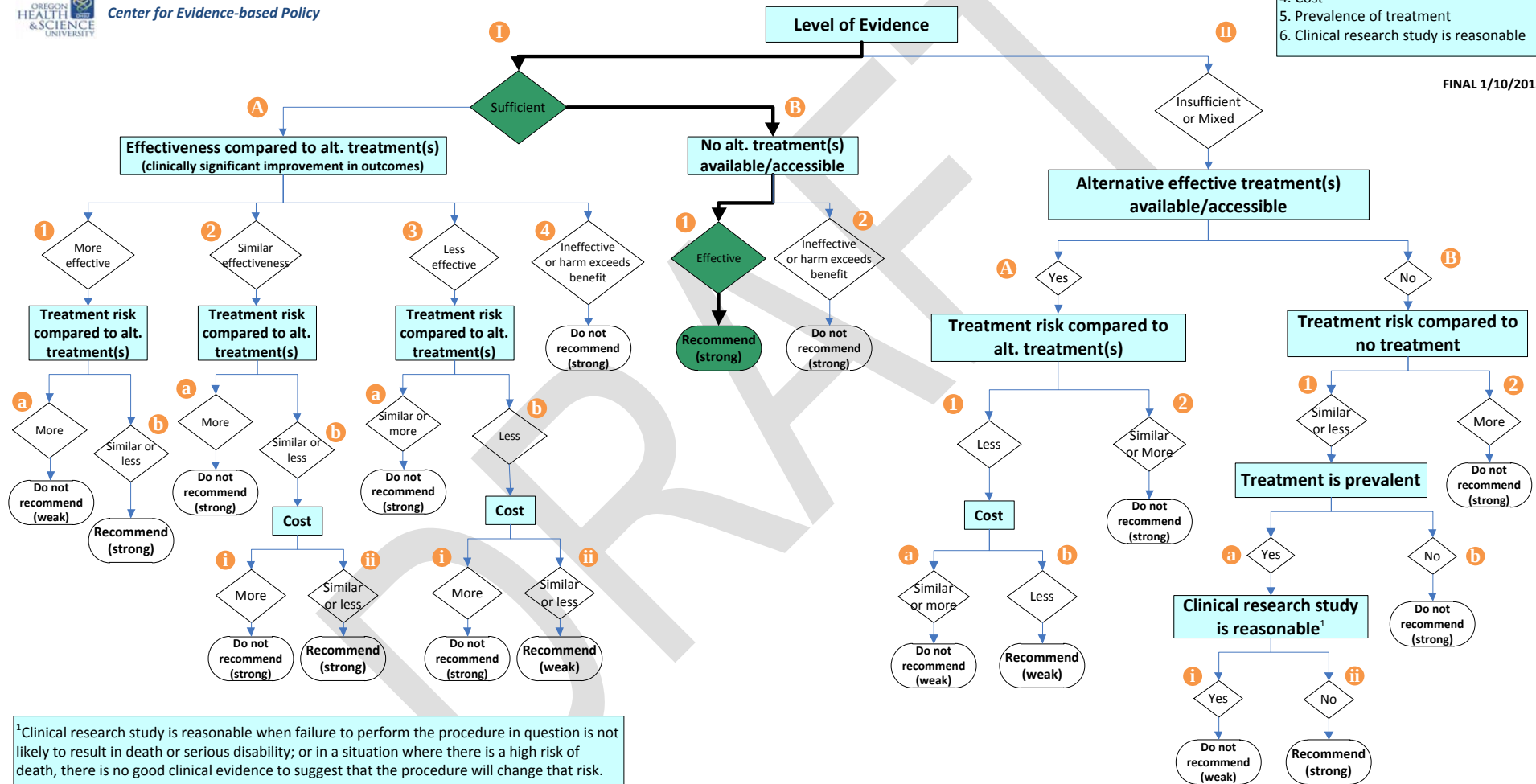
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HERC Guidance Development Framework

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- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Behavioral/Psychosocial Treatment Alone, PBT, Academic Interventions Age ≥ 6 Compared to Pharmacologic Treatment



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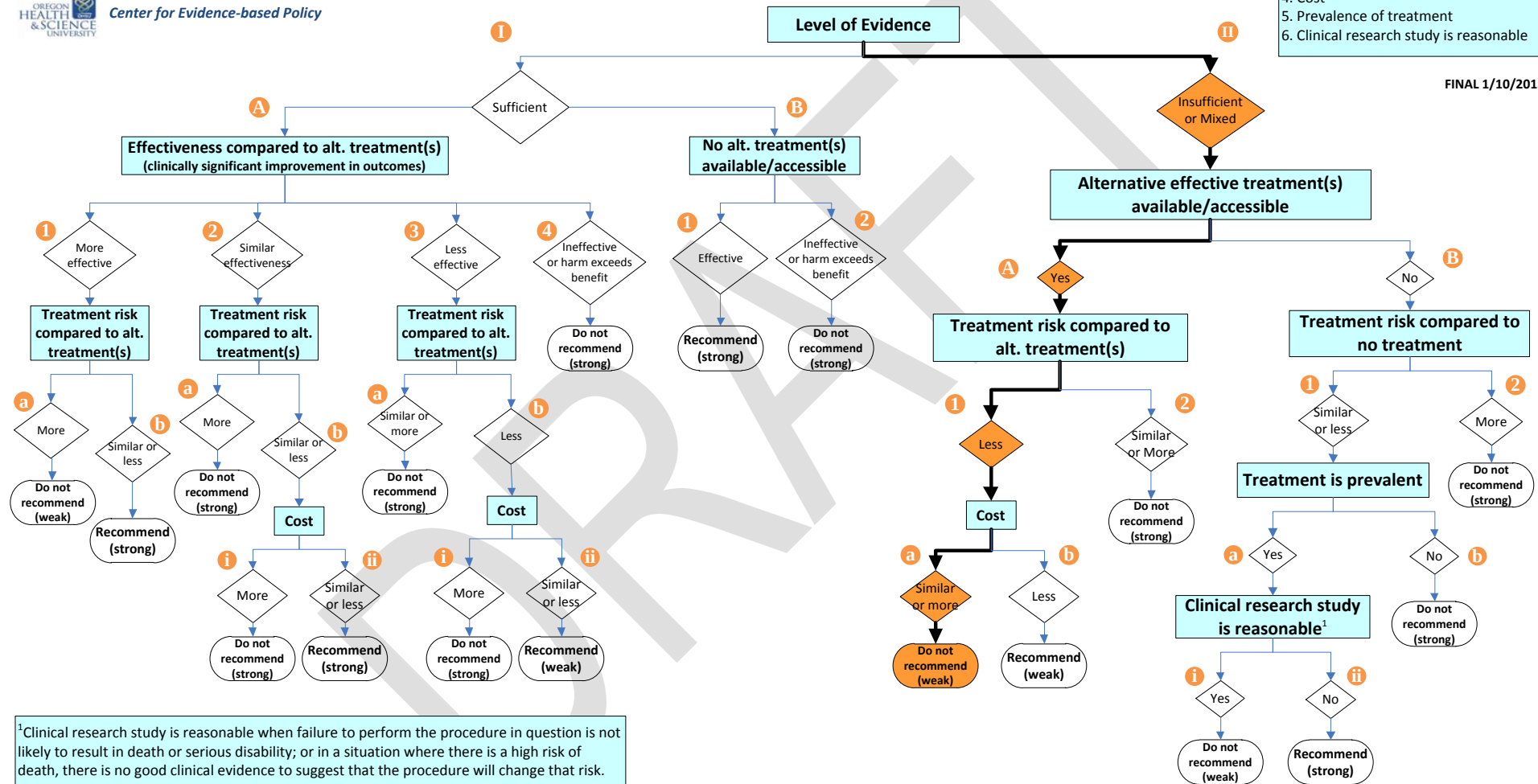
HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN

DRAFT for VbBS meeting materials 8/8/13

HERC COVERAGE GUIDANCE

Children under Age 6

For children under 6 diagnosed with disruptive behavior disorders¹, including those at risk for ADHD, specific parent behavior training² is recommended for coverage as first-line therapy (*strong recommendation*).

Pharmacotherapy³ is recommended for coverage as a second line therapy (*weak recommendation*).

Provider consultation with teachers is recommended for coverage (*weak recommendation*).

Children Age 6 and Over

For children 6 and over who are diagnosed with ADHD¹, pharmacotherapy³ alone (*weak recommendation*) or pharmacotherapy³ with psychosocial/behavioral treatment (*strong recommendation*) are recommended for coverage.

Provider consultation with teachers is recommended for coverage (*weak recommendation*).

¹ Children with comorbid mental health conditions may require additional or different treatments that are not addressed in this guidance.

² Effective studied types of parent behavior training include: Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program. The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.

³ Limited to medications that are FDA-approved for the condition.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

American Academy of Pediatrics (AAP). (2011). Supplemental information. Implementing the key action statements: An algorithm and explanation for process of care for the evaluation, diagnosis, treatment, and monitoring of ADHD in children and adolescents. *Pediatrics*, S11-S121. Retrieved December 5, 2012, from <http://pediatrics.aappublications.org/content/128/5/1007/suppl/DC1>

Charach, A., Dashti, B., Carson, P., Booker, L., Lim, C.G., Lillie, E., et al. (2011). *Attention deficit hyperactivity disorder: Effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Comparative effectiveness review no. 44.* (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02- 0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by inattention, overactivity, and impulsivity. While ADHD can begin before children enter

school, it is most commonly identified and treated in primary school. Boys are classified with ADHD approximately twice as frequently as girls, and primary school-age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population and are considered a “disorder” to a greater or lesser degree. Symptoms are clinically significant when they cause impaired functioning. The DSM-IV criteria include subtypes: (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, and (3) combined inattentive and hyperactive.

Although the condition now classified as ADHD was first described clinically in 1902, few treatments were available until the 1950s, when methylphenidate (brand name, Ritalin) was developed to target the condition. The use of pharmacotherapy has increased through the years, along with refinements in understanding and recognition of the condition as a disorder. The diagnosis of ADHD and prescriptions for its treatment have grown exponentially, particularly in North America. By the end of the 1960s, approximately 150,000 to 200,000 children were treated with stimulants, which represented 0.002% of the U.S. child population at that time. In contrast, the U.S. National Survey of Child Health provides a 2003 estimate of 4.4 million children who were identified at some point as having ADHD, which represents 7.8% of that population, of which 2.5 million (56%) were receiving medication. Within the United States, the estimated prevalence of adult ADHD stands at 4.4%. Prescriptions for the treatment of ADHD have increased as well, with methylphenidate prescriptions increasing from 4 million to 11 million, and prescriptions for amphetamines increasing from 1.3 million to 6 million in an eight year period of time (1991-1999).

Drugs currently FDA approved for treatment of ADHD and their maximum recommended daily dosages are listed in Table 1. In addition, a variety of antidepressants are used off-label to treat this condition.

Table 1. FDA Approved Medications for the Treatment of ADHD

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
<i>Amphetamine preparations</i>		
Mixed amphetamine salts	Adderall	40mg
	Adderall XR	30mg
Dextroamphetamine	Dexedrine, Dextrostat	40mg
	Dexedrine spanule	40 mg
Lisdexamfetamine	Vyvanse	70mg
<i>Methylphenidate preparations</i>		
Dexmethylphenidate	Focalin	20mg

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
	Focalin XR	30mg
Methylphenidate HCL	Methylin, Ritalin, Ritalin LA, Ritalin SR, Metadate CD, Metadate ER	60mg
	Daytrana	30mg
	Concerta	54mg < 13 years/ 72mg ≥ 13 years ¹
SNRIs		
Atomoxetine	Strattera	1.4mg/kg or 100mg
Other		
Guanfacine extended release	Intuniv	4mg
Clonidine extended release	Kapvay	0.4mg/day

Evidence Review

The purpose of this review is to critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior and therefore at high risk for ADHD and to similarly examine the comparative long-term effectiveness and adverse events of interventions for ADHD.

Treatment of Preschoolers with Disruptive Behavior Disorders

For the management of preschoolers with disruptive behavior disorders, including children considered to be at risk for ADHD², evidence was grouped into two broad categories of treatment: behavioral interventions and psychostimulant medication. A total of 31 studies evaluated parent behavior training, which was primarily defined as one of four manualized programs³. Nearly all studies showed positive effects, and pooled results for eight good-quality studies also found a significant improvement in

¹ From AAP 2011 reference

² The ADHD diagnosis has not been widely applied in children under age 6 because of uncertainty regarding the reliability and validity of the diagnostic criteria in this age group. Because ADHD in this age group is commonly identified in the context of other disruptive behaviors, and in children with diagnoses of Disruptive Behavior Disorders including Oppositional Defiant Disorder and Conduct Disorder, the evidence review includes studies of children less than six with Disruptive Behavior Disorders.

³ Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program

Coverage Guidance: Treatment of Attention Deficit Hyperactivity Disorder in Children

DRAFT for VbBS meeting materials 8/8/13

child behavior with parent behavior training. In addition, the single good-quality study of methylphenidate finds that it appears to be effective. The strength of evidence for use of parent behavior training was judged high due to number of studies and consistency of results. The strength of evidence for methylphenidate was judged low because there is only one good-quality study.

Long-term extension (follow-up) studies for the RCTs of parent behavior training suggest that the benefits are maintained for several years, although no long-term study (lasting 12 months or more) of parent behavior training alone included untreated comparison groups, and attrition was high. A recent study examining parent behavior training with and without school-based teacher or child interventions included a no-treatment control. This study showed maintenance of benefits of parent behavior training at two years. Studies do not comment on adverse events related to parent behavior training.

Five studies examining combinations of parent behavior training and school or daycare interventions for preschool children at risk for disruptive behavior disorder and/or ADHD suggest that adding classroom teacher consultation may be important for children in low socioeconomic status (SES) communities, but not for families with educated parents who live in communities with resources, although direct comparisons of identical interventions offered to families of different SES have not yet been performed. All behavioral interventions showed benefits relative to no-treatment controls, and a dose response to the number of parent behavior training sessions attended by parents was also identified, enhancing the overall strength of evidence for effectiveness of parent behavior training.

Several small, short-term trials of psychostimulant medication use in preschoolers, primarily immediate release methylphenidate, suggest that it is efficacious and safe. In addition, the Preschool ADHD Treatment Study (PATs), a large, high quality trial funded by the National Institute of Mental Health also suggests that methylphenidate is effective for improving parent-rated child behavior in preschoolers. This multisite trial had multiple phases, beginning with 10 sessions of parent behavior training. The training was followed by an open label safety lead-in phase of a psychostimulant medication, then a titration phase, a cross-over phase and open-label maintenance phase that lasted 10 months. The PATs study offers information about both the potential benefits and limitations of stimulant medication use in very young children. Limitations include the following: preschool children experience more dose-related adverse events than older children, stimulants interfere with rates of growth, and the presence of three or more comorbid conditions and psychosocial adversity are associated with lessened effectiveness of psychostimulant medication. These findings are supported by two additional “fair” quality RCTs.

In conclusion, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate. This favors the use of parent behavior training for preschoolers at risk for ADHD due to disruptive behavior. A direct comparison has not yet been done.

Long-Term Effectiveness and Safety of Interventions in People Age 6 and Older

Pharmacologic Agents

The long-term effectiveness and safety (at least 12 months of treatment and/or follow up) of several psychostimulants (e.g., methylphenidate immediate release amphetamine, Osmotic-controlled Release Oral delivery System methylphenidate, dextroamphetamine, mixed amphetamine salts, atomoxetine, clonidine and guanfacine extended release) have all been examined prospectively in children and adolescents age 6 and over. The agents examined were all shown to be efficacious for control of inattention, overactivity, and impulsiveness for at least 12 months and up to three years, and few serious adverse events were noted, although guanfacine extended release appears to be less well tolerated than other agents examined. Global ratings of impairment also indicate continued benefit throughout the extension studies for patients still receiving medications. In general, those who remain on medication show continued benefit, and few adverse events are reported for them. With a majority of the studies funded by industry (12 of 21), there may be enhanced representations of effectiveness and safety. Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time.

Fewer children experienced adverse events with methylphenidate than with dextroamphetamine. Concerns about adverse events led to discontinuation of medications for 15% to 20% of children age 6 and over using extended release mixed amphetamine salts. Concerns about exacerbation of tics with stimulants appear to be unfounded, although the sample size remains small. Use of psychostimulants slows the rate of growth, and increases blood pressure and heart rate to a small degree. At a group level, the mean changes are clinically insignificant, although on rare occasions individuals discontinue an agent because of changes in vital signs. There are many similarities between methylphenidate immediate release and other preparations of psychostimulants, both in terms of efficacy and in the side effect profile. Therefore, many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust.

Atomoxetine is both safe and effective for ADHD symptoms over 12 to 18 months among children and for up to three years in adults. Discontinuation in children and teens appears to be higher (26%) due to ineffectiveness and lower (3%) due to adverse events than with other agents, although these are not direct comparisons. As with

psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases. There is only one study of a pharmacologic intervention over an extended time period (three years) in adults with ADHD, and that study found symptom improvement was maintained for those on atomoxetine, and discontinuation due to adverse events was somewhat higher for adults (11%) than for children (3%).

An extension study of guanfacine suggests that this agent is also effective in controlling ADHD symptoms for up to two years; however, high rates (40% to 60%) of somnolence, headache, and fatigue occur when it is used as a monotherapy, especially in the initial six to eight months of treatment. A second study examined concurrent use of psychostimulants and noted improved tolerance to these adverse effects. Changes in vital signs occur, but no clear group trends are noted. Individuals may develop clinically significant hypotension and bradycardia. Serious adverse events include syncope and clinically significant changes on electrocardiogram.

Overall, pharmacologic agents used for controlling the symptoms of inattention, overactivity, and impulsivity of ADHD show maintenance of effectiveness and safety for 12 to 24 months. Following that, attrition from use interferes with the ability to draw conclusions. Along with decreased symptoms, overall functioning is improved.

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Longer Term Outcomes

Evaluation of long-term outcomes (five or more years follow up) following interventions for ADHD is complex due to multiple patterns of services used and very few studies available, with only two RCTs of well-characterized clinical samples, both of boys ages 7 to 9 years with DSM-IV ADHD, combined subtype. The best quality data come from the Multimodal Treatment of ADHD Study, which compared 14 months of management with immediate release methylphenidate to three other interventions: psychosocial and behavioral treatment; the combination of medication management and psychosocial and behavioral treatment; and standard community care. Three years after initiation, the four intervention groups showed comparable outcomes. No clear relationship was identified between duration of medication use and psychiatric or overall functional outcomes at

three years or beyond. In contrast, a few long-term cohort studies lasting five years or more suggest that increased duration of medication was associated with improved grade retention and academic achievement. No prospective studies have been designed to investigate the question of long-term functional outcomes directly. There appear to be long-term academic benefits with medication interventions in some domains.

In conclusion, the evidence for long-term effectiveness of pharmacologic agents for improving ADHD symptoms is based on a single good study for methylphenidate and a single good study for atomoxetine. These studies followed the children for 12 or 14 months and showed benefit with few adverse effects, thereby resulting in low strength of evidence for longer term effectiveness for each of these agents. Similarly, there is a single good study showing benefits for the combination of methylphenidate and psychosocial interventions. The evidence for other pharmaceutical agents is insufficient, as is the evidence pertaining to parent behavior training and academic interventions.

[\[Evidence Source\]](#)

Evidence Summary

For children under age six, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. Classroom teacher consultations in addition to parent behavior training are beneficial to children of lower socioeconomic status. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate.

In children age six and over, there is evidence to support the long-term effectiveness of both methylphenidate and atomoxetine for improving ADHD symptoms, as well as methylphenidate combined with behavioral/psychosocial interventions. There is evidence for only the short-term effectiveness for other FDA approved medications and guanfacine, the latter of which has more frequent adverse events.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Pharmacologic treatment age <6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Pharmacotherapy is recommended for coverage as a second line therapy (<i>weak recommendation</i>)
Parent Behavior Training (PBT) age <6	net benefit without apparent harms	high	modest costs	likely moderate variability in parent preferences for treatment	Specific parent behavior training is recommended for coverage as first-line therapy (<i>strong recommendation</i>)
Behavioral/ psychosocial treatment age <6 (excluding PBT)	no evidence	insufficient	modest costs	likely moderate variability in parent preferences for treatment	<i>No recommendation</i>
Pharmacologic treatment alone and combined with behavioral/ psychosocial interventions age ≥ 6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Pharmacotherapy alone (<i>weak recommendation</i>) or pharmacotherapy with psychosocial/ behavioral treatment (<i>strong recommendation</i>) are considered first-line therapy and are recommended for coverage

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Behavioral/ psychosocial treatment alone, PBT, academic interventions age $\geq$ 6	unable to draw conclusions	insufficient	modest costs	likely moderate variability in parent preferences for treatment	Behavioral/ psychosocial treatment alone, PBT, academic interventions age $\geq$ 6 for primary ADHD are not recommended for coverage (<i>weak recommendation</i>)
School/ daycare based interventions	net benefit in those <6 of low SES, benefit in $\geq$ 6 as element of intensive behavioral treatment, no apparent harms	low	modest costs	likely minimal variability in parent preferences	School/daycare based interventions are outside the purview of this coverage guidance (<i>No recommendation</i>) Provider consultation with teachers is recommended for coverage (based on evidence of children <6 with low SES) (<i>weak recommendation</i>)

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Five quality measures were identified when searching the [National Quality Measures Clearinghouse](#). The Institute for Clinical Systems Improvement developed three measures around diagnosis and management of attention deficit hyperactivity disorder (ADHD) in primary care for school age children and adolescents: 1) Percentage of patients diagnosed with ADHD whose medical record contains documentation that the clinician discussed the need for school-based supports and educational service options for children with ADHD; 2) Percentage of patients treated with psychostimulant medication for the diagnosis of ADHD whose medical record contains documentation of a follow-up visit at least twice a year; and 3) Percentage of patients newly diagnosed with ADHD whose medical record contains documentation of DSM-IV-TR or DSM-PC criteria. These three measures have not been endorsed by the National Quality Forum (NQF).

The National Committee for Quality Assurance developed two HEDIS measures, which are both endorsed by the NQF: 1) Follow-up care for children prescribed ADHD medication (initiation phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who had one follow-up visit with a practitioner with prescribing authority during the 30-day initiation phase; and 2) Follow-up care for children prescribed ADHD medication (continuation and maintenance [C&M] phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who remained on the medication for at least 210 days and who, in addition to the visit in the initiation phase, had at least two follow-up visits with a practitioner within 270 days (9 months) after the initiation phase ended.

Oregon's Coordinated Care Organizations' quality of care objectives include the following measure: Meet or exceed the 90th percentile national Medicaid benchmarks for follow up care for children on ADHD medication.

COMMITTEE DELIBERATIONS – EVIDENCE-BASED GUIDELINE SUBCOMMITTEE

The Evidence-based Guidelines Subcommittee had extensive deliberations on the types and availability of behavioral and psychology treatments available. An additional literature search was performed to determine if additional types of interventions had evidence to support beyond the parent behavioral training, and none were found. The decision was also made to remain silent on the treatment of children over 6 with behavioral treatments alone, due to implementation considerations. Subcommittee members determined the best way to address the coordination with teachers for school-based interventions was through communication/coordination between the provider and teacher being recommended as a covered service.

COMMITTEE DELIBERATIONS – VALUE-BASED BENEFITS SUBCOMMITTEE

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A. GRADE Framework Description

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
312.9	Unspecified disturbance of conduct
314	Hyperkinetic syndrome of childhood
314.0	Attention deficit disorder of childhood
314.00	Attention deficit disorder without mention of hyperactivity
314.01	Attention deficit disorder with hyperactivity
314.1	Hyperkinesis with developmental delay
314.2	Hyperkinetic conduct disorder
314.8	Other specified manifestations of hyperkinetic syndrome
314.9	Unspecified hyperkinetic syndrome
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
90785	Interactive complexity, add-on code to be used in conjunction with codes for primary service
90791	Psychiatric diagnostic evaluation (no medical services)
90792	Psychiatric diagnostic evaluation (with medical services)
90832	Psychotherapy, 30 minutes with patient and/or family member
90834	Psychotherapy, 45 minutes with patient and/or family member
90837	Psychotherapy, 60 minutes with patient and/or family member
90839	Psychotherapy for crisis, first 60 minutes
90840	Add-on for each additional 30 minutes of psychotherapy for crisis, used in conjunction with code 90839
90845	Psychoanalysis
90846	Family psychotherapy without the patient present
90847	Family psychotherapy, conjoint psychotherapy with the patient present
90849	Multiple-family group psychotherapy
90853	Group psychotherapy (other than of a multiple-family group)
90863	Pharmacologic management, including prescription and review of medication, when performed with psychotherapy services; used only as add-on to primary psychotherapy code
98960	Education and training for patient self-management by a qualified, nonphysician health care professional using a standardized curriculum, face-to-face with the patient (could include caregiver/family) each 30 minutes; individual patient
98961	2-4 patients
98962	5-8 patients
99201	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the

Coverage Guidance: Treatment of Attention Deficit Hyperactivity Disorder in Children

DRAFT for VbBS meeting materials 8/8/13

CODES	DESCRIPTION
	presenting problem(s) are self limited or minor. Physicians typically spend 10 minutes face-to-face with the patient and/or family.
99202	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 20 minutes face-to-face with the patient and/or family.
99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history; A detailed examination; Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Physicians typically spend 30 minutes face-to-face with the patient and/or family.
99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 45 minutes face-to-face with the patient and/or family.
99205	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 60 minutes face-to-face with the patient and/or family.
99211	Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.
99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 10 minutes face-to-face with the patient and/or family.
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem

CODES	DESCRIPTION
	focused history; An expanded problem focused examination; Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 15 minutes face-to-face with the patient and/or family.
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 25 minutes face-to-face with the patient and/or family.
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 40 minutes face-to-face with the patient and/or family.
99241	Office consultation for a new or established patient, which requires these 3 key components: A problem focused history; A problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 15 minutes face-to-face with the patient and/or family.
99242	Office consultation for a new or established patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low severity. Physicians typically spend 30 minutes face-to-face with the patient and/or family.
99243	Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Physicians typically spend 40 minutes face-to-face with the patient and/or family.
99244	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical

CODES	DESCRIPTION
	decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 60 minutes face-to-face with the patient and/or family.
99245	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 80 minutes face-to-face with the patient and/or family.
HCPCS Codes	
H2027	Psychoeducational service, per 15 minutes
S9444	Parenting classes, non-physician provider, per session
S9482	Family stabilization services, per 15 minutes
T1027	Family training and counseling for child development, per 15 minutes

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework – ADHD Indications

Pharmacologic Treatment age <6 as 1st Line Therapy



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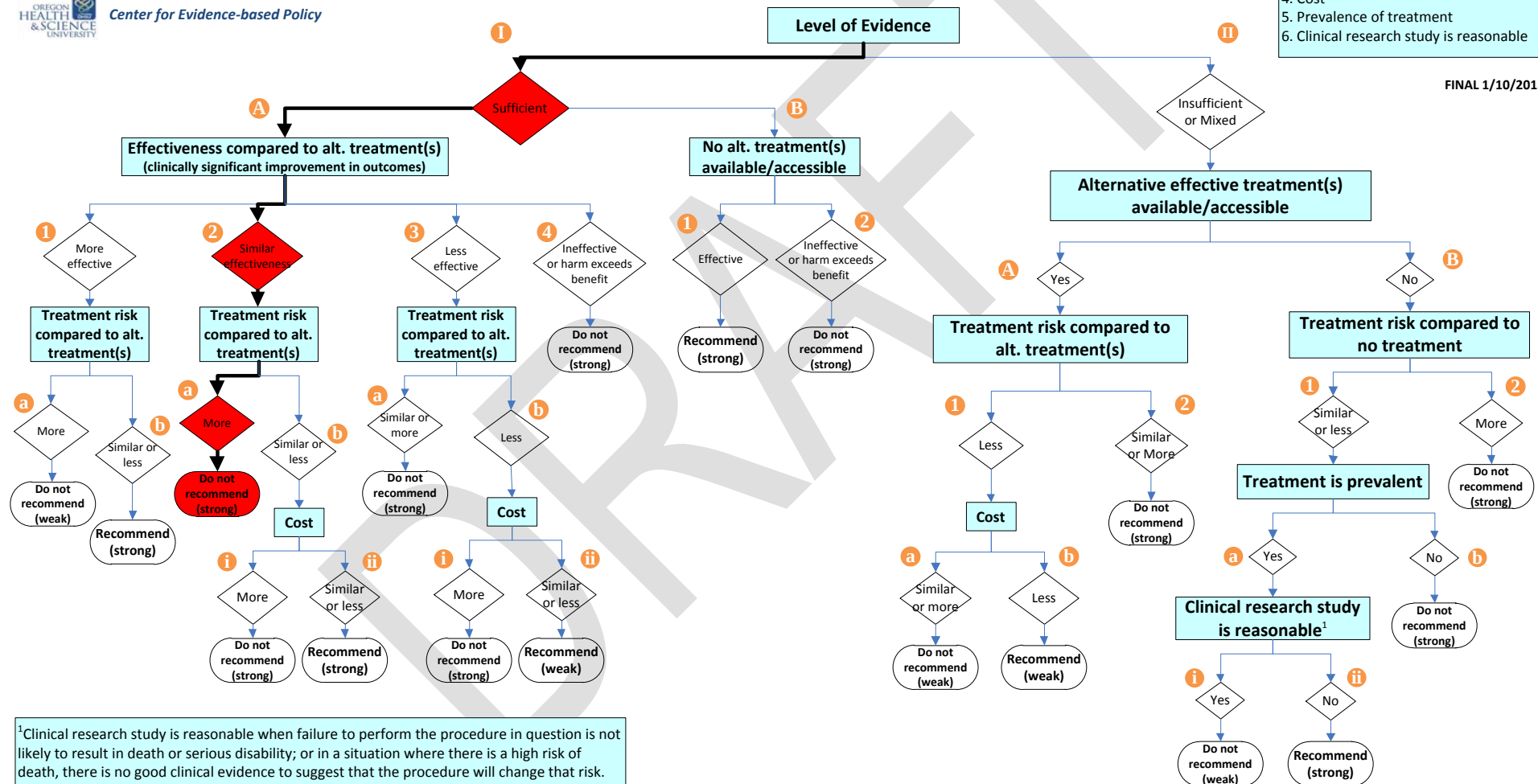
HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

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Pharmacologic Treatment age <6 as 2nd Line Therapy

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Center for Evidence-based Policy

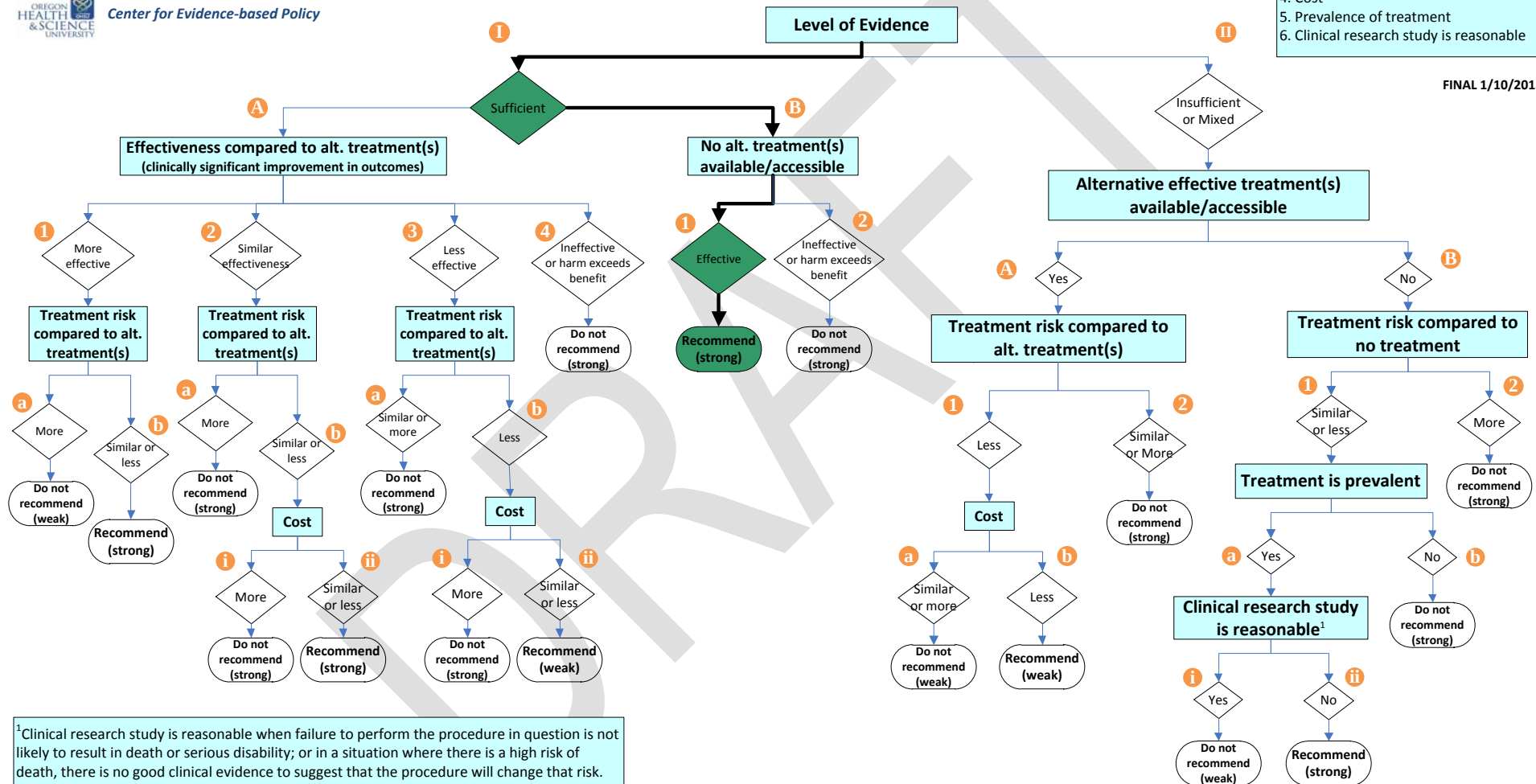
HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Parent Behavior Training (PBT) or School/Daycare Interventions age <6 Compared to Pharmacologic Treatment



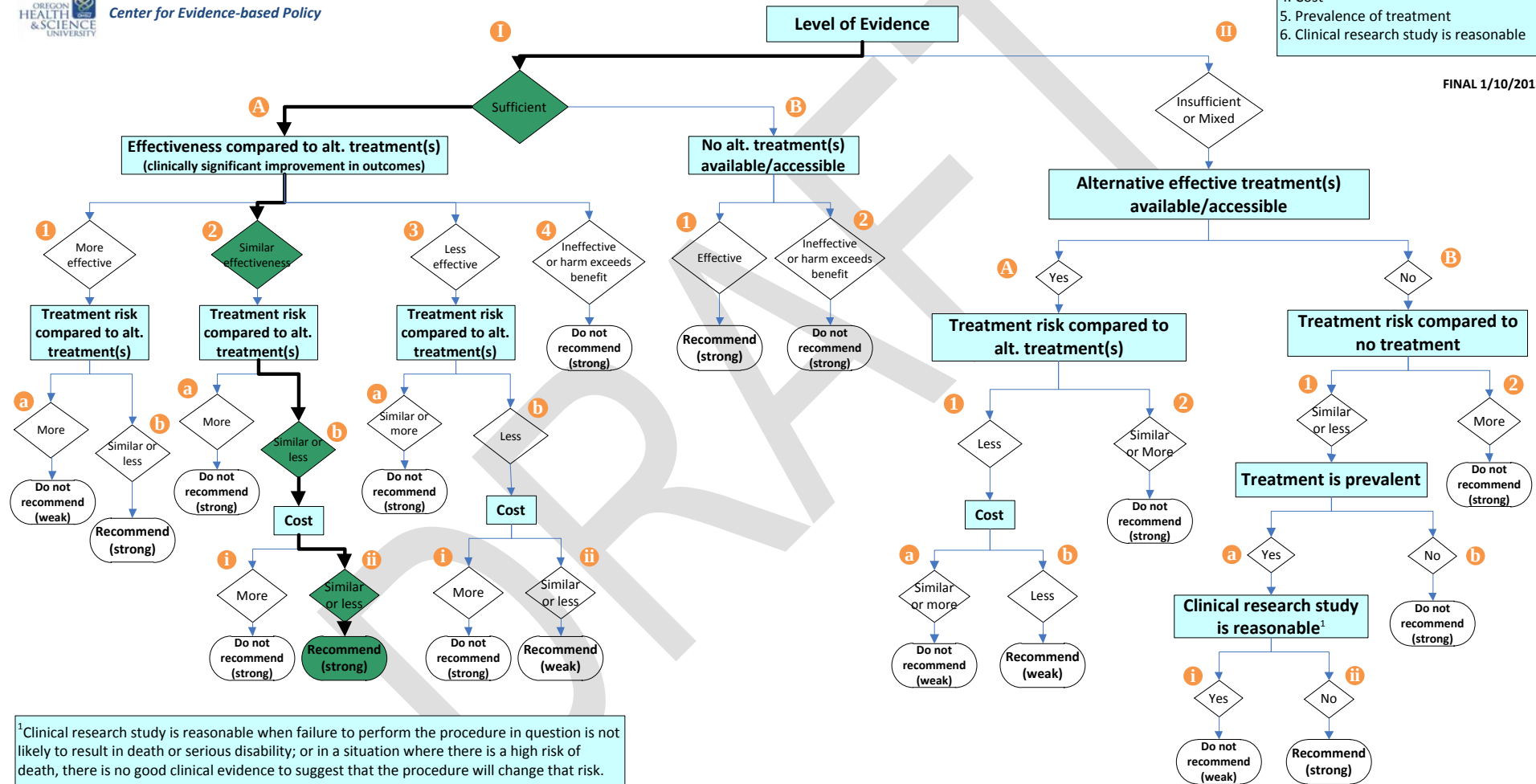
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Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Behavioral/Psychosocial Treatment Alone, PBT, Academic Interventions Age ≥ 6 Compared to Pharmacologic Treatment



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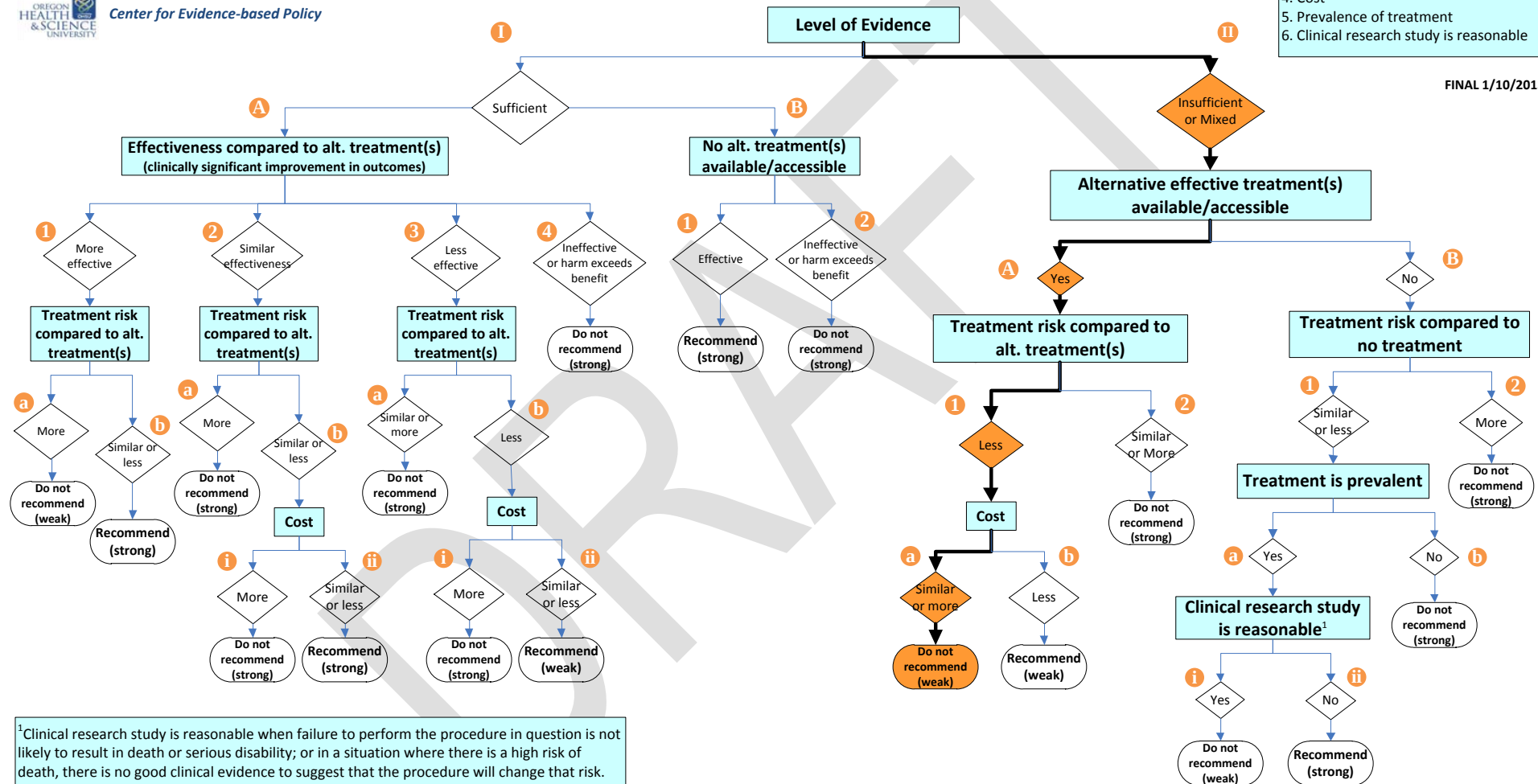
HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Section 4

New Discussion Items

Intraocular steroid implant issue summary

Question: How should the intraocular steroid implants be dealt with on the Prioritized List?

Question Source:

Christina Flaxel, MD. OHSU Department of Ophthalmology; Allergan Pharmaceuticals; Pharmacy & Therapeutics Committee referral

Issue: Intravitreal injections are required for a number of eye conditions. HERC staff were approached by Dr. Flaxel to specifically cover the Retisert implant (intraocular implant for fluocinolone acetonide). Retisert is not currently open for payment for DMAP. Because this involved a specific medication, the issue was referred to the Pharmacy and Therapeutics Committee. P&T reviewed the topic in January 2013 and referred it back to HERC because a surgical operation is required, thus making its coverage relevant to the Prioritized List. Additionally, a letter was received from Allergan Pharmaceuticals requesting coverage for retinal vein occlusion and posterior segment uveitis.

From Dr. Flaxel:

The Retisert implant is a specialized device which elutes fluocinolone acetonide, a potent corticosteroid, into the eye for 30 months. It is surgically implanted by a vitreoretinal surgeon. The Retisert implant is the only FDA approved therapy for non-infectious uveitis, or intraocular inflammation. Uveitis is a potentially blinding condition without appropriate treatment, and patients in whom retisert implants are placed have usually failed therapy with standard immunosuppression and/or local corticosteroid therapy. As such, Retisert implants often represent the last hope of salvaging or maintaining useful vision in patients affected with severe uveitis. We therefore respectfully request it be added to the Prioritized List for therapy in patients in whom it is indicated.

The CMS approved CPT code for implantation is 67027 and the HCPCS for the implant is J7311. The ICD-9 codes involved are 136.1, 360.11, 360.12, 362.18, 363.00, 363.10, 363.12, 363.13, 363.20, 363.21, 363.22, 364.24, 363.54.

Current Prioritized List status:

Code	Code Description	Current Line/List placement
J7311	FLUOCINOLONE ACETONIDE, INTRAVITREAL IMPLANT	DMAP Ancillary Codes File
J7312	INJECTION, DEXAMETHASONE, INTRAVITREAL IMPLANT, 0.1 MG	DMAP Ancillary Codes File

CPT code 67027 (Implantation of intravitreal drug delivery system (e.g., ganciclovir implant), includes concomitant removal of vitreous) is currently on 4 lines on the Prioritized List.

Line	Condition	Treatment
299	RETINAL DETACHMENT AND OTHER RETINAL DISORDERS	RETINAL REPAIR, VITRECTOMY
308	COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	MEDICAL AND SURGICAL TREATMENT
344	PURULENT ENDOPHTHALMITIS	VITRECTOMY
413	CENTRAL SEROUS RETINOPATHY	MEDICAL AND SURGICAL TREATMENT

Code	Code Description	Current Line Placement
67027	Implantation of intravitreal drug delivery system (e.g., ganciclovir implant), includes concomitant removal of vitreous	299,308,344,413
67028	Intravitreal injection of a pharmacologic agent (separate procedure)	299,308,344,473,413

The ICD-9 codes proposed by Dr. Flaxel for pairing are located on the following lines:

ICD-9 Code	Code Description	Line
136.1	Behcet's syndrome	183 POLYARTERITIS NODOSA AND ALLIED CONDITIONS
360.11	Sympathetic uveitis	285 SYMPATHETIC UVEITIS AND DEGENERATIVE DISORDERS AND CONDITIONS OF GLOBE
360.12	Panuveitis	282 ACUTE, SUBACUTE, CHRONIC AND OTHER TYPES OF IRIDOCYCLITIS
362.18	Retinal vasculitis	106 DIABETIC AND OTHER RETINOPATHY
363.00	Focal chorioretinitis, unspecified	106 DIABETIC AND OTHER RETINOPATHY

363.10	Disseminated chorioretinitis, unspecified	106 DIABETIC AND OTHER RETINOPATHY
363.12	Disseminated choroiditis and chorioretinitis, peripheral	106 DIABETIC AND OTHER RETINOPATHY
363.13	Disseminated choroiditis and chorioretinitis, metastatic	106 DIABETIC AND OTHER RETINOPATHY
363.20	Chorioretinitis, unspecified	106 DIABETIC AND OTHER RETINOPATHY
363.21	Pars planitis	413 CENTRAL SEROUS RETINOPATHY
363.22	Harada's disease	106 DIABETIC AND OTHER RETINOPATHY
364.24	Vogt-Koyanagi syndrome	282 ACUTE, SUBACUTE, CHRONIC AND OTHER TYPES OF IRIDOCYCLITIS
363.54	Degeneration of the papillary margin	106 DIABETIC AND OTHER RETINOPATHY

The ICD-9 codes noted by Allergan as pairing with intraocular steroids appear on the following lines

ICD-9 Code	Code description	Current line(s)
362.83	Retinal edema	473 DEGENERATION OF MACULA AND POSTERIOR POLE
363.21	Pars planitis	413 CENTRAL SEROUS RETINOPATHY

The ICD-9 codes suggested for pairing with intraocular steroids by Allergan appear on the following lines:

ICD-9 Code	Code description	Current line(s)
362.30	Retinal vascular occlusion, unspecified	465 VENOUS TRIBUTARY (BRANCH) OCCLUSION; CENTRAL RETINAL VEIN OCCLUSION
362.35	Central retinal vein occlusion	465
362.36	Venous tributary (branch) occlusion	465
362.37	Venous engorgement	686 SENSORY ORGAN CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
363.00-363.08	Focal choroiditis and chorioretinitis	106 DIABETIC AND OTHER RETINOPATHY
363.10-363.15	Disseminated choroiditis and chorioretinitis	106
363.20	Chorioretinitis, unspecified	106
363.22	Harada's disease	106

Evidence review**NICE, 2011**

- 1) Technology appraisal
- 2) Dexamethasone intravitreal implant (Ozurdex) for macular edema secondary to retinal vein occlusion
 - A. Guidance
 1. Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following central retinal vein occlusion.
 2. Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following branch retinal vein occlusion when:
 - a. treatment with laser photocoagulation has not been beneficial,
 - or**
 - b. treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage.
 3. People currently receiving dexamethasone intravitreal implant for the treatment of macular oedema secondary to branch retinal vein occlusion who do not meet the criteria specified in (2) above should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
- 3) Cost effectiveness of dexamethasone compared with best supportive care--ICER of £26,300 per QALY gained (including an incremental costs of £5937 and incremental QALYs of 0.23) for all people with RVO.
- 4) Conclusion: The Committee further concluded that this represented an acceptable level of cost effectiveness in this case and that dexamethasone intravitreal implant for the treatment of RVO represents a cost-effective use of NHS resources when compared with best supportive care.

*Diabetic macular edema***Grover, 2009**

- 1) Cochrane review of implantable steroids for diabetic macular edema
- 2) 7 studies, with 632 diabetic macular edema eyes were included.
- 3) Four examined the effectiveness of intravitreal triamcinolone acetate injection (IVTA), three examined intravitreal steroids implantation (fluocinolone acetonide implant (FAI) or dexamethasone drug delivery system (DDS)). Two trials were at low risk of bias, one was at median risk of bias, two were at high risk of bias and the remaining two were at unclear risk of bias.
- 4) Results: Injectable steroids - The preponderance of data suggest a beneficial effect from IVTA. Comparing IVTA with controls, the mean difference in visual acuity was -0.15 LogMAR (95% CI -0.21 to -0.09) at 3 months (based on three trials), -0.23 LogMAR (95% CI -0.33 to -0.13) at 6 months (two trials), -0.29 LogMAR (95% CI -0.47 to -0.11) at 9 months (one trial), and -0.11 LogMAR (95% CI -0.20 to -0.03) at 24 months (one trial), all in favor of IVTA. The relative risk (RR) for one or more lines improvement in visual acuity was 2.85 (95% CI 1.59 to

5.10) at 3 months (two trials), 1.25 (95% CI 0.66 to 2.38) at 6 months (one trial), and 2.17 (95% CI 1.15 to 4.11) at 24 months (one trial), all in favor of IVTA. We did not find evidence for three or more lines improvement in visual acuity. The mean difference in retinal thickness was -131.97 μ m (95% CI -169.08 to -94.86) at 3 months (two trials), -135.00 μ m (95% CI -194.50 to -75.50) at 6 months (one trial), -133.00 μ m (95% CI -199.86 to -66.14) at 9 months (one trial), and -59.00 μ m (95% CI -103.50 to -14.50) at 24 months (one trial), all in favor of IVTA. The RR for at least one grade macular edema resolution was 5.15 (95% CI 2.23 to 11.88) at 3 months in favor of IVTA (one trial).

Results: Implantable steroids: Two trials reported improved clinical outcome when FAI was compared to standard of care. Beneficial effect was also observed in one dexamethasone DDS trial.

Increased intraocular pressure and cataract formation were side effects requiring monitoring and management.

- 5) Dexamethasone 700ug implant versus observation 58% (33/57) showed improvement in 2 line vision compared to 21% (12/57) in the observation group, RR 2.75 (95% CI 1.59-4.76)
- 6) Fluocinolide implant versus standard of care or observation
 - a. At 12 months, no significant difference in 3 lines of visual acuity, RR 2.73 (95% CI 0.63-11.92)
 - b. At 36 months, marginally statistically significant improvement in 3 lines of visual acuity, RR 1.93 (95% CI 1.02-3.66)

O'Doherty, 2008

- 1) Review of literature for diabetic macular edema treatment
- 2) Reports on single study of Retisert
 - a. 97 patients with DMO randomized to receive either implantation or standard care (laser treatment or observation).⁴
 - b. At 3 years, 58% of implanted eyes versus 30% of controls had resolution of DMO (p,0.001) and associated improvement in visual acuity.
 - c. Adverse effects included a substantially higher risk of cataract formation and glaucoma than that observed in eyes receiving IVTA, with 5% requiring implant removal to control glaucoma.
- 3) Reports on a single study of Psurdex (An injectable, biodegradable intravitreal dexamethasone extended release implant (Posurdex; Allergan, Irvine, California) was evaluated in an RCT, with reported improvements in visual acuity and macular thickness.⁴⁸
- 4) Conclusions: In patients with cystoid macular oedema, evidence would support first-line treatment with intravitreal triamcinolone followed by grid laser at 3 months.⁴⁰ There is no trial that has compared the effects of triamcinolone with those of the antiangiogenic agents. Though the antiangiogenic agents hold an ocular-specific advantage in terms of a low rate of ocular hypertension, there have been some concerns with regard to their possible systemic effects. Therefore, until a large prospective RCCT is published, the choice of intravitreal agent remains a subjective decision.

- 5) Essentially, little evidence supports use of Retisert implant specifically, and no studies identified superiority or noninferiority to intravitreal injections.

Uveitis

Cochrane review underway – “Corticosteroid implants for chronic non-infectious uveitis”

Most of the identified reviews have authors that receive consulting fees from the manufacturers.

P&T summary of evidence of uveitis below

Pharmacy and Therapeutics Committee Review January 2013

Conclusions:

- There is low quality evidence that there is no difference in visual acuity outcomes between fluocinolone acetonide intravitreal implant and standard of care with systemic corticosteroids for the treatment of noninfectious uveitis. There is also low quality evidence that fluocinolone intravitreal implant may control inflammation in the eye faster and more frequently than standard of care, although both approaches decrease inflammation.
- There is moderate quality evidence that fluocinolone acetonide intravitreal implant is associated with more ocular adverse events than standard of care, including glaucoma (Hazard Ratio [HR] 4.2, 95% CI 1.82-9.63) and cataracts (HR 4.12, 95% CI 2.2-7.7).
- There is low quality evidence demonstrating potential benefit of fluocinolone acetonide intravitreal implant and dexamethasone implant for the treatment of diabetic macular edema, however significant complications have also been reported. There is insufficient evidence to support the use for diabetic macular edema or other off-label indications.
- There is insufficient evidence directly comparing fluocinolone acetonide intravitreal implant to dexamethasone intravitreal implant for any indications. There are significant differences in indications and administration techniques between the two agents.
- There is moderate quality evidence demonstrating efficacy of dexamethasone intravitreal implant following central retinal vein occlusion.

The P&T Committee concluded that:

- 1) There is insufficient evidence to support the use of fluocinolone or dexamethasone implants in the use of diabetic macular edema or other off label indications.
- 2) There is insufficient evidence comparing the fluocinolone implant to the dexamethasone implant and due to significant differences, they cannot be used interchangeably.
- 3) There is no clinically significant difference in visual outcomes between fluocinolone and standard of care with systemic steroids for the treatment of noninfectious uveitis. Therefore it would be prudent to only allow coverage of the fluocinolone implant for:
 - a. Chronic non-infectious uveitis affecting the posterior segment of the eye.
 - b. After appropriate trial and fail or intolerance of therapy with systemic

corticosteroids and/or immunosuppressive agents

- 4) There is moderate quality evidence demonstrating efficacy of dexamethasone for central retinal vein occlusion and should be utilized only in those individuals who have failed anti-VEGF therapy.

Because Retisert requires a surgical procedure, the Committee recommended the HERC use the evidence and conclusions to evaluate both the Retisert and Ozurdex implants for line placement.

Commercial policies

Aetna, 2010

- 1) Aetna considers the Retisert (fluocinolone acetonide) intra-vitreous implant medically necessary for the treatment of members with chronic non-infectious uveitis affecting the posterior segment of the eye, and who do not respond to or are intolerant to conventional treatment.
- 2) Aetna considers Retisert experimental and investigational for the treatment of the following indications (not an all inclusive list):
 - a. Anterior uveitis
 - b. Intermediate (pars planitis) uveitis
 - c. Macular edema/central retinal vein occlusion
 - d. Serpiginous choroiditis
 - e. Sympathetic ophthalmia
 - f. Vogt-Koyanagi-Harada disease.

Aetna, 2011

1. Aetna considers Ozurdex (dexamethasone intravitreal implant) medically necessary for the treatment of macular edema secondary to branch or central retinal vein occlusion, and for the treatment of non-infectious uveitis affecting the posterior segment of the eye.
2. Aetna considers Ozurdex experimental and investigational for the treatment of diabetic macular edema, pseudophakic macular edema (Irvine-Gass syndrome) and for all other indications because of insufficient evidence of its effectiveness.

Cost information

Medicare Payment allowance:

HCPCS Code	Short Description	HCPCS Code Dosage	Payment Limit
J7311	Fluocinolone acetonide implant	0.59 MG	\$19,345.00
J7312	Dexamethasone intra implant	0.1 MG	\$195.95

Summary

Central retinal vein occlusion

- There is moderate quality evidence demonstrating efficacy of dexamethasone intravitreal implant following central retinal vein occlusion.

Non-infectious uveitis (posterior segment)

- There is low quality evidence that there is no difference in visual acuity outcomes between fluocinolone acetonide intravitreal implant and standard of care with systemic corticosteroids for the treatment of noninfectious uveitis. There is also low quality evidence that fluocinolone intravitreal implant may control inflammation in the eye faster and more frequently than standard of care, although both approaches decrease inflammation.

Diabetic macular edema

- There is low quality evidence demonstrating potential benefit of fluocinolone acetonide intravitreal implant and dexamethasone implant for the treatment of diabetic macular edema, however significant complications have also been reported. There is insufficient evidence to support the use for diabetic macular edema or other off-label indications.

Harms:

- There is moderate quality evidence that fluocinolone acetonide intravitreal implant is associated with more ocular adverse events than standard of care, including glaucoma (Hazard Ratio [HR] 4.2, 95% CI 1.82-9.63) and cataracts (HR 4.12, 95% CI 2.2-7.7). Significant numbers of study participants required cataract surgery in the implantable ocular steroid group.

HERC Staff Recommendations:

- 1) Chronic posterior uveitis (various ICD-9 codes per Dr. Flaxel and Allergan) is located on Line 106 DIABETIC AND OTHER RETINOPATHY. However, intraocular steroids should continue to not be covered for diabetic macular edema.
 - a. Add 67027 to Line 106
 - b. Add a guideline:

GUIDELINE NOTE XXX INTRAOCULAR STEROID IMPLANTS FOR CHRONIC NON-INFECTIOUS UVEITIS

Line 106

Intraocular steroid implants are only included on Line 106 for pairing with uveitis (363.0x, 363.1x, 363.20, 363.22), and only when the following conditions are met: uveitis is chronic, non-infectious, and affecting the posterior segment of the eye, and there has been appropriate trial and failure, or intolerance of therapy, with systemic corticosteroids and/or immunosuppressive agents.

- 2) Add implantable intraocular steroids to the retinal vein occlusion line 465 VENOUS TRIBUTARY (BRANCH) OCCLUSION; CENTRAL RETINAL VEIN OCCLUSION Treatment: Laser Surgery
 - a. Add 67027 to Line 465
 - b. Rename the *Treatment*: **LASER SURGERY; SURGICAL AND LASER THERAPY**
 - c. Add a guideline to lines 465

GUIDELINE NOTE XXX INTRAOCULAR STEROID IMPLANTS FOR CENTRAL RETINAL VEIN OCCLUSION

Line 465

Intraocular steroid implants are only included on Line 465 for treatment of central retinal vein occlusion (ICD-9 362.35) in those individuals who have failed anti-VEGF therapy.

- 3) Add the following coding specification to line 413
 - a. Coding specification: "CPT 67027 (Implantation of intravitreal drug delivery system) is included on this line for use with medications other than intraocular steroid implants."
 - b. CPT 67027 already is present on this line; ICD-9 363.21 (Pars planitis) would pair with this code. However, there is no evidence for use in types of uveitis other than posterior uveitis, which now pairs on line 106.

- 4) Do not add other suggested diagnoses to a line with pairing for 67027.
 - a. No evidence found for effectiveness or other more specific codes are available for pairing



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3375 S.W. Terwilliger Blvd.
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South Waterfront - Portland

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Astoria

2055 Exchange Street, Ste. 230
Astoria, Oregon 97103
tel 503 338-3803
fax 503 338-7228

Columbia River Eye Clinic

1410 May Street
Hood River, Oregon 97031
tel 541 386-1399
fax 541 386-7067

405 E. 7th Street
The Dalles, Oregon 97058
tel 541 298-5144
fax 541 298-5224

Lower Columbia Eye Clinic

600 Triangle Center, Ste. 400
Longview, Washington 98632
tel 360 423-0220
fax 360 423-0697

Vancouver

16701 SE McGillivray Blvd., Ste. 170
Vancouver, Washington 98683
tel 360 260-7132 - Cornea
tel 360 260-7132 - Neuro-Ophthalmology
tel 360 260-7132 - Pediatric Ophthalmology
tel 360 260-7220 - Retina
fax 360 260-5523



July 10, 2012

Darren D. Coffman
Director, Health Services Commission
1225 Ferry Street NE
Salem, OR 97301

RE: Prioritized List Addition Request

Dear Mr. Coffman:

We occasionally notice that the condition and treatment pairs list is either missing ocular diagnoses or their corresponding treatments. We concluded that there may be a lack of understanding of ocular disease processes or their therapy, including surgical repair. We also feel that many conditions/treatments missing, or below-the-line, meet medical necessity criteria and are considered standard of care, not experimental.

Please consider the following for inclusion on the Prioritized List:

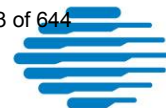
The Retisert implant is a specialized device which elutes fluocinolone acetonide, a potent corticosteroid, into the eye for 30 months. It is surgically implanted by a vitreoretinal surgeon. The Retisert implant is the only FDA approved therapy for non-infectious uveitis, or intraocular inflammation. Uveitis is a potentially blinding condition without appropriate treatment, and patients in whom retisert implants are placed have usually failed therapy with standard immunosuppression and/or local corticosteroid therapy. As such, Retisert implants often represent the last hope of salvaging or maintaining useful vision in patients affected with severe uveitis. We therefore respectfully request it be added to the Prioritized List for therapy in patients in whom it is indicated.

The CMS approved CPT code for implantation is 67027 and the HCPCS for the implant is J7311. The ICD-9 codes involved are 136.1, 360.11, 360.12, 362.18, 363.00, 363.10, 363.12, 363.13, 363.20, 363.21, 363.22, 364.24, 363.54.

Thank you for your consideration of adding this condition/treatment to the Prioritized List. Do not hesitate to contact me if further clarification is needed.

Sincerely,

Christina Flaxel, MD, Retina Service
OHSU - Department of Ophthalmology



May 6, 2013

VIA Electronic Mail

Dorothy Allen
Program Specialist, Oregon Health Policy and Research
Salem Office
General Services Building
1225 Ferry Street, Suite C
Salem, OR 97301

RE: Request for Addition of ICD-9-CM Diagnosis Codes Associated with FDA-Approved Indications for OZURDEX[®]

Dear Ms. Allen:

On behalf of Allergan Inc., the manufacturer of OZURDEX[®] (dexamethasone intravitreal implant),¹ and in follow-up to the approval of OZURDEX[®] for the treatment of retinal vein occlusion and posterior segment uveitis, respectively, we request that Oregon Medicaid add coverage for certain ICD-9-CM diagnosis codes used to report the FDA-approved indications for OZURDEX[®].

We reviewed your coverage policy and found that you currently cover two ICD-9-CM diagnosis codes used to report conditions within OZURDEX[®]'s FDA-approved label – 362.83 “Other disorders; retinal edema”, which is appropriate for reporting retinal vein occlusion, and 363.21 “Other and unspecified forms of chorioretinitis and retinochoroiditis; pars planitis”, which is appropriate for reporting posterior segment uveitis. However, as illustrated in the following table, several additional codes may be used to report retinal vein occlusion and posterior segment uveitis, respectively.

Indication	ICD-9-CM Codes	Descriptor
Retinal vein occlusion*	362.30	Retinal vein occlusion; retinal vein occlusion, unspecified
	362.35	Retinal vein occlusion; central retinal vein occlusion
	362.36	Retinal vein occlusion; venous tributary (branch) occlusion
	362.37	Retinal vein occlusion; venous engorgement
	362.83	Other disorders; retinal edema
Posterior segment uveitis**	363.00 – 363.08	Focal chorioretinitis and focal retinochoroiditis
	363.10 –	Disseminated chorioretinitis and disseminated retinochoroiditis

¹INDICATIONS AND USAGE

1.1 Retinal Vein Occlusion

OZURDEX[®] (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

1.2 Posterior Segment Uveitis

OZURDEX[®] is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Indication	ICD-9-CM Codes	Descriptor
	363.15	
	363.20	Other and unspecified forms of chorioretinitis and retinochoroiditis; chorioretinitis, unspecified
	363.21	Other and unspecified forms of chorioretinitis and retinochoroiditis; pars planitis”
	363.22	Other and unspecified forms of chorioretinitis and retinochoroiditis; Harada’s disease

Consistent with the FDA-approved indications described below, we recommend that OR Medicaid (1) maintain coverage for codes 362.83 and 363.21, and (2) add the additional codes listed in the above table to its list of covered ICD-9-CM diagnosis codes for OZURDEX[®].

* * * *

On June 17, 2009, Allergan announced that the United States Food and Drug Administration (FDA) had approved OZURDEX[®] “as the first drug therapy indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)”. The wording for this indication for use is as follows:

Retinal Vein Occlusion

OZURDEX[®] (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Retinal vein occlusion (RVO) – including BRVO and CRVO – is the second most common retinal vascular disease after diabetic retinopathy.² BRVO and CRVO are commonly associated with macular edema,³ which produces temporary or permanent vision loss.

As detailed in the package insert, FDA’s approval of OZURDEX[®] was based on the results of two multicenter, double-masked, randomized, parallel studies. In each individual study and in a pooled analysis, patients treated with OZURDEX[®] achieved ≥ 15 letters (3 line) improvement in best corrected visual acuity (BCVA) significantly faster than patients treated with sham therapy ($p < 0.01$). The onset of a 3-line improvement in BCVA with OZURDEX[®] typically occurs within the first two months after implantation in approximately 20-30% of subjects. The duration of effect persists approximately 1 – 3 months after onset of this effect.

On September 24, 2010, Allergan announced that the FDA had approved OZURDEX[®] for the treatment of “non-infectious ocular inflammation, or uveitis, affecting the posterior segment of the eye”. The wording of this indication for use is as follows:

² *Id.*

³ Mandelcorn MS et al. Surgical macular decompression for macular edema in retinal vein occlusion. *Can J Ophthalmol.* 2007;42:116-122.

May 6, 2013

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Posterior Segment Uveitis

OZURDEX[®] is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

OZURDEX[®] was approved as an orphan drug for this indication.

Uveitis is characterized by inflammation of the eye's uvea, which is in the middle vascular layer consisting of the iris, ciliary body, and choroid. The posterior segment of the eye comprises the choroid and ciliary body. Posterior uveitis is associated with a variety of severe outcomes, including blindness, cataracts, secondary glaucoma, and macular abnormalities.

The approval of OZURDEX[®] for the treatment of posterior uveitis was supported by a multicenter, masked, randomized study of 153 patients with non-infectious uveitis affecting the posterior segment of the eye. After a single injection, the percentage of patients reaching a vitreous haze score of 0 (where 0 represents no inflammation) was statistically significantly greater for patients receiving OZURDEX[®] versus sham at week 8 (47% vs. 12%). Moreover, 43% of OZURDEX[®] patients achieved a 3-line improvement from baseline in best corrected visual acuity (BCVA) vs. 7% for sham at week 8.

* * * *

The most common adverse reactions reported by greater than 2% of patients in the combined clinical trial results from the 3, randomized, 6-month, sham-controlled studies referenced in the OZURDEX[®] package insert (2 for retinal vein occlusion and 1 for posterior segment uveitis) include: increased intraocular pressure (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%). Increased intraocular pressure peaked at approximately week 8. During the initial treatment period, 1% of the patients who received OZURDEX[®] required surgical procedures for the management of elevated IOP. Following a second injection of OZURDEX[®] in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

* * * *

I hope that you find the information in this letter helpful. If you have any questions related to the clinical reasoning behind this request or the supporting literature, please do not hesitate to contact me at 970.396.5945 or ackerman_alan@allergan.com. If you have questions related to coding, please do not hesitate to contact our Regional Healthcare Policy Manager, Camille Kerr, at kerr_camille@allergan.com. Thank you in advance for your consideration of this request.

Sincerely yours,

Alan Ackerman, Ph.D.

Sr. Medical Scientific Manager, Payer and Health Outcomes | Allergan Medical Affairs | Office: 970-396-5945 | Mobile: 970-396-5945 | ackerman_alan@allergan.com.

Attachment:

See Tab A for a copy of the OZURDEX[®] package insert.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OZURDEX[®] safely and effectively. See full prescribing information for OZURDEX[®].

OZURDEX[®] (dexamethasone intravitreal implant)

Initial U.S. Approval: 1958

RECENT MAJOR CHANGES

- Contraindications, Aphakic Eyes with Rupture of the Posterior Lens Capsule (4.3) 09/2012
- Contraindications, ACIOL and Rupture of the Posterior Lens Capsule (4.4) 09/2012

INDICATIONS AND USAGE

OZURDEX[®] is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (1.1) and for the treatment of non-infectious uveitis affecting the posterior segment of the eye. (1.2)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection only. (2.1)
- The intravitreal injection procedure should be carried out under controlled aseptic conditions. (2.2)
- Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. (2.2)

DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the NOVADUR[®] solid polymer drug delivery system. (3)

CONTRAINDICATIONS

- Ocular or periocular infections (4.1)
- Advanced glaucoma (4.2)
- Aphakic eyes with rupture of the posterior lens capsule (4.3)
- ACIOL and rupture of the posterior lens capsule (4.4)
- Hypersensitivity (4.5)

WARNINGS AND PRECAUTIONS

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. (5.1)
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. (5.2)
- The implant may migrate to the anterior chamber if the posterior lens capsule is not intact. (5.3)

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported by $\geq 20\%$ of patients were increased intraocular pressure and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2013

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE**

- 1.1 Retinal Vein Occlusion
- 1.2 Posterior Segment Uveitis

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Administration

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS**

- 4.1 Ocular or Periocular Infections
- 4.2 Advanced Glaucoma
- 4.3 Aphakic Eyes with Rupture of the Posterior Lens Capsule
- 4.4 ACIOL and Rupture of the Posterior Lens Capsule
- 4.5 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- 5.1 Intravitreal Injection-related Effects
- 5.2 Potential Steroid-related Effects
- 5.3 Risk of Implant Migration

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Retinal Vein Occlusion

OZURDEX[®] (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

1.2 Posterior Segment Uveitis

OZURDEX[®] is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection only.

2.2 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide applied to the periocular skin, eyelid and ocular surface are recommended to be given prior to the injection.

Remove the foil pouch from the carton and examine for damage. Then, open the foil pouch over a sterile field and gently drop the applicator on a sterile tray. Carefully remove the cap from the applicator. Hold the applicator in one hand and pull the safety tab straight off the applicator. **Do not twist or flex the tab.** The long axis of the applicator should be held parallel to the limbus, and the sclera should be engaged at an oblique angle with the bevel of the needle up (away from the sclera) to create a shelved scleral path. The tip of the needle is advanced within the sclera for about 1 mm (parallel to the limbus), then re-directed toward the center of the eye and advanced until penetration of the sclera is completed and the vitreous cavity is entered. The needle should not be advanced past the point where the sleeve touches the conjunctiva.

Slowly depress the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each applicator can only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new applicator must be used, and the sterile field, syringe, gloves, drapes, and eyelid speculum should be changed before **OZURDEX**[®] is administered to the other eye.

3 DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the **NOVADUR**[®] solid polymer drug delivery system.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

OZURDEX[®] (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

4.2 Advanced Glaucoma

OZURDEX[®] is contraindicated in patients with advanced glaucoma.

4.3 Aphakic Eyes with Rupture of the Posterior Lens Capsule

OZURDEX[®] is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

4.4 ACIOL and Rupture of the Posterior Lens Capsule

OZURDEX[®] is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

4.5 Hypersensitivity

OZURDEX[®] is contraindicated in patients with known hypersensitivity to any components of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Intravitreal Injection-related Effects

Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection [*see Patient Counseling Information (17)*].

5.2 Potential Steroid-related Effects

Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

5.3 Risk of Implant Migration

Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients in the First Six Months

MedDRA Term	OZURDEX[®] N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)

Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with **OZURDEX**[®] peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received **OZURDEX**[®] required surgical procedures for management of elevated IOP.

Following a second injection of **OZURDEX**[®] in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

6.2 Postmarketing Experience

The following reactions have been identified during post-marketing use of **OZURDEX**[®] in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **OZURDEX**[®], or a combination of these factors, include: complication of device insertion (implant misplacement), device dislocation with or without corneal edema, endophthalmitis, and hypotony of the eye (associated with vitreous leakage due to injection).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

Topical dexamethasone has been shown to be teratogenic in mice producing fetal resorptions and cleft palate. In the rabbit, dexamethasone produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1 mg/kg/day every other day for 28 days or at 10 mg/kg/day once or every other day at 3 or 5 days between gestation days 23 and 49 had fetuses with minor cranial abnormalities. A 1 mg/kg/dose in pregnant rhesus monkeys would be approximately 85 times higher than an **OZURDEX**[®] injection in humans (assuming 60 kg body weight).

There are no adequate and well-controlled studies in pregnant women. **OZURDEX**[®] (dexamethasone intravitreal implant) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of **OZURDEX**[®] in pediatric patients have not been established.

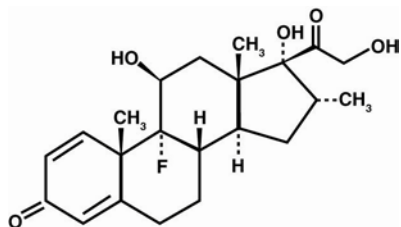
8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

OZURDEX[®] is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the **NOVADUR**[®] solid polymer drug delivery system. **OZURDEX**[®] is preloaded into a single-use, specially designed **DDS**[®] applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The **NOVADUR**[®] system contains

poly (D,L-lactide-co-glycolide) PLGA intravitreal polymer matrix without a preservative. The chemical name for dexamethasone is Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11 β ,16 α)-. Its structural formula is:



MW 392.47; molecular formula: C₂₂H₂₉FO₅

Dexamethasone occurs as a white to cream-colored crystalline powder having not more than a slight odor, and is practically insoluble in water and very soluble in alcohol.

The PLGA matrix slowly degrades to lactic acid and glycolic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells.

12.3 Pharmacokinetics

Plasma concentrations were obtained from 21 patients in two 6 month studies prior to dosing and on Days 7, 30, 60, and 90 following the intravitreal implant containing 0.35 mg or 0.7 mg dexamethasone. In both studies, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 10 of 73 samples in the 0.7 mg dose group and from 2 of 42 samples in the 0.35 mg dose group were above the LLOQ, ranging from 52 pg/mL to 94 pg/mL. The highest plasma concentration value of 94 pg/mL was observed in one subject from the 0.7 mg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In an *in vitro* metabolism study, following the incubation of [¹⁴C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humor, and sclera tissues for 18 hours, no metabolites were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether **OZURDEX**[®] (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of **OZURDEX**[®], dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test.

14 CLINICAL STUDIES

Retinal Vein Occlusion

The efficacy of **OZURDEX**[®] for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) was assessed in two, multicenter, double-masked, randomized, parallel studies.

Following a single injection, **OZURDEX**[®] demonstrated the following clinical results for the percent of patients with ≥ 15 letters of improvement from baseline in best-corrected visual acuity (BCVA):

Number (Percent) of Patients with ≥ 15 Letters Improvement from Baseline in BCVA

Study Day	Study 1			Study 2		
	DEX 700 N=201	Sham N=202	p-value*	DEX 700 N=226	Sham N=224	p-value*
Day 30	40 (20%)	15 (7%)	< 0.01	51 (23%)	17 (8%)	< 0.01
Day 60	58 (29%)	21 (10%)	< 0.01	67 (30%)	27 (12%)	< 0.01
Day 90	45 (22%)	25 (12%)	< 0.01	48 (21%)	31 (14%)	0.039
Day 180	39 (19%)	37 (18%)	0.780	53 (24%)	38 (17%)	0.087

*P-values were based on the Pearson's chi-square test.

In each individual study and in a pooled analysis, time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with **OZURDEX**[®] compared to sham ($p < 0.01$), with **OZURDEX**[®] treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a ≥ 15 letter (3-line) improvement in BCVA with **OZURDEX**[®] occurs within the first two months after implantation in approximately 20-30% of subjects. The duration of effect persists approximately one to three months after onset of this effect.

Posterior Segment Uveitis

The efficacy of **OZURDEX**[®] was assessed in a single, multicenter, masked, randomized study of 153 patients with non-infectious uveitis affecting the posterior segment of the eye.

After a single injection, the percent of patients reaching a vitreous haze score of 0 (where a score of 0 represents no inflammation) was statistically significantly greater for patients receiving **OZURDEX**[®] versus sham at week 8 (primary time point) (47% versus 12%). The percent of patients achieving a 3-line improvement from baseline BCVA was 43% for patients receiving **OZURDEX**[®] versus 7% for sham at week 8.

16 HOW SUPPLIED/STORAGE AND HANDLING

OZURDEX[®] (dexamethasone intravitreal implant) 0.7 mg is supplied in a foil pouch with 1 single-use plastic applicator, NDC 0023-3348-07.

Storage: Store at 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

In the days following intravitreal injection of **OZURDEX**[®], patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist.

Patients may experience temporary visual blurring after receiving an intravitreal injection. They should not drive or use machines until this has resolved.

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*National Institute for
Health and Clinical Excellence*

Issue date: July 2011

Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion

**This guidance was developed using the
single technology appraisal process**

NICE technology appraisal guidance 229

Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion

Ordering information

You can download the following documents from

www.nice.org.uk/guidance/TA229

- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- 'Understanding NICE guidance' – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N2616 (quick reference guide)
- N2617 ('Understanding NICE guidance').

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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	Appendix B: Sources of evidence considered by the Committee	43



NHS Evidence has accredited the process used by the Centre for Health Technology Evaluation at NICE to produce guidance. Accreditation is valid for 3 years from April 2010 and is applicable to guidance produced using the processes described in NICE's 'Guide to the single technology appraisal process' (2009). More information on accreditation can be viewed at www.evidence.nhs.uk

1 Guidance

- 1.1 Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following central retinal vein occlusion.
- 1.2 Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following branch retinal vein occlusion when:
 - treatment with laser photocoagulation has not been beneficial, **or**
 - treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage.
- 1.3 People currently receiving dexamethasone intravitreal implant for the treatment of macular oedema secondary to branch retinal vein occlusion who do not meet the criteria specified in 1.2 above should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Dexamethasone intravitreal implant (Ozurdex, Allergan) incorporates a potent corticosteroid that suppresses inflammation in the eye by inhibiting oedema, fibrin deposition, capillary leakage and phagocytic migration. Corticosteroids inhibit the expression of vascular endothelial growth factor (VEGF), a cytokine that is expressed at increased concentrations in macular oedema and is a potent promoter of vascular permeability. Corticosteroids also prevent the release of prostaglandins, some of which are mediators of cystoid macular oedema.
- 2.2 Dexamethasone intravitreal implant has a marketing authorisation for the treatment of adult patients with macular oedema following

Intravitreal steroids for macular edema in diabetes (Review)

Grover DA, Li T, Chong CCW



This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

<http://www.thecochranelibrary.com>



Intravitreal steroids for macular edema in diabetes (Review)

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[Intervention Review]

Intravitreal steroids for macular edema in diabetes

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ABSTRACT

Background

Macular edema is secondary to leakage from diseased retinal capillaries and is an important cause of poor central visual acuity in patients with diabetic retinopathy.

Objectives

This review evaluated the effectiveness and safety of intraocular steroids in treating diabetic macular edema (DME).

Search methods

We searched CENTRAL, MEDLINE, EMBASE in June 2007, reference lists, Science Citation Index and conference proceedings.

Selection criteria

We included randomized clinical trials (RCTs) evaluating any form of intravitreal steroids for treating DME.

Data collection and analysis

Two authors independently assessed eligibility, methodological quality and extracted data. We performed meta-analyses when appropriate.

Main results

Seven studies, involving 632 DME eyes were included. Four examined the effectiveness of intravitreal triamcinolone acetate injection (IVTA), three examined intravitreal steroids implantation (fluocinolone acetonide implant (FAI) or dexamethasone drug delivery system (DDS)). Two trials were at low risk of bias, one was at median risk of bias, two were at high risk of bias and the remaining two were at unclear risk of bias.

The preponderance of data suggest a beneficial effect from IVTA. Comparing IVTA with controls, the mean difference in visual acuity was -0.15 LogMAR (95% CI -0.21 to -0.09) at 3 months (based on three trials), -0.23 LogMAR (95% CI -0.33 to -0.13) at 6 months (two trials), -0.29 LogMAR (95% CI -0.47 to -0.11) at 9 months (one trial), and -0.11 LogMAR (95% CI -0.20 to -0.03) at 24 months (one trial), all in favor of IVTA. The relative risk (RR) for one or more lines improvement in visual acuity was 2.85 (95% CI 1.59 to 5.10) at 3 months (two trials), 1.25 (95% CI 0.66 to 2.38) at 6 months (one trial), and 2.17 (95% CI 1.15 to 4.11) at 24 months (one trial), all in favor of IVTA. We did not find evidence for three or more lines improvement in visual acuity. The mean difference

in retinal thickness was -131.97 μm (95% CI -169.08 to -94.86) at 3 months (two trials), -135.00 μm (95% CI -194.50 to -75.50) at 6 months (one trial), -133.00 μm (95% CI -199.86 to -66.14) at 9 months (one trial), and -59.00 μm (95% CI -103.50 to -14.50) at 24 months (one trial), all in favor of IVTA. The RR for at least one grade macular edema resolution was 5.15 (95% CI 2.23 to 11.88) at 3 months in favor of IVTA (one trial).

Two trials reported improved clinical outcome when FAI was compared to standard of care. Beneficial effect was also observed in one dexamethasone DDS trial.

Increased intraocular pressure and cataract formation were side effects requiring monitoring and management.

Authors' conclusions

RCTs included in this review suggest that steroids placed inside the eye by either intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory DME. Since the studies in our report focused on chronic or refractory DME, the question arises whether intravitreal steroids therapy could be of value in other stages of DME, especially the earlier stages either as standalone therapy or in combination with other therapies, such as laser photocoagulation.

PLAIN LANGUAGE SUMMARY

Intravitreal steroids for macular edema in people with diabetes

Macular edema, swelling of the center of the retina (the part of the eye responsible for our sharpest vision), is an important cause of poor vision in patients with diabetes. New forms of therapy are desirable because the current treatment including laser photocoagulation does not control all cases of diabetic macular edema (DME) and because laser therapy may destroy normal retinal tissue. Intravitreal steroids in the form of intravitreal triamcinolone acetate injection (IVTA) and surgical implantation of fluocinolone acetonide (FAI) or dexamethasone drug delivery system (DDS) are promising new therapies. This systematic review included seven randomized clinical trials involving 632 eyes from five countries evaluating the effectiveness and safety of intravitreal steroids for treating DME. Two trials were at low risk of bias, one was at median risk of bias, two were at high risk of bias, and the remaining two had an unclear risk of bias. In this systematic review, the preponderance of data suggest a beneficial effect from IVTA. The average improvement in visual acuity was 7.5 letters more (-0.15 LogMAR; 95% CI -0.21 to -0.09) in the IVTA treated eyes than in those treated with other therapies at three months (based on three trials), 11.5 letters more (-0.23 LogMAR; 95% CI -0.33 to -0.13) at six months (two trials), 14.5 letters more (-0.29 LogMAR; 95% CI -0.47 to -0.11) at nine months (one trial), and 5.7 letters more (-0.11 LogMAR; 95% CI -0.20 to -0.03) at 24 months (one trial). Improved clinical outcomes were also reported in FAI and dexamethasone DDS trials. Elevation of intraocular pressure and cataract progression occur in both IVTA and implants treated eyes but appear manageable.

BACKGROUND

Introduction

Diabetic macular edema (DME) is the result of retinal microvascular changes that present in both type I and type II diabetes mellitus. It is the most common cause of visual loss in type II diabetes (Tranos 2004). It can be defined as macular retinal thickening caused by diabetic retinopathy. Since diabetic retinopathy can exist without macular edema the mere presence of diabetic retinopathy does not, by itself, confirm the diagnosis of DME. Other possible causes of macular edema exist and more than one etiology may play a role in the retinal thickening. Diabetic mac-

ular edema must, therefore, be distinguished from other possible independent or contributory causes of the macular edema.

Two types of macular edema have been described: focal and diffuse. Focal macular edema derives from individual microaneurysms or small clusters of microaneurysms and dilated capillaries (Cunha-Vaz 1998). Diffuse macular edema is characterized by diffuse leakage from extensive areas of the posterior retinal capillary bed and a generalized breakdown of the inner blood-retinal barrier (Aroca 2004). The excessive vascular permeability, resulting in the leakage of fluid, lipoproteins, and other plasma constituents into the retina, leads to thickening of the retina (Verma 2004).

Interventions for diabetic macular oedema: a systematic review of the literature

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ABSTRACT

Objectives: This review discusses the evolution of the treatment of diabetic macular oedema and gives helpful guidelines in the treatment of diabetic macular oedema based on available evidence to date.

Methods: A literature search of all English articles from the Medline and Cochrane database was performed. The search was limited to only English randomised controlled clinical trials in humans. Overall, 93 articles were cited from 1979 to 2007. Of these, 31 articles corresponded to subject matter. Studies were evaluated on a standardised data extraction form and tabulated for easy review.

Results: There is good evidence that laser treatment preserves vision in eyes with diabetic macular oedema (DMO). However, laser is a potentially destructive form of treatment which may be of greater benefit in combination with newer forms of treatment such as intravitreal steroid or intravitreal antiangiogenic agents. Current evidence does not support a clear benefit for surgical intervention in DMO.

Conclusions: Although laser treatment remains the cornerstone of treatment in diabetic macular oedema, the literature is beginning to support combination therapy. Using one or two intravitreal injections to reduce central macular thickness followed by focal or grid laser to give a sustained response may offer an alternative to treatment in DMO.

Diabetes mellitus affects 200 million people in the world.¹ Diabetic retinopathy (DR) is the leading cause of blindness in the working-aged population in the USA.² The prevalence of DR increases with duration of diabetes,³ and nearly all persons with type 1 diabetes and more than 60% of those with type 2 have some retinopathy after 20 years.³ Twenty-nine per cent of these have clinically significant diabetic macular oedema (CSDMO).³

Diabetic macular oedema (DMO), which can occur at any stage of DR, is characterised by increased vascular permeability and the deposition of hard exudates at the central retina. Diabetic macular oedema is now the principal cause of vision loss in persons with diabetes.³

Over the past 30 years, our knowledge and understanding of the pathogenesis of diabetic retinopathy have evolved. In conjunction with this evolution of knowledge has been the development of multiple treatments beginning with the use of laser and culminating with the use of intravitreal injections either alone or in combination with traditional treatments. With so much information available, the clinician is now faced with the task of deciphering which treatment is most suitable for a specific patient based on available evidence. In

this review, we discuss the evolution of the treatment of diabetic macular oedema and give helpful guidelines in the treatment of diabetic macular oedema based on available evidence to date.

MATERIALS AND METHODS

We performed a literature search of all English articles from the Medline and Cochrane database using the search words "Diabetic macular oedema/edema," "clinically significant macular oedema," "CSMO," "DMO," "DME," and "macular oedema." We confined our search to randomised controlled clinical trials in humans in the English language. Any additional randomised controlled trials cited in reviewed articles were also analysed. Overall, 93 articles were cited from 1979 to 2007. Of these, 31 articles corresponded to subject matter.

Studies were evaluated on a standardised data extraction form for (1) name of trial, (2) country of origin, (3) year of origin, (4) method of randomisation, (5) Diagnostic criteria for entry, (6) similarity of groups at baseline regarding the most important prognostic indicators, (7) clearly specified eligibility and exclusion criteria, (8) number of patients and eyes, (9) masking of outcome assessor, care provider and patient, (10) reporting of point estimates and measures of variability for outcomes, (11) intention-to-treat analysis, (12) length of follow-up, (13) adverse events and (14) acceptable loss to follow-up rate unlikely to cause bias. The articles were then tabulated to allow easy clarification of results.

RESULTS

Laser treatment

Laser treatment for diabetic retinopathy is one of the oldest forms of treatment. There is good evidence that focal laser treatment preserves vision in eyes with DMO. The ETDRS trial, undertaken in 1985, was the first properly conducted randomised trial to establish the benefits of laser for both diabetic macular oedema and proliferative diabetic retinopathy. The ETDRS randomised 1490 eyes with DMO to receive focal laser treatment or observation. At 3 years, treatment significantly reduced moderate visual loss as compared with observation,⁴ with the greatest benefits in eyes with clinically significant DMO.⁵ In response to the clear benefit outlined in this trial, others began to question whether laser type had any influence on outcome. However, there is currently no definite evidence that the laser type (argon, diode, dye, krypton) or method used influences outcomes⁶⁻¹⁴ (table 1). Olk *et al* reported that not only was there no difference between using argon green

Abbreviated Drug Evaluation: Fluocinolone acetonide intravitreal implant (Retisert®)

Month/Year of Review: January 2013

End date of literature search: September 2012

Generic Name: Fluocinolone acetonide intravitreal implant

Brand Name (Manufacturer): Retisert® (Bausch & Lomb)

FDA Approved Indication:

The Fluocinolone ocular implant is a corticosteroid surgically implanted; indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.¹

Research Questions:

- Is there evidence to support the use of fluocinolone acetonide intravitreal implant over another delivery device and/or standard of care for the treatment of uveitis or other macular edema indications?
- Is there any high quality evidence to support the use of fluocinolone acetonide intravitreal implant over other steroid implant devices?
- Are there certain subpopulations, where corticosteroid intravitreal implants are either more effective or safer than other treatments for uveitis and other macular edema indications?

Conclusions:

- There is low quality evidence that there is no difference in visual acuity outcomes between fluocinolone acetonide intravitreal implant and standard of care with systemic corticosteroids for the treatment of noninfectious uveitis. There is also low quality evidence that fluocinolone intravitreal implant may control inflammation in the eye faster and more frequently than standard of care, although both approaches decrease inflammation.
- There is moderate quality evidence that fluocinolone acetonide intravitreal implant is associated with more ocular adverse events than standard of care, including glaucoma (Hazard Ratio [HR] 4.2, 95% CI 1.82-9.63) and cataracts (HR 4.12, 95% CI 2.2-7.7).
- There is low quality evidence demonstrating potential benefit of fluocinolone acetonide intravitreal implant and dexamethasone implant for the treatment of diabetic macular edema, however significant complications have also been reported. There is insufficient evidence to support the use for diabetic macular edema or other off-label indications.
- There is insufficient evidence directly comparing fluocinolone acetonide intravitreal implant to dexamethasone intravitreal implant for any indications. There are significant differences in indications and administration techniques between the two agents.
- There is moderate quality evidence demonstrating efficacy of dexamethasone intravitreal implant following central retinal vein occlusion.

Recommendations:

- Recommend that the Health Evidence Review Commission evaluate the surgical procedure of the fluocinolone ocular implant for line placement.

Background:

Uveitis is an ocular inflammatory condition that may be related to infection or are non-infective.^{2,3} The standard of care for noninfectious uveitis is local, topical, or oral corticosteroids in combination with immunosuppressive therapy, when indicated.³ The goal of treatment is to suppress inflammation and achieve remission and protection of visual acuity. Topical corticosteroids penetrate well only into the anterior segment of the eye and are useful in the management of anterior uveitis, but do not adequately penetrate the posterior segment of the eye. Periocular steroids are useful in intermediate uveitis and posterior uveitis. However, many patients need systemic steroids, primarily orally with or without immunosuppressive drug therapy. Treatment guidelines from 2000 and 2005 recommend topical, local, or systemic corticosteroids to control ocular inflammation rapidly. To decrease the risk of serious side effects associated with corticosteroid use, guidelines recommend the addition of immunomodulatory therapy as a steroid-sparing agent if inflammation is not controlled within three months with steroid use (≤ 10 mg/day of prednisone or equivalent).^{3,4} Intravitreal implants were developed to deliver a continuous concentration of drug over a prolonged period of time and are either biodegradable or nonbiodegradable. Although this continuous release may reduce the need for intravitreal injections or long-term systemic therapy, surgical implantation of the device carries its own risks, and the implant could potentially increase ocular toxicity due to increased corticosteroid concentrations in the eye over a longer duration.

In 2005, the FDA approved the intraocular fluocinolone implant (Retisert®) for chronic, noninfectious uveitis which is a non-biodegradable implant that delivers drug continuously for about 30 months. The fluocinolone implant is surgically implanted by a vitreoretinal surgeon. Approval for noninfectious uveitis was based on two phase III, randomized, double-masked, historically controlled clinical trials demonstrating a clinically and statistically significant difference in the proportion of patients with recurrence of uveitis within 34 weeks post-implantation compared to the proportion with recurrence in the 34 weeks preceding implantation.⁵ The fluocinolone implant reduced the rate of recurrence from 62% in the year preceding implantation to 20% in the 0.59-mg group and 41% in the 2.1-mg group post implantation. There was also a significant improvement in visual acuity when compared to the nonimplanted eyes ($p < 0.01$). There was no significant difference in the proportion of eyes with deteriorating visual acuity.⁵ There was a significant increase in the incidence of cataracts in the implant eyes compared to the nonimplanted eyes (67% vs. 18%, $p < 0.01$; RR 3.7, 95% CI 2.7 to 5.2) and 93% of implanted eyes underwent cataract surgery.⁵

In 2009 the dexamethasone ocular implant (Ozurdex®) was approved for macular edema following retinal vein occlusion (RVO), and in 2010 also for the treatment of non-infectious uveitis, affecting the posterior segment of the eye. This implant is biodegradable and releases dexamethasone over about 6 months. The dexamethasone ocular implant can be given as an outpatient procedure, while fluocinolone has to be surgically inserted. The safety and efficacy of the dexamethasone intravitreal implant for the treatment of non-infectious uveitis affecting the posterior segment of the eye was studied in a single, multicenter, masked, randomized 26 week trial.⁶ Two hundred and twenty nine subjects were randomized to dexamethasone implant 0.35mg, 0.7mg, or a sham procedure. The primary outcome was the percentage of eyes with a vitreous haze score of 0, which represents no inflammation, at week eight of the trial. Outcome investigators and patients were masked, while treatment investigators were unmasked in order to perform the implant placement. The percentage of eyes with a vitreous haze score of 0 at week eight was significantly greater in both the 0.7-mg (47%; $p < 0.001$) and the 0.35 mg group (36%; $p < 0.001$) than the sham group (12%).⁶ There were also significantly more eyes with improved visual acuity in the dexamethasone implant groups than the sham group. The authors concluded that in this study a single dose of the dexamethasone implant was well tolerated and produced significant improvements in intraocular inflammation and visual acuity that persisted for six months. In addition, it was noted that the 0.7 mg implant demonstrated greater efficacy than the 0.35 implant, with similar safety.⁶

Author: M. Herink, Pharm.D.

Research is also being conducted on evaluating the safety and efficacy of fluocinolone acetonide intravitreal implant as off-label use for the treatment of diabetic macular edema (DME). Previous treatment approaches for DME include laser photocoagulation, intravitreal steroid injections, vitrectomy, and vascular endothelial growth factor (VEGF) inhibitors. Laser photocoagulation has historically been the gold standard but has not been successful in improving vision, only preserving it. Intravitreal steroids are not commonly used due to the risk of elevated intraocular pressure and cataracts.⁷ There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with DME relative to laser treatment and sham injection, with similar improvements across agents.⁸ An additional fluocinolone intravitreal implant (Iluvien®) has been submitted to the FDA for the indication of DME but has not yet been approved.

Systematic Reviews

National Institute for Health and Clinical Excellence

A 2011 technology appraisal was published in 2011 by the National Institute for Health and Clinical Excellence (NICE) on dexamethasone implant for macular edema secondary to retinal vein occlusion.⁹ Dexamethasone intravitreal implant is recommended as an option for macular edema following central retinal vein occlusion (CRVO). It is recommended as an option for macular edema following branch retinal vein occlusion (BRVO) when treatment with laser photocoagulation has not been beneficial or is not considered suitable because of macular hemorrhage.⁹

O'Doherty, et al.

A 2008 review of the literature for diabetic macular edema treatment reported on a single study of fluocinolone implant in 97 patients with DME randomized to receive either the implant or standard of care with laser treatment or observation.¹⁰ Studies were evaluated on a standardized data extraction form; however a specific quality assessment was not defined and risk of bias for the fluocinolone study was not evaluated. At 3 years, 58% of patients had resolution of DME and associated improvement in visual acuity, compared to 30% of patients in the control group ($p < 0.001$). The most common adverse effects included a higher risk of cataract formation and glaucoma in the treatment group compared to control. A total of 5% of patients required removal of the implant to control the glaucoma. Overall, there was little evidence to support the use of the implant and at the time no available studies were available to make conclusions on superiority or noninferiority of fluocinolone acetate implant to other intravitreal injection.

Cochrane Collaboration

A Cochrane review evaluated the effectiveness and safety of intraocular steroids in treatment DME.¹¹ Three of the total seven trials examined intravitreal steroids implantation (fluocinolone or dexamethasone). The authors concluded that evidence suggests that steroids administered either by intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory DME.

Two trials evaluated fluocinolone implant versus standard of care or observation. At 12 months, there was no evidence of effect on three or more lines improvement in visual acuity (RR 2.73, 95% CI 0.63 to 11.93). The other trial demonstrated a marginal statistically significant effect on three or more lines in visual acuity at 36 months (RR 1.93, 95% CI 1.02 to 3.66). Data was insufficient to combine for a meta-analysis and both trials had a high risk of bias. The dexamethasone implant trial included participants with various underlying causes of macular edema. In a subgroup analysis of DME patients, 58% in the dexamethasone group showed a two-line improvement in vision compared to 21% in the observation group (RR 2.75, 95% CI 1.59 to 4.76) at 3 months. This suggests a beneficial effect from dexamethasone and possible evidence of benefit with the use of fluocinolone. There were many methodology limitations in the fluocinolone data, making it difficult to draw strong conclusions on the magnitude of effect.

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Systemic therapy vs. Implant therapy:*The Multicenter Uveitis Steroid Treatment Trial Research Group*

A recent fair quality randomized, partially masked, controlled trial reported 24-month results of an evaluation of fluocinolone acetonide implant compared to systemic therapy with oral corticosteroids and immunosuppressive drugs when indicated (standard of care) for noninfectious intermediate uveitis, posterior, or panuveitis.¹² The Multicenter Uveitis Steroid Treatment (MUST) Trial compared 129 participants in the implant group to 126 participants in the systemic therapy group. Appropriate randomization methods were used. Patients, clinicians, and coordinators were unable to be masked; however visual acuity outcome examiners were masked. Most baseline demographics and characteristics were similar between groups; however eyes with uveitis in the implant group had poorer visual field sensitivity than those in the systemic group.

Both groups experienced improvement of best-corrected visual acuity (BCVA; a measure of visual acuity) during follow-up at all time points. There was no statistically significant difference between the treatment groups in improvement in visual acuity at 24 months, with a mean improvement from baseline of 6.0 letters in the implant group compared to 3.2 letters in the systemic group (estimated treatment effect 2.70, 95% CI -1.16 to 6.68; $p=0.16$). At 24 months, 21% and 13% of eyes assigned to implant or systemic therapy, respectively, had gained at least 15 letters ($p=0.065$). Both groups experienced control of active uveitis, however more frequent in the implant group (88% vs. 71%, $p=0.001$). Authors concluded that both groups were successful in controlling inflammation in the majority of cases, without clear evidence indicating superiority of effectiveness for either group. The implant has the potential to achieve inflammatory control faster and more often and ocular complications of uveitis or treatment were more common in the implant group.

The implant group had a more than 4-fold higher rate of incidence of intraocular pressure (IOP) elevation ≥ 10 mmHg, absolute IOP of ≥ 30 mmHg, and of needing medical and surgical treatments for elevated IOP. Glaucoma developed in 17% and 4.0% in the implant and systemic groups, respectively (HR=4.2, 95% CI 1.82-9.63; $p=0.0008$). Those in the implant group also experienced higher cumulative 24-month risk of both cataract (91% vs. 45%, HR 4.12 95% CI 2.2-7.7; $p<0.0001$) and cataract surgery (80% vs. 31%, HR 3.3 95% CI 2.2-5.0; $p<0.0001$). Adverse systemic events were infrequent in both groups and there was no significant difference in risk of hospitalizations.

Pavesio, et al.

A previous poor-fair quality 3-year, open label, randomized, phase 2b/3 superiority study compared fluocinolone implant with standard of care in subjects with unilateral or bilateral noninfectious posterior uveitis.¹³ The study was conducted from April 2002 through August 2005 at 37 centers across 10 countries. Subjects were randomized to a 0.59-mg fluocinolone implant ($n=66$) or SOC ($n=74$) with either systemic prednisolone or equivalent corticosteroid monotherapy or, if deemed necessary, combination therapy with an immunosuppressive agent plus a lower dose of prednisolone or equivalent corticosteroid. Approved immunosuppressants included cyclosporine A, methotrexate, cyclophosphamide, mycophenolate mofetil, azathioprine, and tacrolimus. Subjects were allocated to receive either an implant or SOC as determined by a centrally administered randomization procedure. It was not possible to mask study treatments; however efforts were made to avoid selection bias. Treatment allocation was masked until the confirmation of inclusion of the subject and some outcome assessments were masked. There was a statistically significant difference between the treatment groups in gender ($p=0.02$); other baseline characteristics were similar between the two groups.

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The primary outcome was time to first recurrence of uveitis, and 2-year results are included in the study. Using uveitis activity as a primary outcome may bias the results against systemic therapy because systemic regimens rely on tapering medications until uveitis activity returns and then increasing the medication to control inflammation.¹⁴ Subjects that received fluocinolone had delayed onset of observed recurrence of uveitis and statistically significant lower rate or percentage of subjects who had at least 1 recurrence compared with SOC (34.8% vs. 64.9%; $p<0.01$). The mean time to first recurrence was 6.4 ± 7.0 months and 7.1 ± 7.2 months for implanted eyes and the SOC eyes, respectively. There was no statistically significant difference in visual acuity between the two groups, as measured by improvement in at least 3 lines in BCVA (17.2% of implanted eyes vs. 14.3% of SOC; $p=0.66$). There were no treatment related nonocular adverse events in the fluocinolone group compared to 25.6% of subjects receiving SOC.

Treatment emergent ocular adverse events occurred in 98.5% of implanted eyes versus 79.7% of SOC eyes with a greater number of serious ocular events in implant eyes. Adverse events commonly observed significantly more in eyes with the implant compared to placebo included cataracts requiring extraction (87.8% vs. 19.3%, $p<0.01$), and increased IOP requiring surgery (21.2% vs. 2.7%, $p<0.01$). Other serious ocular events included 3 cases of endophthalmitis (4.5%) in the plant group compared to none in the SOC eyes. None of the subjects in the implant group experienced a nonocular adverse event related to treatment, whereas 19 (25.7%) subjects in the SOC group did. The authors concluded that based on the results of the study, the fluocinolone acetate intravitreal implant seemed to be more effective than SOC therapy in controlling the intraocular inflammation in those with posterior uveitis. It was also associated with increased rates of cataract development and elevated IOP which were managed by surgical or medical treatment.

Diabetic macular edema:

Pearson, et al.

A prospective, fair quality, randomized, 4 year clinical trial studied reported the 3-year efficacy and safety results evaluating fluocinolone implant compared to standard of care in 196 patients with diabetic macular edema (DME).¹⁵ This was evaluator-masked only (patients and investigators were not masked) trial comparing 0.59 mg fluocinolone implant ($n=127$) to standard of care ($n=69$) with focal/grid laser photocoagulation or observation at the investigators' discretion. The primary efficacy outcome was ≥ 15 letter increase in visual acuity at 6 months, measured by masked, certified examiners using a standardized Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Demographic characteristics were similar between the two groups. Improvements in visual acuity were seen in both treatment groups. Though 31.1% of patients reached the primary endpoint, the results were not statistically different from standard of care ($p=0.015$). At both 6 and 9 months, visual acuity was significantly higher with the implant than with standard of care ($p<0.0012$ and $p<0.002$, respectively), but the difference was not significant at 1 year ($p=0.119$) or 3 years ($p=0.1566$). There was also a significant difference in change from baseline in macular edema at 6 months and 1 year, but no difference was seen at 3 years ($p=0.861$).

There was a higher rate of ocular adverse events in eyes treated with the implant than in eyes receiving standard of care (100% vs. 88.4%). The most common adverse effects in implanted eyes were elevated intraocular pressure (69.3%), worsening cataract (55.9%), vitreous hemorrhage (40.2%), and pruritus (38.6%). The most frequent adverse events in SOC eyes were macular edema (36.2%), reduced visual acuity (23.2%), worsening cataract (21.7%), and pruritus (21.7%). Rates of nonocular adverse events were similar in both groups.

Campochiaro et al.

Two identical fair-quality randomized, double blind, sham injection-controlled studies were conducted comparing low (0.2 mcg/day) and high dose (0.5 mcg/day) fluocinolone acetate intravitreal inserts in 956 patients with DME over a 36-month period. The primary outcome measure was the percentage of

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subjects with improvement in baseline BCVA of 15 letters or more at month 24. In the modified intention to treat analysis, both of the fluocinolone insert groups had more subjects showing an improvement in BCVA letter score of 15 or more at 24 month (26.1% in the low-dose group, 26.7% in the high-dose group, 13.0% in the sham group/ $p < 0.001$).

The most common serious adverse event was cataract surgery, which occurred in 50.9% of patients in the high-dose implant group, 41.1% in the low-dose group, and 7.0% in the sham group. Increased IOP and glaucoma also occurred more frequently in the implant groups than in the sham group. Overall attrition was 19% in the high-dose group, 19.9% in the low-dose group, and 22.7% in the sham group. Withdrawals due to adverse events were higher in the high-dose group than both the low-dose group and the sham group (5.1%, 1.1%, and 1.6%, respectively). The incidence of serious cardiovascular events was similar in the 3 groups (sham 10.3%, low-dose 12.0%, and high-dose 13.2%). However, myocardial infarction occurred in 4.0% of patients in the low dose implant group compared to 1.1% in the sham group ($p = 0.0347$). The authors suggested this is highly likely a result of chance because the release of fluocinolone within the eye is so low that levels are not measurable in the systemic circulation.

Dexamethasone: Haller, et al.

A prospective, poor quality, randomized, single-masked controlled trial evaluated the safety and efficacy of two doses of the dexamethasone implant compared to observation in patients with DME.¹⁶ The primary outcome was the proportion of eyes that achieved an improvement in BCVA of 10 letters or more at day 90. A statistically significant difference in the primary outcome was shown at day 90 (33% vs. 12%, $p = 0.07$, 95% CI for difference, 6.14% to 35.96%). The differences between the low and high dose dexamethasone groups (300 mcg and 700 mcg) were not statistically significant. There was no significant difference in the number of cataract between the groups. There was a significant difference in the number of subjects experiencing increased IOP in the dexamethasone groups compared to observation (14.5% vs. 9.4% vs. 0%; $p = 0.006$).¹⁶ This was a sub-analysis of a larger study including patients with macular edema from additional causes including retinal vein occlusion, uveitis, and Irvine-Gass syndrome, and therefore should be interpreted with caution.

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AETNA Clinical Policy Bulletin:
Retisert (Fluocinolone Acetonide Intra-vitreous Implant)



Number: 0719

Policy

Aetna considers the Retisert (fluocinolone acetonide) intra-vitreous implant medically necessary for the treatment of members with chronic non-infectious uveitis affecting the posterior segment of the eye, and who do not respond to or are intolerant to conventional treatment.

Aetna considers Retisert experimental and investigational for the treatment of the following indications (not an all inclusive list):

- Anterior uveitis
- Intermediate (pars planitis) uveitis
- Macular edema/central retinal vein occlusion
- Serpiginous choroiditis
- Sympathetic ophthalmia
- Vogt-Koyanagi-Harada disease.

See also [CPB 795 - Ozurdex \(Dexamethasone Intravitreal Implant\)](#)

Background

Uveitis, an intra-ocular inflammatory disease, entails a large group of inflammatory diseases involving the iris, the ciliary body and the uvea. It is a significant cause of visual impairment. Multiple causes can be responsible for ocular inflammation that can result either from infectious or autoimmune disease. Uveitis can be classified by the location of inflammation: (i) anterior uveitis, (ii) posterior uveitis, (iii) intermediate uveitis, and (iv) panuveitis (diffused). The most common causes of posterior uveitis or panuveitis are Behcet's disease, toxoplasmosis, and Vogt-Koyanagi-Harada syndrome (Chung and Choi, 1989; Khairallah et al, 2004).

The incidence of uveitis varies from 14 to 28 per 100,000. According to the anatomical classification, about 30 to 60% (average 47%) are related to anterior uveitis; 6 to 30% (average 21%) are posterior uveitis; 7 to 15% (average 12%) are intermediate uveitis; and 7 to 69% (average 20%) are panuveitis. A specific diagnosis can be established in more than 70% in most series (Guex-Crosier, 1999).

Corticosteroids represent the mainstay of short-term medical therapy for ocular inflammation, especially in children (Hesselink et al, 2004). They can be administered systemically or via periocular injections. Song (2004) noted that corticosteroids are usually included in 1st-line therapy for the treatment of posterior uveitis because of its rapid onset of action and favorable

safety profile; and systemic immunosuppressive agents also play an important role in the management of this condition. Immunosuppressive agents take several weeks for their full effect and are considered when long-term therapy is anticipated. When long-term therapy is anticipated, immunosuppressants may be added. This approach allows for the reduction and eventual discontinuation of treatment with corticosteroids. Combination therapy of various immunosuppressive agents may decrease relapse rate, however, immunosuppressants can be associated with serious side effects, and requires careful monitoring. Moreover, the role of new therapeutic approaches in the treatment of uveitis such as anti-tumor necrosis factor alpha treatment or immunosuppression with drugs including tacrolimus, sirolimus, and interleukin-2 receptor antibodies is being investigated (Efthimiou and Markenson, 2005). Furthermore, chlorambucil, a cytotoxic alkylating anti-neoplastic agent, has been reported to be a safe and effective alternative for preserving vision in patients with otherwise treatment resistant (i.e., systemic steroids and immunomodulatory therapy) uveitis (Miserocchi et al, 2002).

Uveitis often requires long-term medical therapy. In a pilot study, Tanner et al (1998) examined the safety and effectiveness of posterior, sub-Tenon's steroid injections (PSTSI) in the treatment of posterior and intermediate uveitis. A total of 28 PSTSI injections (40 mg triamcinolone) were given and the results analyzed with a 6 month prospective follow-up in 13 cases. These investigators concluded that PSTSI significantly decreases cystoid macular edema, with a corresponding increase in visual acuity, in patients with posterior uveitis. Also, systemic immunosuppression may be reduced or discontinued with the avoidance of associated systemic side effects, and the technique has a high level of patient acceptability. This is in agreement with the findings of Lafranco Dafflon et al (1999) who reported that PSTSI (n = 53 with 162 injections of 40 mg triamcinolone) are very effective in restoring visual acuity in patients with chronic uveitis of the posterior segment, without systemic complications. However, this benefit was attained at the expense of intra-ocular hypertension, a complication that was found more frequently than expected. Mean duration of follow-up was 448 +/- 57 days.

Menezo et al (2005) evaluated the visual outcome and corticosteroid dose requirement in patients with non-infectious uveitis affecting the posterior segment treated with corticosteroids and additional second-line immunosuppression. Seventy-two patients (141 eyes) with uncontrolled non-infectious uveitis on systemic prednisolone were treated with at least one second-line immunosuppressive agent in addition to systemic prednisolone and followed for at least 3 months. At the end of the follow-up period (mean of 55.5 months), 70 eyes (49.6%) had visual acuity of 6/9 or better. There was a reduction in the mean maintenance dose of prednisolone required before the introduction of the second-line agent (19 mg/day +/- 2 SE) when compared to the mean maintenance dose of prednisolone at the end of the data collection (9 mg/day +/- 1 SE; $p < 0.001$). There was also a significant reduction in the number of disease relapses requiring an increase in prednisolone dose after starting the second-line agents as compared to the year before ($p < 0.02$). These investigators concluded that in patients with uveitis affecting the posterior segment, the addition of all second-line immunosuppressive therapy was effective in allowing reduction of the dose of systemic prednisolone to 10 mg/day or less, in controlling intraocular inflammation, reducing the number of relapses and in maintaining vision. Because of their side-effects, immunosuppressive treatment should be individualized and monitored closely but its addition is beneficial in the short and longer term.

An intra-vitreous implant that can deliver fluocinolone acetonide to posterior eye tissue for up to 3 years has been developed recently (Retisert, Bausch & Lomb Inc., Rochester, NY). Retisert is the world's first intra-vitreous drug implant for the treatment of non-infectious uveitis affecting the posterior segment of the eye, which affects an estimated 175,000 people in the United States. This sight-threatening inflammatory disease primarily affects people between the ages of 20 and 50. In May 2000, the Retisert was granted fast-track status by the United States Food and Drug Administration (FDA) and in July 2000 it received Orphan Drug designation from the FDA for posterior uveitis. On April 11, 2005, the FDA approved the single-indication orphan drug Retisert (fluocinolone acetonide intra-vitreous implant) for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

The FDA's approval of Retisert was based on results from two randomized, double-masked, multi-center clinical studies demonstrating that in eyes treated with Retisert there was: (i) a statistically significant decrease in the recurrence of uveitis from approximately 40 - 54% for the 34-week period pre-implantation to approximately 7 - 14% for the 34-week period post-implantation; (ii) a statistically significant decrease in the use of adjunctive therapy including systemic corticosteroid and/or immunosuppressive therapy from approximately 47 - 63% at the time of implantation to approximately 5 - 10% at 34 weeks post-implantation, (iii) a statistically significant decrease in patients needing periocular corticosteroid injections from about 50 - 65% for the 34 week period pre-implantation to approximately 3 - 6% for the 34 week period post-implantation; and (iv) statistically significant improvement of three or more lines of visual acuity in approximately 19 - 21% of treated eyes at 34 weeks post-implantation.

In a randomized controlled trial (n = 32), Jaffe et al (2005) examined the safety and effectiveness of a fluocinolone acetonide intra-vitreous implant in the treatment of patients with a history of recurrent non-infectious posterior uveitis. Patients were randomized to receive either a 0.59-mg or a 2.1-mg fluocinolone acetonide intra-vitreous implant. They were observed every 4 to 6 weeks for the first 3 months and then every 3 months thereafter. Main outcome measures were pre-operative and post-operative ocular inflammation, visual acuity (VA), anti-inflammatory medication use, and safety. Mean follow-up duration was 683 +/- 461 days (range, 204 to 1817). The average number of recurrences in the 12 months before implantation was 2.5 episodes per eye. None of these eyes experienced a recurrence for the first 2 years after implantation. There was a reduction in systemic and local therapy use in the device-implanted eyes. Of the patients who remained on systemic medication after implantation, nearly 70% had a reduced dosage by the 1st year of study, and 85% by 2nd year (reduced dosage is defined as a reduction of dosage and/or a discontinuation of a medication for patients on combination therapy). The posterior sub-Tenon's capsule injection rate significantly decreased from a mean of 2.2 injections per eye per year to 0.07 injections per eye per year ($p < 0.0001$). The most common adverse event was increases in intra-ocular pressure (IOP). At baseline, 11.0% of eyes used pressure-lowering agents, versus 56.1% over the follow-up period ($p = 0.005$). There were no device explantations or patients lost to follow-up during the investigation. These investigators concluded that the fluocinolone acetonide intra-vitreous implant effectively controlled intra-ocular inflammation in the studied population. Elevated IOP and cataracts that occurred in fluocinolone device-implanted eyes were managed by standard means. The fluocinolone acetonide sustained drug delivery implant seems to be promising in patients with

posterior uveitis who do not respond to or are intolerant to conventional treatment.

In a randomized, controlled, phase IIb/III, open-label, multi-center trial, Pavesio et al (2010) assessed the safety and effectiveness of Retisert compared with standard therapy in subjects with non-infectious posterior uveitis (NIPU). Subjects with unilateral or bilateral NIPU (n = 140) received either a 0.59 mg Retisert (n = 66) or standard of care (SOC; n = 74) with either systemic prednisolone or equivalent corticosteroid as monotherapy (greater than or equal to 0.2 mg/kg daily) or, if judged necessary by the investigator, combination therapy with an immunosuppressive agent plus a lower dose of prednisolone or equivalent corticosteroid (greater than or equal to 0.1 mg/kg daily). Main outcome measure was time to first recurrence of uveitis. Eyes that received Retisert experienced delayed onset of observed recurrence of uveitis ($p < 0.01$) and a lower rate of recurrence of uveitis (18.2 % versus 63.5 %; $p < 0.01$) compared with SOC study eyes. Adverse events frequently observed in implanted eyes included elevated IOP requiring IOP-lowering surgery (occurring in 21.2 % of implanted eyes) and cataracts requiring extraction (occurring in 87.8 % of phakic implanted eyes). No treatment-related non-ocular adverse events were observed in the implant group, whereas such events occurred in 25.7 % of subjects in the SOC group. The authors concluded that Retisert provided better control of inflammation in patients with uveitis compared with systemic therapy.

In a retrospective, non-comparative case series, Mahajan et al (2009) examined if the Retisert implant can achieve control of inflammation and a reduced need for oral corticosteroids or immunosuppressives in patients with sympathetic ophthalmia (SO). A total of 8 patients with active SO were included in this study, and were followed-up for a period of 6 months to 2 years. Main outcome measures included presence or absence of intra-ocular inflammation, VA, IOP, need for further surgery, and the need for additional use of oral or locally injected corticosteroids and/or immunosuppressives. All patients demonstrated a significant reduction in the systemic medication needed to maintain control of inflammation. Two patients had recurrent inflammatory episodes requiring the resumption of an oral immunosuppressive. Vision was improved or stabilized in all 8 patients. The authors concluded that the fluocinolone acetonide implant provides inflammatory control and reduces the dependence on systemic immunosuppression in patients with SO. These findings need to be validated by well-designed studies.

Vogt-Koyanagi-Harada (VKH) disease is a multi-system disorder, characterized by the T-cell-mediated autoimmune process directed against melanocytic antigens in the ocular, nervous, auditory and integumentary systems. The ocular hallmarks of the disease involve severe bilateral panuveitis associated with exudative retinal detachment. In an interventional case series study, Khalifa and colleagues (2009) described the use of Retisert in 2 patients with VKH disease requiring high-dose systemic corticosteroid therapy to control their inflammation and bilateral serous retinal detachments. Upon tapering of systemic corticosteroids, 1 patient had recurrent serous retinal detachments and the other patient's anterior chamber and vitreous inflammation returned. The authors concluded that their experience with Retisert in VKH has been mixed with an inability to fully taper off of systemic corticosteroids.

The most common adverse events associated with the implantation of Retisert include eye pain, procedural complications, cataract progression, which is managed by standard cataract surgery,

and IOP, which is managed with the use of IOP-lowering eye drops or filtering surgery. Contraindications for Retisert include viral diseases of the cornea and conjunctiva, ocular mycobacterial and fungal infections of the eye, and hypersensitivity to ingredients or other corticosteroids.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

67027

HCPCS codes covered if selection criteria are met:

J7311 Fluocinolone acetonide, intravitreal implant

ICD-9 codes covered if selection criteria are met:

363.00 - 363.08 Focal chorioretinitis and focal retinochoroiditis

363.10 - 363.15 Disseminated chorioretinitis and disseminated retinochoroiditis

363.20 Chorioretinitis, unspecified

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

360.11 Sympathetic uveitis [sympathetic ophthalmia]

362.07 Diabetic macular edema

362.53 Cystoid macular degeneration

362.83 Retinal edema

363.54 Central choroidal atrophy, total [serpiginous choroiditis]

364.00 Acute and subacute iridocyclitis, unspecified

364.01 Primary iridocyclitis

364.02 Recurrent iridocyclitis

364.03 Secondary iridocyclitis, infectious

364.04 Secondary iridocyclitis, noninfectious

364.10 Chronic iridocyclitis, unspecified

364.11 Chronic iridocyclitis in diseases classified elsewhere

364.21 Fuchs' heterochromic cyclitis

364.23 Lens-induced iridocyclitis

364.24 Vogt-Koyanmagi-Harada disease

364.3 Unspecified iridocyclitis [anterior uveitis]

Other ICD-9 codes related to the CPB:

360.12 Panuveitis

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Conditions Originating in the Perinatal Period

Question: where should ICD-9 760-779 (Conditions originating in the perinatal period) be located?

Question source: HERC staff, DMAP

Issue: The codes in the 760-765 series are mostly located on the 4 dysfunction lines (lines 78,318,375,407). A few reside only on a more disease specific line. The remainder of codes in this series (766-779) appear to generally be on appropriate disease-specific lines. DMAP has received requests for pairing for certain codes in this series and HERC staff found the inappropriate pairings on review and require HERC input on placement.

From Debbie Guillory, OHSU Coder:

This is from the 2013 ICD-9 book Page 17 in the Guidelines:

Codes from categories 760-763, maternal causes of perinatal morbidity and mortality, are assigned only when the maternal condition has actually affected the fetus or newborn. The fact that the mother has an associated medical condition or experiences some complication of pregnancy, labor or delivery does not justify the routine assignment of codes from these categories to the newborn record.

Coding tips in the section include:

A newborn condition is clinically significant when it has implication for the newborn's future health care. Do not assign unless the mother's condition has actually affected the fetus or newborn.

Recommendation:

- 1) Code placement as shown in the following table

ICD-9 Code	Code description	Current line(s)	Recommended Line(s)	Comments
760	Fetus or newborn affected by maternal conditions which may be unrelated to present pregnancy	78: NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS 318: NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 375: NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 407: DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF- DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	2 BIRTH OF INFANT	Some codes in this series are already on line 2
761	Fetus or newborn affected by maternal complication of pregnancy	78, 318, 375, 401	2 BIRTH OF INFANT	
762	Fetus or newborn affected by complications of placenta, cord, and membranes	78, 318, 375, 401	2 BIRTH OF INFANT	
763	Fetus or newborn affected by other complications of labor and delivery	2 BIRTH OF INFANT	2 BIRTH OF INFANT	
764	Slow fetal growth and fetal malnutrition	78, 318, 375, 401	2 BIRTH OF INFANT	656.5 (Poor fetal growth) is on line 1 Pregnancy
765.01- 765.05 765.11- 765.15	Extreme immaturity, under 1,499 grams Other preterm infants, under 1,499 grams	20 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS) 78, 318, 375, 401	20 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS)	

765.00 765.10 765.06- 765.09	Extreme immaturity, unspecified [weight] Other preterm infants, unspecified [weight] Extreme immaturity, 1,500grams-2,500 grams and over	25 LOW BIRTH WEIGHT (1500-2500 GRAMS) 78, 318, 375, 401	25 LOW BIRTH WEIGHT (1500-2500 GRAMS)	
765.2	Weeks of gestation	20 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS) 25 LOW BIRTH WEIGHT (1500-2500 GRAMS) 78, 318, 375, 401	2 BIRTH OF INFANT 20 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS) 25 LOW BIRTH WEIGHT (1500-2500 GRAMS)	Some codes are are line 20, some on line 25. Proposal would have all on both lines

Fluoride Varnish

Question: Should fluoride varnish treatment be added to the prevention line(s)?

Question source: DMAP/HERC staff

Issue: DMAP is requesting that D1206 (Topical application of fluoride varnish) be added to line 3 PREVENTIVE SERVICES, BIRTH TO 10 YEARS OF AGE. It has been the intention of the HERC that fluoride varnish be available for PCPs and/or their staff to apply during well child checks. The procedure code is only currently on line 58 PREVENTIVE DENTAL SERVICES and does not pair with well child visit codes..

HSC history

In May, 2007, the HOSC added fluoride varnish to line 58, but the minutes reflect that the intention was to allow treatment “in PCPs offices.” In December, 2008, the HOSC affirmed that they wished for fluoride varnish to be applied in PCP offices, and directed HSC staff to work with DMAP to ensure that the billing for these services was possible. There was some discussion at the 2008 meeting about limiting the varnish application to children under age 6 (presumably older children would have access to fluoride through the schools). Subsequent discussions with DMAP indicated that the dental plans and DMAP recommended use up to 4 times a year for high-risk children, which Medicaid children are by definition.

Evidence:

1) MED 2009

- a. Evidence based review
- b. Good evidence of effectiveness of fluoride varnish twice per year through age 16

2) American Dental Association 2006

- a. Recommends fluoride varnish through age 18 for moderate and high risk children twice per year

Current DMAP OAR:

410-123-1260(3) Preventative Services:

(b) Topical fluoride treatment:

(A) For adults (19 years of age and older) -- Limited to once every 12 months;

(B) For children (under 19 years of age) – Limited to twice every 12 months;

(C) For children under 7 years of age, topical fluoride varnish may be applied by a medical practitioner during a medical visit

(D) Additional topical fluoride treatments may be available, up to a total of 4 treatments per client within a 12-month period, when high-risk conditions or oral health factors are clearly documented in chart notes for the following clients who:

- (i) Have high-risk oral conditions due to disease process, medications, other medical treatments or conditions, or rampant caries;

- (ii) Are pregnant;
 - (iii) Have physical disabilities and cannot perform adequate, daily oral health care;
 - (iv) Have a developmental disability or other severe cognitive impairment that cannot perform adequate, daily oral health care; or
 - (v) Are under seven year old with high-risk oral health factors, such as poor oral hygiene, deep pits and fissures (grooves) in teeth, severely crowded teeth, poor diet, etc;
- (E) Fluoride limits include any combination of fluoride varnish (D1206) or other topical fluoride (D1208)

Current guideline for line 58 PREVENTIVE DENTAL SERVICES

GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE

Line 58

Dental cleaning and fluoride treatments are limited to once per 12 months for adults and twice per 12 months for children up to age 19 (D1110, D1120, D1203, D1204, D1206). More frequent dental cleanings and/or fluoride treatments may be required for certain higher risk populations. Additionally, assessment (D0191) may be performed once per 12 months for adults and twice per 12 months for children up to age 19.

Recommendation:

- 1) Add D1206 to lines 3 and 4
 - a. Add to line 3 (Preventive services with evidence of effectiveness) for the ICD-10 Prioritized List
- 2) Modify GN17 as shown below
 - a. D1203 and D1204 are no longer valid codes

GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE

Lines 3,4,58

Dental cleaning ~~and fluoride treatments are~~ is limited to once per 12 months for adults and twice per 12 months for children up to age 19 (D1110, D1120, ~~D1203, D1204, D1206~~). More frequent dental cleanings ~~and/or fluoride treatments~~ may be required for certain higher risk populations. Additionally, assessment (D0191) may be performed once per 12 months for adults and twice per 12 months for children up to age 19.

Fluoride varnish (D1206) is included on lines 3 and 4 for use with children 18 and younger during well child preventive care visits. Fluoride treatments (D1206 and D1208) are included on line 58 PREVENTIVE DENTAL SERVICES for use with adults and children during dental visits. The total number of fluoride applications provided in all settings is not to exceed four per twelve months for a child at high risk for dental caries and two per twelve months for a child not at high risk. The number of fluoride treatments is limited to once per 12 months for average risk adults and up to four times per 12 months for high risk adults.

Professionally applied topical fluoride

Evidence-based clinical recommendations

American Dental Association Council on Scientific Affairs

Editor's note: See the summary of these topical fluoride recommendations bound into this issue of JADA after page 1120.

Definition of evidence-based dentistry. The American Dental Association defines the term "evidence-based dentistry" as follows:

Evidence-based dentistry (EBD) is an approach to oral health care that requires the judicious integration of systematic assessments of clinically relevant scientific evidence relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences.

In adopting this definition for EBD, the American Dental Association recognizes that treatment recommendations should be determined for each patient by his or her dentist, and that patient preferences should be considered in all decisions. Dentists' experience and other circumstances, such as patients' characteristics, also should be considered in treatment planning. EBD does not provide a "cookbook" that dentists must follow, nor does it establish a standard of care. Box 1 lists definitions of terms commonly used in

Background. With the dramatic increase in the amount of scientific information available about oral health, an evidence-based approach to oral health care and the practice of dentistry is necessary. There is a need to summarize, critique and disseminate scientific evidence and to translate the evidence into a practical format that is used easily by dentists. The evidence-based clinical recommendations in this report were developed by an expert panel established by the American Dental Association Council on Scientific Affairs that evaluated the collective body of scientific evidence on the effectiveness of professionally applied topical fluoride for caries prevention. The recommendations are intended to assist dentists in clinical decision making.

Types of Studies Reviewed. MEDLINE and the Cochrane Library were searched for systematic reviews and clinical studies of professionally applied topical fluoride—including gel, foam and varnish—through October 2005.

Results. Panelists were selected on the basis of their expertise in the relevant subject matter. The recommendations are stratified by age groups and caries risk and indicate that periodic fluoride treatments should be considered for both children and adults who are at moderate or high risk of developing caries. Included in the clinical recommendations is a summary table that can be used as a chairside resource.

Clinical Implications. The dentist, knowing the patient's health history and vulnerability to oral disease, is in the best position to make treatment decisions in the interest of each patient. These clinical recommendations must be balanced with the practitioner's professional expertise and the individual patient's preferences.

Key Words. Fluoride; caries; caries prevention; evidence-based dentistry; clinical recommendations.

JADA 2006;137(8):1151-9.

Address reprint requests to the American Dental Association Council on Scientific Affairs, 211 E. Chicago Ave., Chicago, Ill. 60611.

Issue: Should there be coverage for annual MRI in patients with established diagnosis of Multiple Sclerosis?

Question Source: OHP Medical Director

Question: Local practice is to require annual MRI for monitoring, but is this supported by evidence?

Background: MS is largely a clinical diagnosis, and while imaging is utilized to make the initial diagnosis, clinical and functional outcomes are more important later, even during relapse. Currently, most MS patients receive yearly MRIs to monitor status; however, there is a question of whether this monitoring affects outcomes or changes disease management.

Current Prioritized List Status

MRI CPT codes are in the Diagnostic List

70551 MRI, brain without contrast

72141 MRI, cervical spine without contrast

72146 MRI, thoracic spine without contrast

72148 MRI, lumbar spine without contrast

Line 268 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM

Evidence Summary: There is no quality evidence that recommends monitoring at specific intervals after initial diagnosis. The outcomes measured in published research related to treatment effectiveness are all measurements of symptoms or function, and not imaging related.

- 1) **NICE Clinical Guideline 2003** (update expected in 2014)
 - a. “further neurological investigation should not be undertaken unless the diagnosis of MS itself is in doubt”
- 2) **NICE 2004 Full Guidance**
 - a. Although difficult to draw conclusions from these results given the large variation, it would appear that MRI is a reasonable although not excellent investigation when making the diagnosis of MS
 - b. The utility of MRI scans in clinical practice (as opposed to as part of research) is still not supported by much evidence, although major resources are involved in their use.
 - c. Research question: “Should second or subsequent MRI scans ever be undertaken?”
 - d. A review of evidence suggested that MRI has had little direct impact on therapeutics or patient outcomes (Kent, 1994).

MRI in Multiple Sclerosis

- e. From the research point of view there appears to be much interest in MRI results as a potentially more objective outcome measure than EDSS in measuring disease progression. However, it is not clear how MRI results can be translated into patient-based outcomes (like quality of life) and evidence on the relationship between MRI and clinical progression is not conclusive.

3) European Federation of Neurological Societies Summary of Guidelines in MS 2011

- a. Initial MRI should be conducted as part of the diagnosis of MS (Level A recommendation)
- b. Follow up MRIs are required to demonstrate disease dissemination in time (Level B recommendation)
- c. Repeat scanning beyond the two initial studies (to establish diagnosis and dissemination in time or space) need to be considered by the neurologist individually according to the clinical circumstances that are appropriate for each patient and is not routinely recommended as the disease becomes more likely to manifest clinically in the longer term
- d. Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g., mechanical compression) or atypical symptoms develop

2) American Academy of Neurology

- a. Guideline only for initial MRI for diagnosis, and doesn't discuss monitoring.

Summary: If the diagnosis is not in question, there is no role for repeat imaging because the management of multiple sclerosis relies on clinical symptoms and function.

HERC Staff Recommendations

- 1) Adopt a new diagnostic guideline as presented below

DIAGNOSTIC GUIDELINE DX: MRI IN MULTIPLE SCLEROSIS

MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.

*National Institute for
Clinical Excellence*

Multiple sclerosis

**Management of multiple sclerosis
in primary and secondary care**

Clinical Guideline 8

November 2003

Developed by the National Collaborating
Centre for Chronic Conditions

Clinical Guideline 8

Multiple sclerosis

Management of multiple sclerosis in primary and secondary care

Issue date: November 2003

To order copies

Copies of this guideline can be ordered from the NHS Response Line; telephone 0870 1555 455 and quote reference number N0366. A version for people who want to understand what NICE has told the NHS, called *Multiple sclerosis: Understanding NICE Guidance – Information for People with Multiple Sclerosis, Their Families and Carers, and the Public*, is also available from the Response Line; quote reference number N0367 for an English only version and N0368 for an English and Welsh version.

This document has been circulated to the following:

- Primary care trust (PCT) chief executives
- Local health board (LHB) chief executives
- NHS trust chief executives in England and Wales
- Strategic health authority chief executives in England and Wales
- Medical and nursing directors in England and Wales
- Clinical governance leads in England and Wales
- Audit leads in England and Wales
- NHS trust, PCT and LHB libraries in England and Wales
- Patient advice and liaison co-ordinators in England
- Consultant neurologists in England and Wales
- Consultants in rehabilitation medicine in England and Wales
- Directorate nurse managers for physiotherapy, occupational therapy, rehabilitation in England and Wales
- Heads of physiotherapy in England and Wales
- GPs in England and Wales
- Practice nurses in England and Wales
- NHS Director Wales
- Chief Executive of the NHS in England
- Chief Medical, Nursing and Pharmaceutical Officers in England and Wales
- Medical Director & Head of NHS Quality – Welsh Assembly Government
- Commission for Health Improvement
- NHS Clinical Governance Support Team
- Patient advocacy groups
- Representative bodies for health services, professional organisations and statutory bodies, and the Royal Colleges

This guidance is written in the following context:

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Health professionals are expected to take it fully into account when exercising their clinical judgment. The guidance does not, however, override the individual responsibility of health professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Multiple sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system (brain and spinal cord). The disease process is one of episodes where white matter within the brain or spinal cord becomes inflamed and then destroyed by the person's own immune system. These inflamed areas become scarred, giving the disease its name: **multiple** areas of hardening (**sclerosis**) within the brain or spinal cord. Many of these episodes do not cause any symptoms, but when sudden symptoms occur the person is said to have had a relapse.

MS usually starts in early adult life. Once present the disease never goes; there is no cure and the person lives with the diagnosis for life. For many people with MS, the disease causes little trouble, but for others it causes problems that can affect all aspects of their own life and that of their family.

There are recognised ways of describing different patterns of MS.

- **Relapsing/remitting MS** – symptoms come and go. Periods of good health or remission are followed by sudden symptoms or relapses (80% of people at onset).
- **Secondary progressive MS** – follows on from relapsing/remitting MS. There are gradually more or worsening symptoms with fewer remissions (about 50% of those with relapsing/remitting MS develop secondary progressive MS during the first 10 years of their illness).
- **Primary progressive MS** – from the beginning, symptoms gradually develop and worsen over time (10–15% of people at onset).

Between three and seven people per 100,000 population are diagnosed with MS each year and about 100 to 120 people per 100,000 population have MS. From these rates it is estimated that in England and Wales about 1800 to 3400 people are newly diagnosed with MS each year and that 52,000 to 62,000 people have MS.

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Specialised services

- 1 Specialist neurological and neurological rehabilitation services should be available to every person with MS, when they need them. This is usually when they develop any new symptom, sign, limitation on activities, or other problem, or when their circumstances change.

Rapid diagnosis

- 2 An individual who is suspected of having multiple sclerosis should be referred to a specialist neurology service, and seen rapidly within an audited time. The individual should be seen again after all investigations necessary to confirm or refute the diagnosis have been completed (also rapidly within an audited time). *

Seamless services

- 3 Every health commissioning organisation should ensure that all organisations in a local health area agree and publish protocols for sharing and transferring responsibility for and information about people with MS, so as to make the service seamless from the individual's perspective.

A responsive service

- 4 All services and service personnel within the healthcare sector should recognise – and respond to – the varying and unique needs and expectations of each person with MS. The person with MS should be involved actively in all decisions and actions.

Sensitive but thorough problem assessment

- 5 Health service professionals in regular contact with people with MS should consider in a systematic way whether the person with MS has a 'hidden' problem contributing to their clinical situation, such as fatigue, depression, cognitive impairment, impaired sexual function or reduced bladder control.

Self-referral after discharge

- 6 Every person with MS who has been seen by a specialist neurological or neurological rehabilitation service should be informed about how to make contact with the service when he or she is no longer under regular treatment or review. The individual should be given guidance on when such contact is appropriate.

* The Guideline Development Group debated the meaning of the word 'rapidly'. In this context, it is taken to mean that the exact time will vary according to clinical need but should be, in the opinion of the development group, no longer than 6 weeks from referral to being seen by a neurologist, and a further 6 weeks until any necessary investigations are completed.

The following guidance is evidence based. The grading scheme used for the recommendations (A, B, C, D, DS, HSC) is described in Appendix A; a summary of the evidence on which the guidance is based is provided in the full guideline (see Section 5).

1 Guidance

1.1 General principles

1.1.1 Communication

1.1.1.1 All communication with all people with MS should comply with the general principles of good communication, shown in Appendix E, Table 1.

D

1.1.1.2 Some people with MS may not be able to follow everything fully or remember complex details. This includes people who have no obvious disability. So, when talking to the person with MS, the healthcare professional should:

D

- be straightforward
- check the person has understood
- back up what was said with written (and other) material
- reinforce as necessary.

1.1.2 Emotional support

1.1.2.1 A person with MS may benefit from emotional support; this should be considered by each individual and team in contact with the individual. Where possible, that emotional need should be met directly or through referral to a suitable resource.

D

1.1.3 Encouraging autonomy/self-management

1.1.3.1 People with MS should be enabled to play an active part in making informed decisions in all aspects of their MS healthcare by being given relevant and accurate information about each choice and decision.

D

1.1.3.2 As far as possible, people with MS should be helped to manage their own general health through the following.

D

- Information and advice provided in written, audio or other media on:
 - specific activities that promote health maintenance and prevent complications
 - changes in their health that may require them to take further action
 - the condition and its management (including both local and sources of further information and support in clear and accessible language).

This function could be fulfilled by working in conjunction with local voluntary organisations.

- And, through acquiring the skills needed to:
 - seek, evaluate and use advice and help available
 - communicate effectively with healthcare professionals (for example, through participation in the Expert Patient Programme).

1.1.4 Support to family and carers

1.1.4.1 Family members (including any schoolchildren) living in the same house as the person with MS, and any family members delivering substantial support even if living elsewhere, should be supported by:

D

- asking about their physical and emotional health and well-being, especially in the case of children aged 16 years or less, and offering advice and referring on for additional support if necessary
- providing them with general factual information about MS; this should only be extended to include more specific information related to the person with MS with the permission of that person
- ensuring that they are willing to undertake support of personal activities of daily living (such as dressing and toileting), are safe and competent at such tasks, and that the person with MS is happy for them to provide such assistance
- informing them about social services carer assessment and support procedures.

1.1.5 Assessment and measurement

1.1.5.1	The review checklist shown in Appendix E, Table 2 should be used each time a person with MS starts a new 'episode of care' (including initial diagnosis), and whether or not the presenting issues relate to the MS. The healthcare professional should:	D
	• record the information for future comparison • refer to the specific recommendations made in this document if any problem is identified.	
1.1.5.2	Healthcare staff who frequently undertake MS-specific assessments or treatments should:	D
	• be familiar with simple methods for detecting impairment and limitations on activities • be trained in their use and interpretation (if used).	
1.1.5.3	All healthcare staff within a local health community should use the same simple methods for common assessments.	D
1.1.5.4	When initially assessing an individual, and when undertaking any treatment, healthcare staff should consider the characteristics of a measure (see resource pack on the NICE website: www.nice.org.uk) recognising that:	D
	• formally evaluated measures may not exist or be practical • personalised measures should be considered, including comparing the outcome against goals agreed (goal attainment scaling).	
1.1.5.5	Before embarking on any course of treatment, the healthcare professional should be satisfied that the individual fully understands the implications of the treatment, and is able to participate in it as necessary.	D

Further guidance may be found at the Department of Health consent website (www.doh.gov.uk/consent/index.htm).

1.2 Teamwork

1.2.1 Teams and goal setting

1.2.1.1 When several healthcare and other professionals are involved with a person with MS, they should work together with the person and his or her family, as a team:

D

- towards common agreed goals
- using an agreed common therapeutic approach.

1.2.1.2 The goals set should:

D

- be agreed as relevant and important by the person with MS
- cover both short-term specific actions and longer-term outcomes
- be challenging or ambitious but achievable
- be set both at the level of individuals and at the level of the team as a whole
- be formulated in such a way as to leave no doubt as to when they have been met.

1.2.1.3 Goal attainment scaling should be considered as one way of setting goals and evaluating progress.

D

1.2.2 Specialist services

1.2.2.1 Every healthcare commissioning authority should ensure that all people with MS have ready access to a specialist neurological service for:

D

- diagnosis of MS initially, and of subsequent symptoms as necessary
- provision of specific pharmacological treatments, especially disease-modifying drugs, and enacting the risk-sharing scheme for interferon beta and glatiramer acetate.

1.2.2.2 The healthcare commissioning authority should also ensure that its population has ready access to a specialist neurological rehabilitation service. This should be available to all people with MS when the presenting problem is outside the competence of the first point of contact, for:

D

- undertaking assessment (that is, diagnosis) when the person has complex problems
- undertaking specific pharmacological or other therapies
- providing an integrated programme of rehabilitation when the person has complex problems
- monitoring change, especially when the person with MS has more severe impairments or limitations on activities
- giving advice to other services.

1.2.2.3 As a minimum, the specialist neurological rehabilitation service should have as integral members of its team, specialist:

D

- doctors
- nurses
- physiotherapists
- occupational therapists
- speech and language therapists
- clinical psychologists
- social workers.

The team should either have as team members, or through agreed mechanisms, ready access to other local relevant specialist services with expertise in treating neurologically disabled people, to cover:

D

- dietetics
- liaison psychiatry
- continence advisory and management services
- pain management services

- chiropody and podiatry
- ophthalmology services.

D

1.2.3 Working across organisations

1.2.3.1 All parts of the healthcare system, social services and other statutory services should have agreed protocols that specify:

D

- how responsibility for people with MS is shared with other groups or organisations
- what agreed descriptive information (that is, a common dataset) about the person with MS should always be shared
- the point of contact within any service or organisation, and how contact should be made.

1.2.3.2 People with MS should be able to identify and contact:

D

- a named person in their health area who is responsible for all NHS services for local people with MS (including co-ordination and collaboration with other statutory services)
- a named person in their health area with clinical expertise who is able to respond to any inquiry on clinical problems (and to guide the person to the most appropriate local service)
- a named person within any healthcare team with whom they are involved.

1.2.4 Timing of actions

To be useful (that is, to be effective and efficient) it is important that any intervention is timely.

1.2.4.1 Any action recommended within these guidelines should be undertaken within a time that takes into account:

D

- risk of direct harm associated with any delay
- distress or discomfort being experienced or likely to occur
- risk of secondary complications associated with delay

- risk of harm to others (for example, carers) associated with delay
- any nationally recommended targets for timing
- action being taken by any other person or service.

D

1.2.5 Within team communication – a conceptual framework

- 1.2.5.1 All individual clinicians, professional groups and organisations involved in the care of those with MS should use the World Health Organization's International Classification of Functioning (WHO ICF) model of illness, and its vocabulary.

D

1.2.6 Support over time

- 1.2.6.1 Services should cater for the varying needs of people with MS over time, by:

D

- responding in a timely and flexible way to the intermittent acute needs of people with MS, especially in the early phases
- identifying and reducing the risks of complications that might develop in the individual
- making fully available, to people with MS, population-based programmes of health promotion and/or disease prevention (such as screening for cervical carcinoma), specifically taking into account an individual's possible impairments and activity limitations.

- 1.2.6.2 When any 'episode of care' (medical or rehabilitation treatment programme) ends (that is, when no further benefit is anticipated), the healthcare team should:

D

- ensure that any necessary long-term support needs are met
- ensure that the person with MS knows who to contact and how to contact them, in the event that the person with MS experiences a change in his/her situation
- discuss with the person with MS whether they want a regular review of their situation and, if so, agree on a suitable and reasonable interval and method of review (for example, by phone or post or as an outpatient).

1.2.6.3	Health services should ensure that there are mechanisms to allow good communication between health and social services at all times.	D
1.2.6.4	Individuals who are severely impaired and markedly dependent should have their support needs reviewed at least yearly, and they should have these needs met as necessary and in accordance with their wishes, through one or more of the following: • additional support in the home • respite care in the home • respite care in another age-appropriate setting • moving into a residential or nursing home.	D

1.3 Diagnosis

1.3.1 Involving the individual in the diagnostic process

1.3.1.1	An individual should be informed of the potential diagnosis of MS, as soon as a diagnosis of MS is considered reasonably likely (unless there are overwhelming patient-centred reasons for not doing so). This should occur before undertaking further investigations to confirm or refute the diagnosis.	C
1.3.1.2	Throughout the process of investigating and making the diagnosis of MS, the healthcare professional should: • find out what and how much information the individual wants to receive. (This should be reviewed on each occasion.) • discuss the nature and purpose of all investigations, especially the likely outcomes and their implications for the individual.	C
1.3.1.3	If a diagnosis of MS is confirmed, the individual should be told by a doctor with specialist knowledge about MS. (This is usually a consultant or experienced specialist registrar.) See also the recommendations for good communication (Appendix E, Table 1).	C

1.3.1.4 After the diagnosis has been explained, the individual should be:

- offered in the near future* at least one more appointment to see wherever possible the doctor who gave the original diagnosis D
- put in touch with, or introduced to, a skilled nurse or other support worker, ideally with specialist knowledge of MS and/or other neurological conditions and counselling experience D
- offered written information about local and national disease-specific support organisations including details of local rehabilitation services C
D
- offered information about the disease, preferably in the form of an information pack, specific to the newly diagnosed. A

1.3.1.5 Within 6 months of diagnosis, the individual should be offered the opportunity to participate in an educational programme to cover all aspects of MS.

B

1.3.2 Making the diagnosis of MS

There is no single specific diagnostic test available, but in practice, the diagnosis can be made clinically in most people.

1.3.2.1 When an individual presents with a first episode of neurological symptoms or signs suggestive of demyelination (and there is no reasonable alternative diagnosis), a diagnosis of MS should be considered.

D

1.3.2.2 When an individual presents with a second or subsequent set of neurological symptoms, which are potentially attributable to inflammatory or demyelinating lesions in the central nervous system (and again, there is no reasonable alternative diagnosis), the individual should be referred to an appropriate expert for investigation.

D

* The Guideline Development Group debated the meaning of the words "in the near future". In this context, it is taken to mean that the exact time will vary according to clinical need but should be, in the opinion of the development group, no longer than 4 weeks.

1.3.2.3	A diagnosis of MS should be made clinically:	D
	• by a doctor with specialist neurological experience • on the basis of evidence of CNS lesions scattered in space and time • primarily on the basis of the history and examination.	
1.3.2.4	When doubt about the diagnosis remains, further investigation should:	D
	• exclude an alternative diagnosis, or • find evidence that supports the potential diagnosis of MS. – Dissemination in space should usually be confirmed, if necessary, using a magnetic resonance imaging (MRI) scan, interpreted by a neuro-radiologist if possible, using agreed criteria such as those described by McDonald and colleagues*. – Dissemination in space may also be confirmed using evoked potential studies. Visual evoked potential studies should be the first choice. – Dissemination in time should be confirmed clinically, or using the MRI criteria described by McDonald and colleagues*.	
1.3.2.5	Other tests supportive of the diagnosis of MS, such as analysis of the cerebrospinal fluid (CSF), should only be used either when the investigation is being undertaken to exclude alternative diagnosis or when the situation is still clinically uncertain.	D
1.3.2.6	The diagnosis of MS is clinical and an MRI scan should not be used in isolation to make the diagnosis.	DS
1.3.2.7	A computed tomography (CT) brain scan should only be used to exclude alternative diagnoses that can be diagnosed using that investigation.	DS
1.3.2.8	Any CSF samples taken from individuals who might have MS should be tested for the presence of oligoclonal bands and should be compared with serum samples.	DS
1.3.2.9	The evidence supporting the diagnosis and its degree of certainty should always be documented formally in the medical notes and letters discussing the diagnosis. This allows the diagnosis to be critically reviewed and reinvestigated if necessary.	D

* McDonald et al. (2001) Recommended diagnostic criteria for MS. *Annals of Neurology*; 50: 121–7

1.3.3 Diagnosis of an acute episode

General diagnosis

- 1.3.3.1 If a person with MS has a relatively sudden (within 12–48 hours) increase in neurological symptoms or disability, or develops new neurological symptoms, a formal assessment should be made to determine the diagnosis (that is, the reason for the change). This should be recorded clearly. D
- 1.3.3.2 This diagnostic assessment should: D
- be undertaken within a time appropriate to the clinical presentation
 - consider the presence of an acute infective cause
 - involve a GP or acute medical/neurological services.
- 1.3.3.3 Further neurological investigation should not be undertaken unless the diagnosis of MS itself is in doubt. D

Diagnosis of optic neuritis

Acute, sometimes painful, reduction or loss of vision in one eye, optic neuritis, is a relatively common presenting symptom of MS.

- 1.3.3.4 Every individual presenting with an acute decline in visual acuity, with or without associated pain, should be seen by an ophthalmologist for diagnosis. D
- 1.3.3.5 If the diagnosis is confirmed as optic neuritis, without any other specific cause and possibly due to MS, the ophthalmologist should discuss the potential diagnosis with the individual (unless there are overwhelming patient-centred reasons for not doing so). A further referral to a neurologist for additional assessment should be offered. D

Diagnosis of transverse myelitis

An acute episode of weakness or paralysis of both legs, with sensory loss and loss of control of bowels and bladder, is an emergency that may be due to transverse myelitis, and it may be a symptom of MS.

- 1.3.3.6 Every person presenting with symptoms and signs of acute spinal cord dysfunction should be investigated urgently, especially to exclude a surgically treatable compressive lesion. D

- 1.3.3.7 If a diagnosis of transverse myelitis is made (and there is no previous history of neurological dysfunction), the individual should be informed that one of the possible causes is MS.

D

1.4 Treatment

1.4.1 Treatment of acute episodes

Acute episodes of neurological symptoms are thought to arise from a process whereby the cerebral white matter becomes inflamed as the individual's own immune system starts to damage the myelin sheaths of the nerves (part of the white matter). Treatment recommendations are independent of whether the symptoms arise from a first presentation or a subsequent relapse.

- 1.4.1.1 Any individual who experiences an acute episode (including optic neuritis) sufficient to cause distressing symptoms or an increased limitation on activities should be offered a course of high-dose corticosteroids. The course should be started as soon as possible after onset of the relapse and should be **either**:

A

- intravenous methylprednisolone, 500 mg–1 g daily, for between 3 and 5 days

or

- high-dose oral methylprednisolone, 500 mg–2 g daily, for between 3 and 5 days.

- 1.4.1.2 An individual should be given a clear explanation of the risks and benefits involved in taking corticosteroids.

D

- 1.4.1.3 Frequent (more than three times a year) or prolonged (longer than 3 weeks) use of corticosteroids should be avoided.

D

- 1.4.1.4 Other medicines for the treatment of an acute relapse should not be used unless as part of a formal research protocol.

D

1.4.2 Rehabilitation for an acute episode

- 1.4.2.1 When a person with MS experiences a sudden increase in disability or dependence the individual should be:

- given support, as required and as soon as practical, both in terms of equipment and personal care

D

- referred to a specialist neurological rehabilitation service. The urgency of the referral should be judged at the time, and this referral should be in parallel with any other medical treatment required.

A

1.4.3 Interventions affecting disease progression

- 1.4.3.1 People with relapsing-remitting MS, and those with secondary progressive MS in which relapses are the dominant clinical feature, who meet the criteria developed by the Association of British Neurologists are eligible for treatment under the risk-sharing scheme. See Health Service Circular 2002/004 (www.doh.gov.uk/pricare/drugsmultiplesclerosis.htm) and Appendix E, Table 3 (page 61).

HSC

- 1.4.3.2 People with MS should be advised that linoleic acid 17–23 g/day may reduce progression of disability.

A

Rich sources of linoleic acid include sunflower, corn, soya and safflower oils.

- 1.4.3.3 The following treatments should not be used except in specific circumstances, detailed below.

Circumstances :

- after full discussion and consideration of all the risks
- with formal evaluation, preferably in a randomised or other prospective study
- by an expert in the use of these medicines in MS

D

with close monitoring for adverse events.

Treatments:

- azathioprine
- mitoxantrone
- intravenous immunoglobulin
- plasma exchange
- intermittent (4-monthly) short (1–9 days) courses of high-dose methylprednisolone.

A

1.4.3.4 The following treatments should not be used (because research evidence does not show beneficial effects on the course of the condition):

A

- cyclophosphamide
- anti-viral (for example, aciclovir, tuberculin)
- cladribine
- long-term treatment with corticosteroids
- hyperbaric oxygen
- linomide
- whole-body irradiation
- myelin basic protein (any type).

1.5 Altering the risk of relapses

1.5.1 Infections and immunisations

Infections may be associated with a worsening of disability, most often through indirect mechanisms such as an increased temperature. In some cases, infection may trigger a relapse.

1.5.1.1 People with MS should be offered immunisation against influenza.

C

1.5.1.2 People with MS should have any other immunisation they need, with advice that there is no known risk of causing a relapse of their MS.

C

1.5.2 Pregnancy

There is no evidence that pregnancy influences the overall course of the condition over time.

1.5.2.1 Women with MS who wish to become pregnant should be advised that the risk of relapse decreases during pregnancy, and increases transiently postpartum.

C

1.5.2.2 When giving birth, women with MS should have the analgesia that seems most appropriate and acceptable to them, without fear of its affecting their MS.

C

1.5.3 Stress (various types)

Putative stresses include emotional stress, trauma, and stresses caused by medical intervention. In the absence of conclusive evidence, it has only been possible to make a recommendation on stress relative to surgery.

- 1.5.3.1 People with MS should be encouraged to have any surgery they need, using whichever anaesthetic technique is appropriate. They should be informed that there is no known increase in the risk of relapse.

B

1.6 Rehabilitation and maintenance of functional activities and social participation

This section focuses on the ways in which health services can help people with MS to maximise their level of functional activities (that is, minimise disability and dependence) and help them maintain social roles. The general items addressed in this section should be looked at in conjunction with the specific recommendations given in Section 1.5.

1.6.1 General points

- 1.6.1.1 If a person with MS starts to experience a new limitation on his or her activities, the cause should be identified medically, and the following considered:

- is it due to an unrelated disease?
- is it due to an incidental infection?
- is it due to a relapse of the MS?
- is it part of a gradual progression?

D

- 1.6.1.2 If the limitation persists, despite treatment of any identified cause, the person with MS should be seen and assessed by a multidisciplinary service, specialised in neurologically based disability.

D

This service should implement a rehabilitation programme.

A

- 1.6.1.3 The components of the rehabilitation programme should include the following.

- Establishing the wishes and expectations of the person with MS.

D

- Assessing and, if necessary, measuring relevant factors, in order to identify and agree goals with the person; these might include one or more of the following:
 - identifying and treating any treatable underlying impairments
 - giving task-related practice of a specific activity or activities
 - providing suitable equipment (with training in its use)
 - altering the environment as needed
 - teaching others how to assist with (or take over) tasks.
- Monitoring progress against set goals; the goals should be reviewed and reset, until no further goals exist and no further interventions are needed.

D

- 1.6.1.4 Where possible, both assessment and task-related practice should take place in the environment most appropriate to the task (for example, home, work or leisure).

D

1.6.2 Vocational activities – employment and education

- 1.6.2.1 Any person with MS who is in work or education should be asked specifically whether they have any problems, for example motor, fatigue or cognitive difficulties.
- 1.6.2.2 Any individual who has problems that affect their work or education should be seen for further assessment of their difficulties, preferably by a specialist vocational rehabilitation service, or specialist neuro-rehabilitation service.
- 1.6.2.3 The results of the assessment should be used:
- to advise the person with MS on strategies, equipment, adaptations and services available to assist with vocational difficulties; and/or
 - to advise the employer or others, with permission from the person with MS, on strategies, equipment and adaptations to assist; and/or
 - to give information to the disability employment advisor, if involved (see recommendation 1.6.2.4).
- 1.6.2.4 The person should always be informed about available vocational support services (currently including Disability Employment Advisers and the Access to Work Scheme), and that there may be adjustments at work to which they are entitled under the Disability Discrimination Act.

D

D

D

D

- 1.6.2.5 Any individual who cannot stay in or find alternative employment should be advised about other options such as voluntary work and where to find information about these options.

D

1.6.3 Leisure and social interaction

- 1.6.3.1 Any person with MS whose participation in or enjoyment of a leisure or social activity becomes limited should be referred to a specialist neurological rehabilitation service which should:

D

- identify whether previous activities are still achievable and, if not, help the person consider new activities
- assess for, and then teach, the skills and techniques that could help achieve these activities
- if necessary refer the person to local services that might help them establish and continue leisure and social activities.

1.6.4 Mobility

- 1.6.4.1 Any person with MS who experiences reduced mobility (and it affects or threatens his or her activities) should be seen and assessed by a specialist neurological rehabilitation service. The assessment should determine which interventions are needed:

D

- identification and treatment of any underlying impairment, especially weakness, fatigue, spasticity, ataxia, sensory loss and loss of confidence
- task-related practice of a specific mobility activity or activities (for example, walking, transferring, using a wheelchair, climbing stairs)
- provision of suitable equipment, including wheelchairs, driving equipment and adaptive technology (with training in its use)
- alteration of the environment to increase independent mobility
- teaching others how to safely assist with (or take over) tasks such as walking, climbing stairs, moving in bed or transferring.

1.6.4.2 Physiotherapy treatments aimed at improving walking should be:

A

- offered to a person with MS who is, or could be, walking
- given at home or on an outpatient basis, depending on the preference of the person with MS and local resources.

1.6.5 Activities of daily living

Activities of daily living are usually divided into personal, domestic and community activities.

1.6.5.1 Any person with MS who experiences a limitation in personal, domestic or community activities should receive a comprehensive multidisciplinary assessment. This should be carried out by a team experienced in the treatment and management of MS, and should cover the person's previous and current functioning in the following areas:

D

- personal activities such as dressing, eating, using the toilet and washing
- domestic activities such as cooking, washing and ironing clothes, keeping the house clean and dealing with household bills
- community activities such as shopping, using public transport, negotiating the environment safely (for example, avoiding traffic) and accessing other public amenities
- any caring or support activities within the home, including caring for children.

1.6.5.2 A comprehensive assessment of this type should:

D

- actively involve the person with MS, encouraging them to think about and define what they need to continue to achieve their goals and aspirations
- take place on more than one occasion and in different environments
- take into account the individual's priorities, interests, goals and potential

- consider environmental factors, and the support available from family and carers
 - take into account both current and future needs.
- 1.6.5.3 After the assessment, a programme of interventions should be developed for the person with MS, with the aim of increasing and maintaining independence wherever possible. The programme of interventions should be agreed by the individual. The interventions specified should be goal-directed, and designed to meet the individual's priorities, interests and potential.
- 1.6.5.4 If the individual agrees, the programme of interventions should be shared with social services, and this must occur if social services are to be responsible for maintenance interventions.
- 1.6.5.5 There should be regular monitoring to check how effective the interventions are, with a view to changing them if necessary.
- 1.6.5.6 At the end of the planned programme, the person should know how to obtain a re-assessment if their situation changes.

1.6.6 Equipment, adaptations and personal support

- 1.6.6.1 Every person with MS whose activities are persistently affected should be assessed by a specialist neurological rehabilitation service to determine how their environment might be improved, enabling for example:
- an increase in the person's independence
 - the impact on their activities to be minimised
 - a reduction in risk to the person or their carers.
- The environmental changes considered should include the following:
- provision of (or changes in) equipment
 - alterations in the structure of the building
 - provision of (or change in) the personal support provided.

Equipment and adaptations

1.6.6.2	If a person with MS depends on someone else for an activity (especially in mobility), an expert should assess whether an aid or adaptation, including an environmental control system, could be of benefit. For example, it may increase the independence of the person with MS, and/or minimise the stress on, or risk for, the person who assists them. The person with MS or, if necessary, their family and/or carers, should be taught how to use the equipment. Ability and safety in using the equipment should be checked at least once, after a suitable interval.	D
1.6.6.3	The service providing or recommending the equipment should ensure the equipment's continuing appropriateness and safety, at appropriate intervals.	D

Personal support

1.6.6.4	If a person with MS receives support or supervision from someone, for any particular activity, an assessment should be made to determine whether a greater level of independence could be achieved.	D
1.6.6.5	If personal support is provided by family, friends or paid carers, an expert should offer knowledge and skills to help the carer(s) provide assistance in ways that maintain the dignity and utmost independence of the person with MS, while also not threatening the health or well-being of the carers.	D
1.6.6.6	If support is given on a daily basis for more than 1 hour, then the level and appropriateness of the support offered should be monitored, at a minimum, on a yearly basis. It should also be reviewed after any significant medical event (for example, infection, relapse, complication, departure of family member). Any person involved in hands-on activities, especially physical moving and handling, should be taught appropriate safe techniques for the individual situation, and should be able to seek further tuition or advice when they need it.	D

1.7 Managing specific impairments

The range of potential symptoms is vast; only the more common ones are covered in these guidelines. In most people there will be several if not many symptoms, and although this section is subdivided by symptom, in practice the overall situation of the individual must always be borne in mind before acting. Thus for each impairment there is an unwritten first recommendation – do not start or modify treatment until all aspects of the individual's clinical situation have been established and understood, and the wishes and expectations of the person with MS have been established.

1.7.1 Fatigue

- 1.7.1.1 Each professional in contact with a person with MS should consider whether fatigue is a significant problem or a contributing factor to their current clinical state.

D

If fatigue is disrupting the individual's life, then the following recommendations apply.

- 1.7.1.2 The presence of significant depression should be considered; if significant depression is present, it should be treated.

D

- 1.7.1.3 Other factors causing fatigue, such as disturbed sleep, chronic pain and poor nutrition, should be identified and treated if possible.

D

- 1.7.1.4 Some medicines may exaggerate fatigue, thus any medication being taken should be reviewed.

D

- 1.7.1.5 General advice and training on how to manage fatigue should be given, including encouragement to undertake aerobic exercise and to use energy-conservation techniques.

D

- 1.7.1.6 At present, no medicines targeted at fatigue should be used routinely, although people with fatigue should be informed that a small clinical benefit might be gained from taking amantadine 200 mg daily.

D

A

1.7.2 Bladder problems

Bladder dysfunction

1.7.2.1	Each professional in contact with a person with MS should consider whether the person has any problems controlling bladder function. Problems may include frequency or urgency of micturition, sleep disturbance from nocturia (awaking with need to empty bladder), difficulty in passing urine or incontinence of urine.	D
1.7.2.2	Any person with MS who has bladder symptoms should: • have their post-micturition residual bladder volume measured using a simple measure such as ultra-sonography of the bladder • be assessed for the presence of a urinary tract infection clinically and, if necessary, using an appropriate dipstick for nitrites and leucocyte esterase. Treatment should be provided, if necessary. (See also Section 1.7.3.)	D
1.7.2.3	Urgency or urge incontinence sufficient to be bothersome or cause incontinence should be treated in the first instance using: • advice on changes to clothing and/or toilet arrangements (for example, provision of a commode downstairs) • intermittent self-catheterisation if there is a high residual volume, and the person is able and willing • anticholinergic medicines such as: – oxybutynin or – tolterodine • checking for an increased post-voiding residual volume if symptoms recur.	D
1.7.2.4	Any person who has nocturia should be offered desmopressin (100–400 µg orally or 10–40 µg intranasally) at night, to control the symptom.	A
1.7.2.5	Any person who wishes to control urinary frequency during the day (for example, when travelling), and who has failed with other measures, should be offered desmopressin (100–400 µg orally or 10–40 µg intranasally), but desmopressin should never be used more than once in 24 hours.	A

- 1.7.2.6 Any person with MS who, despite treatment, has incontinence more than once a week should:
- be referred to a specialist continence service for further assessment and advice **D**
 - be considered for a course of pelvic floor exercises preceded by a course of electrical stimulation of the pelvic floor muscles (if such a course is available). **A**
B
- 1.7.2.7 Any person with MS who experiences persistent incontinence should be offered a convene drain (for men) or pads (for women). **D**
- 1.7.2.8 Any person who has continued bladder symptoms despite pharmacological and other treatments should be considered:
- for intermittent self-catheterisation taught by a suitably trained specialist, or
 - for longer-term urethral catheterisation as a means of control, with suprapubic catheterisation being considered especially when active sexual function is still wanted. **See recommendations below on use of catheters.** **D**
- 1.7.2.9 Intravesical botulinum toxin should only be used by suitably trained doctors in the context of clinical research. **D**

1.7.3 Urinary tract infections

- 1.7.3.1 Any person with MS at risk of urinary tract infections should not be recommended prophylactic use of antibiotics or cranberry juice. **A**
- 1.7.3.2 If a person with MS experiences new urinary tract symptoms, or develops general malaise and/or worsening of existing symptoms with a raised temperature, they should:
- be given a urine dipstick test for infection, and culture, if necessary **D**
 - be offered treatment with an appropriate antibiotic. **A**
- 1.7.3.3 Any person with MS with more than three confirmed episodes of urinary tract infection in a period of 1 year should be assessed by a continence specialist for residual urine and other evidence of risk factors, and offered appropriate treatment and guidance. **D**

- 1.7.3.4 The general principles of care for people with long-term urinary catheters, as described in the NICE guideline on prevention of healthcare-associated infection in primary and community care (see Section 6) should be followed. Of particular note in treating a person with MS are:

Long-term indwelling catheters should:

- be used only after all reasonable non-invasive methods have been tried
- be reviewed regularly, to check whether alternative less invasive methods can be used.

D

Drainage systems from the catheter should:

- be emptied regularly, before the bag is over-full
- bladder installations and wash-outs should not be routinely used.

D

A

1.7.4 Bowel problems

- 1.7.4.1 Each professional in contact with a person with MS should consider whether the person has any problems controlling bowel function. Potential problems include urgency, difficulty, pain, constipation or incontinence.

D

- 1.7.4.2 Any person with MS who has apparent constipation (pain on or difficulty with defecation, bowels open less than twice a week) should be offered advice on fluid intake and dietary changes that might help, and then be considered for oral laxatives.

D

- 1.7.4.3 Any individual with faecal incontinence should be assessed for constipation with overflow, possibly exacerbated by laxative use.

D

- 1.7.4.4 If a person with MS has apparent constipation (pain on or difficulty with defecation, bowels open less than twice a week) despite treatment with oral laxatives, he or she should be considered for the routine use of suppositories or enemas.

D

1.7.5 Weakness and cardio-respiratory fitness

1.7.5.1	Each professional in contact with a person with MS should consider whether muscular weakness is a significant problem, or contributing factor, to the person's current clinical state. If so, the person should be assessed to determine the nature and cause of the weakness.	D
1.7.5.2	People with a limitation of their activities should be assessed for weakness of voluntary motor control using a valid technique.	D
1.7.5.3	People with motor weakness should be shown and advised to undertake exercises and techniques to maximise strength and endurance appropriate to their circumstances, including aerobic training.	D
	Usually, specific exercises should be selected and explained by a neuro-physiotherapist.	B
1.7.5.4	People with motor weakness should be taught techniques and given equipment, such as orthoses, needed to optimise performance of activities appropriate to their circumstances.	D
1.7.5.5	People with weakness sufficient to cause postural abnormalities should be assessed for specialist supportive equipment, including but not limited to seating.	D

1.7.6 Spasticity and spasms

1.7.6.1	Each professional in contact with a person with MS who has any muscle weakness should consider whether spasticity or spasms are a significant problem, or a contributing factor, to the person's current clinical state.	D
1.7.6.2	If spasticity or spasms are present, then simple causative or aggravating factors such as pain and infection should be sought and treated.	D
1.7.6.3	Every person with MS who has persistent spasticity and/or spasms should be seen by a neuro-physiotherapist to assess and advise on physical techniques, such as passive stretching and other physical techniques, to reduce spasticity and especially to avoid the development of contractures. Families and carers should be taught how to prevent problems worsening, and a monitoring system should be put in place.	D

- 1.7.6.4 More active specific measures should be considered only if the spasms or spasticity are causing pain or distress, or are limiting (further) the individual's dependence and activities. In this case, both benefits and risks should be considered carefully. A specific goal (or goals) should be set, but will rarely include improved performance in activities.

D

- 1.7.6.5 Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin.

A

The following should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable:

- tizanidine
- diazepam
- clonazepam, or
- dantrolene.

A

D

D

D

Combinations of medicines, and other medicines such as anticonvulsants, should only be used after seeking further specialist advice.

D

- 1.7.6.6 People with MS who have troublesome spasticity and spasms unresponsive to simpler treatments should be seen by a team specialising in the assessment and management of spasticity.

D

The team should consider using one or more of the following:

- standing and weight-bearing through legs
- splints
- serial casting
- special or customised seating, such as tilt-in-space chairs
- intrathecal baclofen
- phenol injections to motor points or intrathecally.

D

D

C

D

A

D

1.7.6.7 Intramuscular botulinum toxin should not be used routinely, but can be considered for relatively localised hypertonia or spasticity that is not responding to other treatments. It should be used when specific goals can be identified, and:

- in the context of a specialist service that can consider all aspects of rehabilitation (for example, seating)
- by someone with appropriate experience and expertise
- followed by active input from a neuro-physiotherapist.

B

1.7.7 Contractures at joints

1.7.7.1 Any person with MS who has weakness and/or spasticity sufficient to limit the regular daily range of movement around a joint should be considered at risk of developing a contracture at that joint, and should be considered for preventative measures.

D

1.7.7.2 Any person with MS at risk of developing contractures should have the underlying impairments assessed and ameliorated if possible (see sections on weakness [1.7.5] and spasticity [1.7.6]).

D

1.7.7.3 Any person with MS at risk of developing contractures should be informed; the individual, and or carer(s) should be taught how to undertake preventative measures, such as regular passive stretching of the joint(s) at risk and appropriate positioning of limbs at rest. In more severe instances, specialist advice should be obtained on seating and positioning, including positioning in bed.

D

1.7.7.4 Any person with MS who develops a contracture should be assessed by a suitable specialist for specific treatment; the assessment should take into account the problems caused by the contracture, the discomfort and risk of any treatment and the wishes of the person. At the same time, renewed efforts should be made to reduce the underlying causes and to prevent further contracture.

D

1.7.7.5 Specific treatment modalities to be considered should include prolonged stretching using:

- serial plaster casts
- other similar methods, such as standing in a standing frame and using removable splints.

A

D

These are usually combined with:

- local botulinum toxin injection, and
- surgery when necessary.

D

D

1.7.8 Ataxia and tremor

1.7.8.1 Any person with MS who experiences a limitation of activities due to tremor should be assessed:

D

- by a specialist rehabilitation team for medicines, treatment techniques and equipment (using the general principles of goal setting and evaluation recommended)

and, if problems remain severe and intractable, the person should be assessed:

- by a neurosurgical team from a specialist centre, for suitability for an operation to reduce ataxia (after being given a full explanation of its major risks and possible benefits).

1.7.9 Sensory losses

1.7.9.1 Any person with MS who experiences a limitation of activities not otherwise explained should be assessed for sensory losses.

D

1.7.9.2 Any person with sensory disturbance sufficient to limit activities should be seen and assessed by a specialist rehabilitation team; the individual should be given advice on techniques and equipment to ameliorate their limitations, and advice on personal safety.

D

1.7.10 Visual problems

Difficulty in reading or seeing television is not uncommon, and the usual reason (other than the lack of glasses) is that the control over eye movement is poor. Actual loss of visual function due to optic neuritis is rare.

1.7.10.1 Each professional in contact with a person with MS should consider whether the individual's vision is disturbed, by considering, for example, the individual's ability to read the text of a newspaper, book or other written material and to see the television.

D

1.7.10.2 Any person with MS who is unable to read normal print or to see the television should be assessed for glasses by an optometrist.

D

1.7.10.3 Any individual who experiences reduced visual acuity, despite using suitable glasses, should be assessed in a specialist ophthalmology clinic.

D

1.7.10.4 Any person with MS who has nystagmus that causes reduced visual acuity or other visual symptoms should be offered a time-limited trial of treatment with oral gabapentin. This should be initiated and monitored by a suitable specialist.

D

1.7.10.5 Any person with MS who is unable to read (due to low visual acuity) or to see television, despite all available treatment, should be:

D

- assessed for low-vision equipment and adaptive technology
- referred to the appropriate specialist social services team
- registered as partially sighted.

1.7.11 Pain

Pain may arise either directly from the neurological damage (neuropathic pain) or from musculoskeletal problems due to reduced mobility. People with MS may also have pain from unrelated causes.

1.7.11.1 Each professional in contact with a person with MS should ask whether pain is a significant problem for the person, or whether it is a contributing factor to their current clinical state.

D

1.7.11.2 All pain, including hypersensitivity and spontaneous sharp pain, suffered by a person with MS should be subject to full clinical diagnosis, including a referral to an appropriate specialist service if needed.

D

Musculoskeletal pain

1.7.11.3 Every person with MS who has musculoskeletal pain secondary to reduced or abnormal movement should be assessed by specialist therapists to see whether exercise, passive movement, better seating or other procedures might be of benefit.

D

1.7.11.4 If non-pharmacological means are proving unsuccessful in managing the musculoskeletal pain (arising from reduced movement and/or abnormal posture), the individual should be offered appropriate analgesic medicines.	D
1.7.11.5 Any person with MS who has continuing unresolved secondary musculoskeletal pain should be considered for transcutaneous nerve stimulation or antidepressant medication.	A
1.7.11.6 Treatments that should not be used routinely for musculoskeletal pain include ultrasound, low-grade laser treatment and anticonvulsant medicines.	A
1.7.11.7 Cognitive behavioural and imagery treatment methods should be considered in a person with MS who has musculoskeletal pain only if the person has sufficiently well-preserved cognition to participate actively.	A

Neuropathic pain

1.7.11.8 Neuropathic pain, characterised by its sharp and often shooting nature, and any painful hypersensitivity, should be treated using anticonvulsants such as carbamazepine or gabapentin, or using antidepressants such as amitriptyline.	A
1.7.11.9 If the neuropathic pain remains uncontrolled after initial treatments have been tried, the individual should be referred to a specialist pain service.	D

1.7.12 Cognitive losses

About half of all people with MS may have impaired ability to learn and remember, to plan, to concentrate and to handle information quickly. The relatively high frequency of these losses is often not appreciated by clinicians, but equally must not be assumed.

1.7.12.1 Healthcare staff should always consider whether the person with MS has any impairment of attention, memory and executive functions sufficient to be a problem, or to be a contributing factor to their current clinical status.	D
1.7.12.2 When a person with MS is being involved in making a complex medical decision, or is starting a course of complex treatment that requires their active participation, they should have their cognition sensitively assessed to ascertain their ability to understand and participate adequately, and to determine what support they may need.	D

1.7.12.3 Any person with MS experiencing problems due to cognitive impairment should:

- have their medication reviewed, to minimise iatrogenic cognitive losses
- be assessed for depression, and treated if appropriate.

D

1.7.12.4 Any person with MS complaining of cognitive problems, and any person where this is suspected clinically, should be:

- offered a formal cognitive assessment, coupled with specialist advice on the implications of the results
- advised, if necessary, about any vulnerability to financial or other abuse that may arise, and how to reduce the risk
- asked whether the results can be communicated to other people.

D

1.7.12.5 Any person with MS whose level of dependence or whose social behaviour cannot be easily understood in terms of other known impairments or factors should be offered a formal neuro-psychological assessment by a specialist clinical psychologist (and speech and language therapist if appropriate); it should be investigated whether cognitive or communicative losses are a contributing factor and, if so, appropriate management should be recommended.

D

1.7.13 Emotionalism

1.7.13.1 A person with MS may comment (or it may be noticed) that they may cry or laugh with minimal provocation and with little control; the individual should be offered a full assessment of their emotional state by someone with suitable expertise.

D

1.7.13.2 If the emotionalism is sufficient to cause concern or distress to the person with MS, or their family, then treatment with an antidepressant should be offered:

- usually a tricyclic antidepressant, or
- a selective serotonin re-uptake inhibitor.

B

D

- 1.7.13.3 If the person with MS still has uncontrolled emotionalism, is unwilling or unable to take antidepressants or is not responsive to antidepressants, then advice on behavioural management strategies should be offered by a suitable expert.

D

1.7.14 Depression

- 1.7.14.1 If depression is suspected, the person with MS should be assessed:

- by asking "Do you feel depressed?", or using a similar screening method
- clinically if necessary
- by a liaison psychiatrist if severe depression is present.

DS

D

D

- 1.7.14.2 In any person with MS who is depressed, a list of possible contributing factors (such as chronic pain and social isolation) should be drawn up.

D

- 1.7.14.3 Assessment and interventions should be undertaken to ameliorate those contributing factors, where possible.

D

- 1.7.14.4 Specific antidepressant medication, or psychological treatments such as cognitive behavioural therapy, should be considered, but only as part of an overall programme of depression management.

D

A

D

- 1.7.14.5 Other concurrent psychological diagnoses, especially anxiety, should be considered.

D

1.7.15 Anxiety

- 1.7.15.1 Any person with MS whose function or happiness is being adversely affected by anxiety should be offered specialist assessment and management.

D

- 1.7.15.2 In people with MS with marked anxiety, psychologically based treatment should be offered.

A

- 1.7.15.3 Pharmacological treatment of anxiety should be through using antidepressants or benzodiazepines.

D

The Committee on Safety of Medicines (CSM) guidelines on the use of benzodiazepines (reproduced in the *British National Formulary*) should be used.

1.7.16 Swallowing difficulties

Dysphagia (disturbance of swallowing) may lead to choking and aspiration of food or liquid into the lungs. It is more common in those with severe impairment. Facilities for the insertion of percutaneous endoscopic gastrostomy (PEG) tubes are widely available.

1.7.16.1 Any person with MS who is unable to transfer from bed to chair independently or who has any symptoms or signs of bulbar dysfunction such as any abnormality of eye movements, slurring of speech or ataxia, should be asked whether they have difficulties with chewing, or swallowing food or fluids (for example, coughing), also whether they have altered their diet because of previous problems.

D

1.7.16.2 Any person with MS with any bulbar symptoms or signs, and any person with MS who has a chest infection, should have their swallowing assessed by a competent person (using a standardised swallowing test).

DS

1.7.16.3 People with MS who, on formal assessment, have an abnormality of swallowing should be further assessed by a specialist speech and language therapist. Advice should be given on specific swallowing techniques, and on adapting food consistencies and dietary intake. Further diagnostic assessment (for example, by videofluoroscopy) should be undertaken if:

D

- first-line therapy and advice are ineffective
- a specific objective of the investigation can be identified.

1.7.16.4 Any person with MS who has difficulty swallowing for more than a few days should be assessed by a neurological rehabilitation team, to review the need for:

D

- adjustments to or provision of seating that will increase ease and safety of swallowing and feeding
- chest physiotherapy
- short-term use of nasogastric tube, especially if recovery is anticipated.

1.7.16.5 Any person with MS who has swallowing difficulties for more than 1 month should have his or her weight or nutritional status checked on a monthly basis (using a validated nutritional measure if needed). Dietary intake should be reviewed if there is continuing weight loss or evidence of malnutrition.	D
1.7.16.6 If PEG feeding is anticipated as being a likely future option, discussions with the person with MS should be commenced at an early stage and their wishes documented.	D
1.7.16.7 If swallowing difficulties persist, a PEG tube should be considered if any of the following occur:	D
• recurrent chest infections • inadequate food and/or fluid intake • prolonged or distressing feeding • nasogastric tube in situ for over 1 month.	
1.7.16.8 If PEG placement is indicated and agreed, the PEG tube should be inserted by a suitable specialist. Before the person with MS is discharged from hospital, full training should be given to any family members and carers who are going to be involved in feeding.	A
1.7.17 Speech difficulties	
1.7.17.1 Any person with MS who has dysarthria sufficient to affect communication with people outside the home or over the phone, and any person who is concerned about their speech sound or clarity, should be assessed and given advice by a specialist speech and language therapist.	B
1.7.17.2 Any person with MS whose ability to communicate is affected significantly by dysarthria should be taught techniques to improve and maintain speech production and clarity; tuition should be provided by a specialist speech and language therapist, working with any other members of the neurological rehabilitation service who are involved.	D
1.7.17.3 Any person who continues to have difficulties in communication should be considered for, and if appropriate taught the use of, alternative non-verbal means of assisting with or replacing speech.	D

1.7.17.4 Any person with MS who cannot communicate effectively should be assessed by a specialist speech and language therapist for an augmentative aid to communication, which should then be provided as soon as possible. The family members, carers and other frequent communicators with any person with MS who has significant communication difficulties should have discussions with the speech and language therapist on how best to help the person communicate.

D

1.7.18 Sexual dysfunction

MS may disturb the normal sexual physiology, and it may result in other impairments (such as spasms) that make normal sexual behaviour difficult. These may make it difficult for the person to establish or maintain partnership relations. Both aspects are important and should be considered together.

Male sexual function

1.7.18.1 Men with MS:

- should be asked whether they experience erectile dysfunction (relative or absolute) and, if so, whether it is of concern
- who have persisting erectile dysfunction and who do not have contraindications should be offered sildenafil 25–100 mg
- who do not respond to sildenafil should be assessed for the general and specific factors that might cause or worsen erectile dysfunction and that are amenable to treatment (such as depression, anxiety, vascular disease, diabetes and taking medicines that may cause erectile dysfunction). Other specific treatments such as alprostadil or intra-cavernosal papaverine should then be considered.

D

A

D

Female sexual function

1.7.18.2 Women with MS should be asked whether they experience sexual dysfunction (such as failure of arousal or lubrication or anorgasmia) and, if so, whether it is of concern.

D

1.7.18.3 Women with sexual dysfunction should be assessed for the general and specific factors that might cause or worsen sexual dysfunction and that are amenable to treatment (such as depression, anxiety, vascular disease, diabetes and taking medicines that may cause sexual dysfunction).

D

Partnership relations

1.7.18.4 Every person (or couple) with MS should be asked sensitively about, or given the opportunity to remark upon, any difficulties they may be having in establishing and/or maintaining wanted sexual and personal relationships; they should be offered information about locally available counselling and supportive services.

D

1.7.18.5 Every person (or couple) with persisting sexual dysfunction should be offered the opportunity to see a specialist (with particular expertise in sexual problems associated with neurological disease) and offered, as appropriate, advice on lubricants and the use of sexual aids, and other advice to ameliorate their sexual dysfunction.

D

1.7.19 Pressure ulcers

A pressure ulcer (decubitus ulcer or pressure sore) is an area of broken skin that is secondary to unrelieved pressure on the skin, often exacerbated by slight trauma – for example, when being moved. Pressure ulcers may range from minor breaks to very large deep areas of dead tissues extending over many square centimetres and down to bone. Once present they can be difficult to heal, and can cause general malaise and worsening of most impairments, and they carry a risk of generalised or localised infections. Many people with MS are at high risk of developing pressure ulcers because they may have, for example, limited mobility, impairment of sensory functioning and reduced cognitive function. Most pressure ulcers can be avoided by good anticipatory management. (See also the NICE Clinical Guideline on prevention of pressure ulcers [referenced in Section 6].)

D

1.7.19.1 Every person with MS who uses a wheelchair should be assessed for their risk of developing a pressure ulcer. The individual should be informed of the risk, and offered appropriate advice.

D

1.7.19.2 Every person with MS who uses a wheelchair daily should be assessed by a suitably trained person, whenever they are admitted to hospital (for whatever reason), for their need for pressure-relieving devices and procedures. The assessment should be clinical, specifically taking into account the risk features associated with MS, and not simply the recording of a pressure ulcer risk score; it should lead to the development and documentation of an action plan to minimise risk, including:

- optimisation of nutritional status

D

• provision of suitable equipment	B
• documentation of agreed manual handling techniques.	D
1.7.19.3 Every person with MS who is provided with a wheelchair by a statutory organisation (NHS or social services), or whose wheelchair seating is being reassessed, should specifically be considered for pressure-relieving procedures and devices – not only in the wheelchair, but in all other activities, especially transfers and sleeping.	D
1.7.19.4 For every person with MS considered to be at risk on their bed (in hospital or in the community):	
• an appropriate specialist mattress should be provided wherever they are lying down	A
• regular turning should not be depended upon as a policy for preventing pressure ulcers	A
• the skin areas at risk should be inspected to ensure that adequate protection is being provided.	D
1.7.19.5 If a pressure ulcer occurs, it should be considered an adverse event worthy of investigation, and advice should be sought from a specialist service.	D
1.7.19.6 Any person with MS who develops a pressure ulcer should be nursed on a low-loss mattress (while in bed).	A
The ulcer should be dressed according to appropriate local guidelines.	D

1.7.20 Complementary therapies

1.7.20.1 People with MS should be informed that there is some evidence to suggest that the following items might be of benefit, although there is insufficient evidence to give more firm recommendations:	A
• reflexology and massage	
• fish oils	
• magnetic field therapy	
• neural therapy	
• massage plus body work	

- t'ai chi
- multi-modal therapy.

A

1.7.20.2 A person with MS who wishes to consider or try an alternative therapy should be recommended to evaluate any alternative therapy themselves, including the risks and the costs (financial and inconvenience).

D

1.7.20.3 A person with MS should be encouraged to discuss any alternative treatments they are considering, and to inform their doctors and other professionals if they decide to use any.

D

2 Notes on the scope of the guidance

All NICE guidelines are developed in accordance with a scope document that defines what the guideline will and will not cover. The scope of this guideline was established at the start of the development of this guideline, following a period of consultation; it is available from www.nice.org.uk/article.asp?a=15233

In summary, the aim was to develop a guideline that is relevant to adults of all ages with MS, and considers the full range of care that should be routinely available from the NHS, including appropriate use of mainstream pharmacological therapy, physical therapy, rehabilitation and psychosocial treatments.

The guideline was developed for the NHS and, although it comments on the interface with other sectors, it does not consider them in detail.

3 Implementation in the NHS

3.1 In general

Local health communities should review their existing practice for multiple sclerosis against this guideline as they develop their Local Delivery Plans. The review should consider the resources required to implement the recommendations set out in Section 1, the people and processes involved, and the timing over which full implementation is envisaged. Priorities for implementation are set out at the start of this document. It is in the interests of people with MS that the implementation timeline is as rapid as possible.

Relevant local clinical guidelines, care pathways and protocols should be reviewed in the light of this guidance and revised accordingly.

This guideline should be used in conjunction with the developing National Service Framework for long-term neurological conditions, which will define the broader context of neurological services.

3.2 Audit

Suggested audit criteria are listed in Appendix D.

4 Research recommendations

The following research recommendations have been identified for this NICE guideline, not as the most important research recommendations, but as those that are most representative of the full range of recommendations. The Guideline Development Group's full set of research recommendations is detailed in the full guideline produced by the National Collaborating Centre for Chronic Conditions (see Section 5).

4.1 Epidemiology of relapses, impairments and activity limitations

4.1.1 There should be a prospective study on an epidemiologically sound defined population to establish reasonable estimates of:

- the frequency of relapses sufficient to cause increased limitation on activities
- the prevalence and yearly incidence of the most common impairments described in this guideline document
- the prevalence and yearly incidence of the most common limitations on activity including work described in this document
- the direct and indirect costs of the condition and how they relate to levels of limitation on activity, including not only NHS direct costs but all direct costs.

4.2 Diagnosing MS

4.2.1 There should be a prospective study on an epidemiologically sound population to investigate the most cost-effective protocols for investigating people presenting with (potential) MS to establish:

- the sensitivity and specificity of MRI scanning in people with different levels of clinical diagnostic certainty
- the role of other investigations in confirming or positively excluding the diagnosis of MS
- the prognostic value of MRI scan information over 5 years.

4.3 Rehabilitation assessment protocols

4.3.1 There should be a programme of research to develop and evaluate protocols, procedures or data-collection tools that can be used by any profession to:

- identify the probable presence of most common impairments
- quantify approximately activity performance in personal and household activities of daily living
- identify areas of activity limitation that are present in people with MS.

4.4 Specialist neurological rehabilitation services

4.4.1 A programme of research into the relative costs (direct and indirect) and benefits (direct and indirect) should be undertaken comparing:

- current rehabilitation practice with rehabilitation given by a specialist neurological rehabilitation service
- primarily inpatient with primarily outpatient or home-based neurological rehabilitation.

4.5 Acute relapse management – methylprednisolone and rehabilitation

4.5.1 A programme of research should investigate the management of acute relapse including comparing the costs and benefits associated with policies of:

- oral methylprednisilone against intravenous methylprednisolone
- hospital admission with early discharge once rehabilitation has started and support has been arranged against home care with rapid response care and rehabilitation input (with steroids if indicated).

4.6 Disease-modifying drugs

4.6.1 A programme of research into disease-modifying treatments sponsored and run by an organisation independent of either health purchasers or pharmaceutical companies should be set up to investigate interferon beta, glatiramer acetate, linoleic acid and azathiaprine (and any other newly licensed medicines) in terms of:

- benefits, specifically in terms of activity performance
- costs, including the medicines and all associated monitoring, etc.
- dis-benefits, both immediate side effects and longer-term rates of withdrawal and side effects
- effects of stopping treatment after 2 and 4 years.

4.7 Relationship between impairments and limitations in activities

4.7.1 A programme of research extending over many years should be instigated to investigate the nature and extent of relationships between impairments and activities and how they change over time.

5 Full guideline

NICE originally commissioned the Royal College of Physicians (RCP) and the Chartered Society of Physiotherapy (CSP) to develop this guideline. When the National Collaborating Centre for Chronic Conditions was formed in April 2001, it assumed the management responsibility, but with continuing leadership from the executive leads from the RCP and CSP. The Centre established a Guideline Development Group, which reviewed the evidence and developed the recommendations. The full guideline, *Multiple Sclerosis – National Clinical Guidelines for NHS Management in Primary and Secondary Care*, is published by the National Collaborating Centre for Chronic Conditions; it is available on its website (www.rcplondon.ac.uk/pubs/books) and on the website of the National Electronic Library for health (www.nelh.nhs.uk). The members of the Guideline Development Group are listed in Appendix B. Information about the Institute's Guideline Review Panel is given in Appendix C.

The booklet *The Guideline Development Process – Information for the Public and the NHS* has more information about the Institute's guideline development process. It is available from the Institute's website and copies can also be ordered by telephoning 0870 1555 455 (quote reference N0038).

6 Related NICE guidance

National Institute for Clinical Excellence (2002) Multiple sclerosis – beta interferon and glatiramer acetate for the treatment of multiple sclerosis. *NICE Technology Appraisal Guidance* No. 32. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk

National Institute for Clinical Excellence (2002) Guidance on the use of computerised cognitive behavioural therapy for anxiety and depression. *NICE Technology Appraisal Guidance* No. 51. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk

National Institute for Clinical Excellence (2003) Infection control. Prevention of healthcare-associated infection in primary and community care. *NICE Clinical Guideline* 2. London: National Institute for Clinical Excellence. Available from www.nice.org

National Institute for Clinical Excellence (2003) Pressure ulcer prevention. Pressure ulcer risk assessment and prevention, including the use of pressure-relieving devices (beds, mattresses and overlays) for the prevention of pressure ulcers in primary and secondary care. *NICE Clinical Guideline 6*. London: National Institute for Clinical Excellence. Available from www.nice.org

NICE is in the process of developing the following guidance.

- Anxiety: management of generalised anxiety disorder and panic disorder (with or without agoraphobia) in primary, secondary and community care. Clinical guideline. (Publication expected June 2004)
- Cannabinoids (cannabis derivatives) for the treatment of the symptoms of multiple sclerosis. Technology appraisal. (Publication date to be confirmed)
- Depression: the management of depression in primary and secondary care. Clinical guideline. (Publication expected May 2004)
- Pressure ulcers: the management of pressure ulcers in primary and secondary care. Clinical guideline. (Publication expected May 2005)

7 Review date

The process of reviewing the evidence is expected to begin 4 years after the date of issue of this guideline. Reviewing may begin earlier than 4 years if significant evidence that affects the guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

A version of this guideline for people with multiple sclerosis, their families and carers and the public is available from the NICE website (www.nice.org.uk) or from NHS Response Line (telephone 0870 1555 455 and quote reference number N0367 for an English version and N0368 for a version in English and Welsh).

Appendix A: Grading scheme

The grading scheme and hierarchy of evidence used in this guideline (see Table) is adapted from Eccles and Mason (2001).

Recommendation grade	Evidence
A	Directly based on category I evidence
B	Directly based on: - category II evidence, or - extrapolated recommendation from category I evidence
C	Directly based on: - category III evidence, or - extrapolated recommendation from category I or II evidence
D	Directly based on: - category IV evidence, or - extrapolated recommendation from category I, II or III evidence
DS	Evidence from diagnostic studies
HSC	Health Service Circular 2002/004
Evidence category	Source
Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Adapted from Eccles M, Mason J (2001) How to develop cost-conscious guidelines. <i>Health Technology Assessment</i> 5 (16)	

Appendix B: The Guideline Development Group

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Consensus Reference Group

To support the development of this guideline, a Consensus Reference Group (CRG) was formed. The CRG met early in the development process to ensure that the aims and the clinical questions addressed by the guideline were appropriate. The CRG met again at the end of the process to review the recommendations drafted by the Guideline Development Group. The group used formal consensus techniques in their consideration of clinically important areas where there was insufficient evidence or disagreement over the interpretation of the evidence.

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Appendix C: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The Panel includes experts on guideline methodology, health professionals and people with experience of the issues affecting patients and carers. The members of the Guideline Review Panel were as follows.

Dr Bernard Higgins (Chair)

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Dr Robert Higgins

Consultant in Renal and General Medicine
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Dr Marcia Kelson

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Dr John Young

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Appendix D: Technical detail on the criteria for audit

Suggested measures for auditing MS services in the NHS

Key priority for implementation, or recommendation	Criterion: data items needed	Exceptions: interpreting the data	Definitions and other comments
1. Specialist neurological and neurological rehabilitation services should be available to every person with MS, when they need them. This is usually when they develop any new symptom, sign, limitation on activities or other problem, or when their circumstances change.	The presence (or not) of a specific contract between the health commissioning organisation (primary care trust or local health board) and: • specialist neurology services • specialist neurological rehabilitation services and the quantity of service delivery with a currency to be agreed but, probably, for a defined population on a yearly basis: • number of new cases of possible MS seen by neurology service • number of confirmed cases seen by neurology (for disease diagnosis and treatment, including interferon beta) • number of people seen by neurology for methylprednisolone treatment • number of new cases seen by neuro-rehabilitation service • number of cases seen (excluding new) • equipment provided or maintained.	There are no exceptions. These data are not currently collected, and there are no data to predict a likely caseload and so initial data will be to establish a baseline that could be compared with known epidemiological figures on incidence and prevalence. The neurology rate of seeing confirmed cases is likely to be higher where neuro-rehabilitation services are limited. The effects on other services of regular monitoring of patients in the risk-sharing scheme are unpredictable.	The neurology contract may be split to cover the specific work associated with the risk-sharing scheme and the remaining work.

Key priority for implementation, or recommendation	Criterion: data items needed	Exceptions: interpreting the data	Definitions and other comments
2. An individual who is suspected of having multiple sclerosis should be referred to a specialist neurology service and be seen rapidly within an audited time. The individual should be seen again after all investigations necessary to confirm or refute the diagnosis have been completed (also rapidly within an audited time).	The time in weeks - from referral with diagnosis of 'possible MS' to being seen in a specialist neurology clinic and, in those requiring further investigation, the time in weeks - from being seen in the neurology clinic to being seen again after any investigations organised.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline that could be compared to other time-scales suggested in other conditions. Any standard set should recognise that: - some people with MS will need urgent investigation because serious alternative disease (for example, spinal cord compression in case of transverse myelitis) is possible, whereas - other people with MS may have had symptoms for years and may not be overly concerned, but - in general, uncertainty is itself stressful.	Some people will be diagnosed as definitely having MS, a small number will be diagnosed as definitely having some other condition (such as stroke), a large number will not achieve a diagnosis of any alternative condition and the majority of these will be experiencing somatisation (symptoms associated with no known disease, possibly related to emotional dysfunction).

Key priority for implementation, or recommendation	Criterion: data items needed	Exceptions: interpreting the data	Definitions and other comments
3. Every health commissioning organisation should ensure that all organisations in a local health area agree and publish protocols for sharing and transferring responsibility for and information about people with MS, so as to make the service seamless from the individual's perspective.	The presence (or not) of agreed protocols for identifying and sharing responsibility: • between different parts of health organisation, and • between health and social services. The time in weeks between initial contact about a problem with any service, including community NHS and social services, and contact with the 'final' service that can and does take responsibility for resolving the problem. The number of onward referrals made by services after initial contact before making contact with the final effective service.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline. Any standards set should: • focus on areas of concern locally (to people with MS and/or service providers and/or commissioners) initially • recognise that generic protocols (for example, for urinary incontinence) may be totally appropriate, and that not all protocols need to be MS specific.	The presence or absence of protocols should be easily established, but it will be difficult to agree what protocols should exist as it would be unrealistic for every eventuality to have a protocol. Protocols could be given to every person with MS on making contact with the service to help them help themselves. It will be difficult to agree when the person has reached the final service. However, a method of people with MS collecting these data has been used and found to be effective, and so this is an achievable process.
4. All services and service personnel within the healthcare sector should recognise – and respond to – the varying and unique needs and expectations of each person with MS. The person with MS should be involved actively in all decisions and actions.	The number of complaints made to each service organisation that might reflect a failure to be responsive and to involve the person with MS actively.	There are no exceptions. These data are not currently collected, either specifically in relation to people with MS or specifically in relation to a service being responsive and patient-centred. It may not be appropriate to set a standard, and current NHS policies on complaints and the improvement of services should use the data.	As this standard should apply to all people making contact with NHS services (and other statutory services), it may not be necessary to separate out people with MS. A patient-centred audit of services would be able to monitor this without involving formal complaints.

Key priority for implementation, or recommendation	Criterion: data items needed	Exceptions: interpreting the data	Definitions and other comments
5. Health service professionals in regular contact with people with MS should consider in a systematic way whether the person with MS has a 'hidden' problem contributing to their clinical situation, such as fatigue, depression, cognitive impairment, impaired sexual function or reduced bladder control.	No data can realistically be collected on a routine basis. However, many specialist services may wish to develop and use a formal structured assessment protocol (centres participating in the risk-sharing scheme will do so) and for these services the data to collect would be: the number of people with MS who had a formal documented (that is, able to be found in the notes) assessment on first contact in any episode.	These data are not currently collected by any service, and so initial data will be needed to establish a baseline for any service doing this. The data should only refer to an agreed initial 'screening' assessment aimed to detect major problems needing further attention. An episode is a series of ongoing attendances, all of which concern a specified programme of care, and does not include monitoring visits.	Any specialist service that decides to use a formal structured approach to assessment should monitor its use.
6. Every person with MS who has been seen by a specialist neurological or neurological rehabilitation service should be informed how to make contact with the service when no longer under regular treatment or review. The individual should be given guidance on when such contact is appropriate.	The presence (or not) of a formal procedure for responding to self-referral by someone with MS in the: - neurology service - neuro-rehabilitation service. The time taken between initial contact by person with MS, and initial clinical contact by the service.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline. It is important to recognise that 'initial clinical contact by the service': - is more than a simple routine letter acknowledging the contact, but - is not necessarily seeing the person in a clinic or their own home, and - implies a reasoned, personal response with action as necessary.	Often the response needed may be no more than reassurance or the provision of information. Some – perhaps many – centres already offer this level of service but probably in an intermittent and variable way.

Key priority for implementation, or recommendation	Criterion: data items needed	Exceptions: interpreting the data	Definitions and other comments
The commissioning health organisation should require all healthcare services including community services: • to report every pressure ulcer that occurs in a person with MS, and • to undertake and report an investigation into what could have been done to avoid its occurrence, and • to agree actions that should reduce the risk of the same situation leading to a pressure ulcer.	The presence (or not) in all health service organisations of a procedure to identify and report every new (and existing) pressure ulcer. Presentation of reports on each pressure ulcer identified in a person with MS. Count of (a) new and (b) prevalent pressure ulcers in people with MS. Presentation of an action plan derived from the report.	There are no exceptions. Data on pressure ulcers are not currently collected in relation to people with MS, and so initial data will be needed to establish a baseline. Ideally none should occur, but in reality some will occur. Not every pressure ulcer represents a direct failure of the healthcare system. Some will reflect failures in other organisations (for example, social services), others will reflect the choices of the person with MS and a few may be 'inevitable'.	Properly executed, this audit could save huge resources but it requires continued vigilance by all staff to detect and report pressure ulcers, which will be inhibited by any suggestion that the inquiry will attribute blame to any individual or organisation. Pressure ulcers may be first recorded or detected in one organisation that was not responsible for the person at the time of occurrence, but once detected a full investigation should still be initiated.

Appendix E: Supplementary information

Table 1 Principles of good communication in healthcare

Principle	Comment
<i>In any communication the healthcare professional should:</i>	
Communicate in a suitable environment, usually a quiet area or room free from distraction or interruption	Privacy and quiet are important
Seek agreement from the person with MS that anyone present can be there and ensure that as far as possible anyone she or he wants present is there	Consider especially students and family
Start by asking what the person knows or believes already	Establishes expectations
Establish the nature and extent of the information that the person wishes to receive	Establishes expectations
Consider carefully the balance between the benefits and the risks associated with giving each item of information	Once given, information cannot be withdrawn
Tailor the communication to the person's: • specific situation • communicative and cognitive abilities • culture	Makes information relevant
Limit information given to that within their own knowledge, referring on to others as necessary for more detailed information	Do not give information if uncertain about it
Clarify specifically any options and choices the person may need to choose, specifying: • likely outcomes of each choice • benefits and risks of each choice	Both in diagnosis and treatment
Offer back-up with information being given: • in different ways (e.g. written leaflets, tapes) • by different people (e.g. specialist nurse) • at another time (e.g. follow-up appointment)	Information is often forgotten
Inform the person with MS about any recommended local or national sources of further information, including employment and voluntary sector sources	Allows person with MS to follow up and take more control
Consider need for emotional support during process especially if the information might be stressful, and arrange emotional support if needed.	Should be considered an intrinsic part of the process. (See 1.1.2.1)
Document in notes and inform other healthcare staff closely involved what has been communicated, especially the general practitioner.	Ensures consistency over time and across settings

Table 2 Review checklist

This is not a list of questions to be asked of every person with MS on every occasion. It is a list to remind clinicians of the wide range of potential problems that people with MS may face, and which should be actively considered as appropriate. A positive answer should lead to more detailed assessment and management. (See Sections 1.6 and 1.7.)

Initial question It is best to start by asking an open-ended question such as: <i>"Since you were last seen or assessed has any activity you used to undertake been limited, stopped or affected?"</i>
Activity domains Then, especially if nothing has been identified, it is worth asking questions directly, choosing from the list below those appropriate to the situation based on your knowledge of the person with MS: <i>"Are you still able to undertake, as far as you wish:</i> • vocational activities (work, education, other occupation)? • leisure activities? • family roles? • shopping and other community activities? • household and domestic activities? • washing, dressing, using toilet? • getting about (either by walking or in other ways) and getting in and out of your house? • controlling your environment (opening doors, switching things on and off, using the phone)?" If restrictions are identified, then the reasons for these should be identified as far as possible considering impairments (see below), and social and physical factors (contexts).
Common impairments It is worth asking about specific impairments from the list below, again adapting to the situation and what you already know: <i>"Since you were last seen have you developed any new problems with:</i> • fatigue, endurance, being overtired? • speech and communication? • balance and falling? • chewing and swallowing food and drink? • unintended change in weight? • pain or painful abnormal sensations? • control over your bladder or bowels? • control over your movement? • vision and your eyes? • thinking, remembering? • your mood? • your sexual function or partnership relations? • how you get on in social situations?"
Final question Finally, it is always worth finishing with a further open-ended question: <i>"Are there any other new problems that you think might be due to MS that concern you?"</i>

Table 3 Summary of the criteria suggested by the Association of British Neurologists and agreed by the Department of Health to determine eligibility for treatment using interferon beta and glatiramer acetate for people with MS within the 'risk-sharing scheme'¹

- A People with **relapsing/remitting** MS should be offered **interferon beta** (any type) provided that the following four conditions are met:
- can walk 100 metres or more without assistance
 - have had at least two clinically significant relapses in the past 2 years
 - are aged 18 years or older
 - do not have contraindications (see specific Summary of Product Characteristics [SPC] for details)
- B People with **relapsing/remitting** MS should be offered **glatiramer acetate** provided that the following four conditions are met:
- can walk 100 metres or more without assistance
 - have had at least two clinically significant relapses in the past 2 years
 - are aged 18 years or older
 - do not have contraindications (see SPC for details)
- C People with **secondary progressive** MS should be offered **interferon beta** (any type licensed for this use) provided the following conditions are met:
- can walk 10 metres or more with or without assistance
 - have had at least two disabling relapses in the past 2 years
 - have had minimal increase in disability due to gradual progression over the past 2 years
 - are aged over 18 years
 - do not have contraindications (see specific SPC for details)
- D People with MS offered treatment with **interferon beta** should have the following **stopping criteria** discussed and agreed before starting treatment:
- intolerable side effects
 - becoming or trying to become pregnant
 - occurrence of two disabling relapses within a 12-month period
 - secondary progression with an observable increase in disability over a 6-month period
 - loss of ability to walk, with or without assistance, that has persisted for longer than 6 months
- E People with relapsing–remitting MS offered treatment with **glatiramer acetate** should have the following **stopping criteria** discussed and agreed before starting treatment:
- intolerable side effects
 - being pregnant or planning pregnancy
 - occurrence of two disabling relapses within a 12-month period
 - development of secondary progressive MS
 - loss of ability to walk, with or without assistance, that has persisted for longer than 6 months.

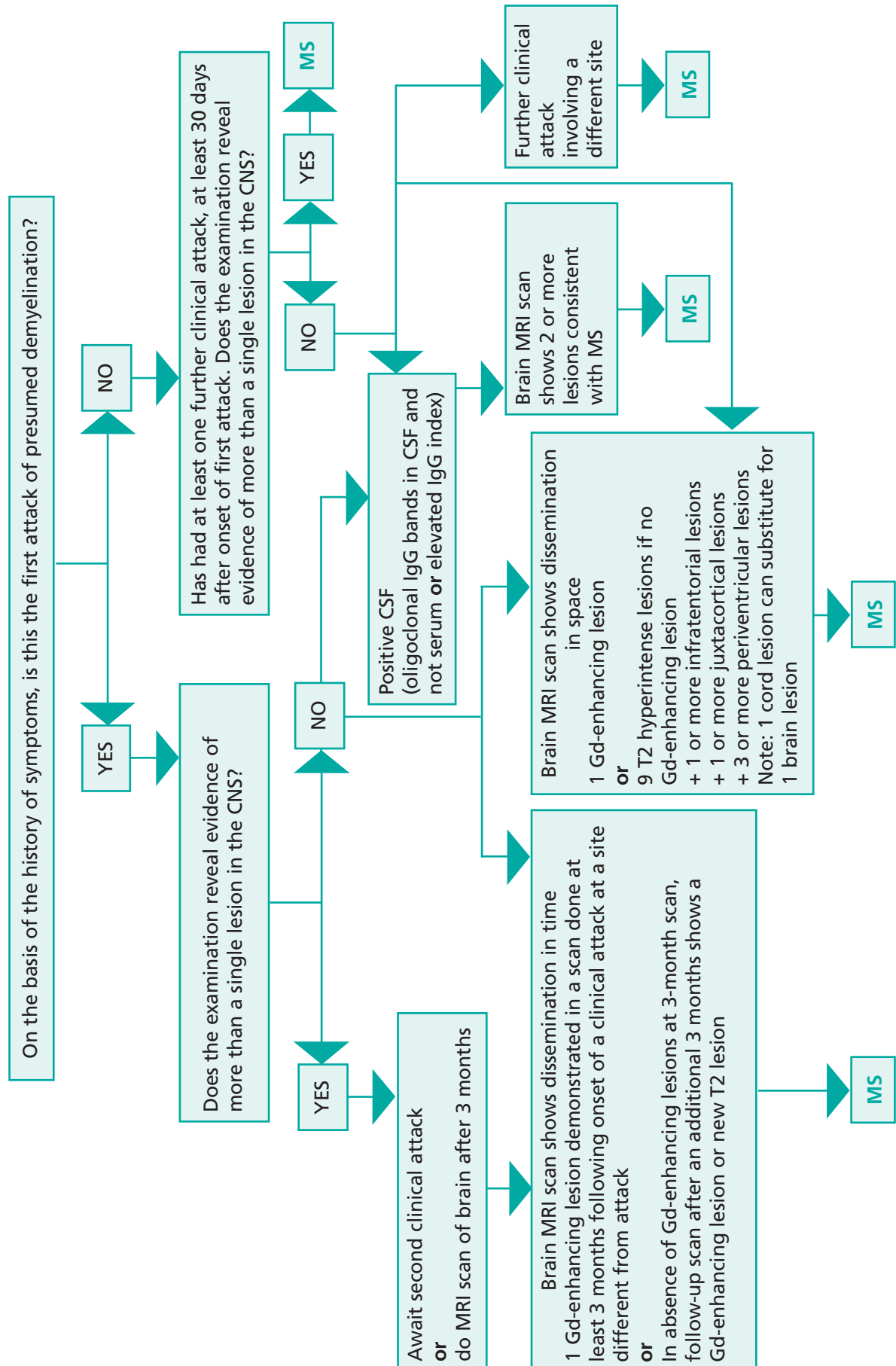
¹ For further details see Health Service Circular 2002/004 (www.doh.gov.uk/pricare/drugsmultiplesclerosis.htm)

Appendix F: Diagnosis of multiple sclerosis

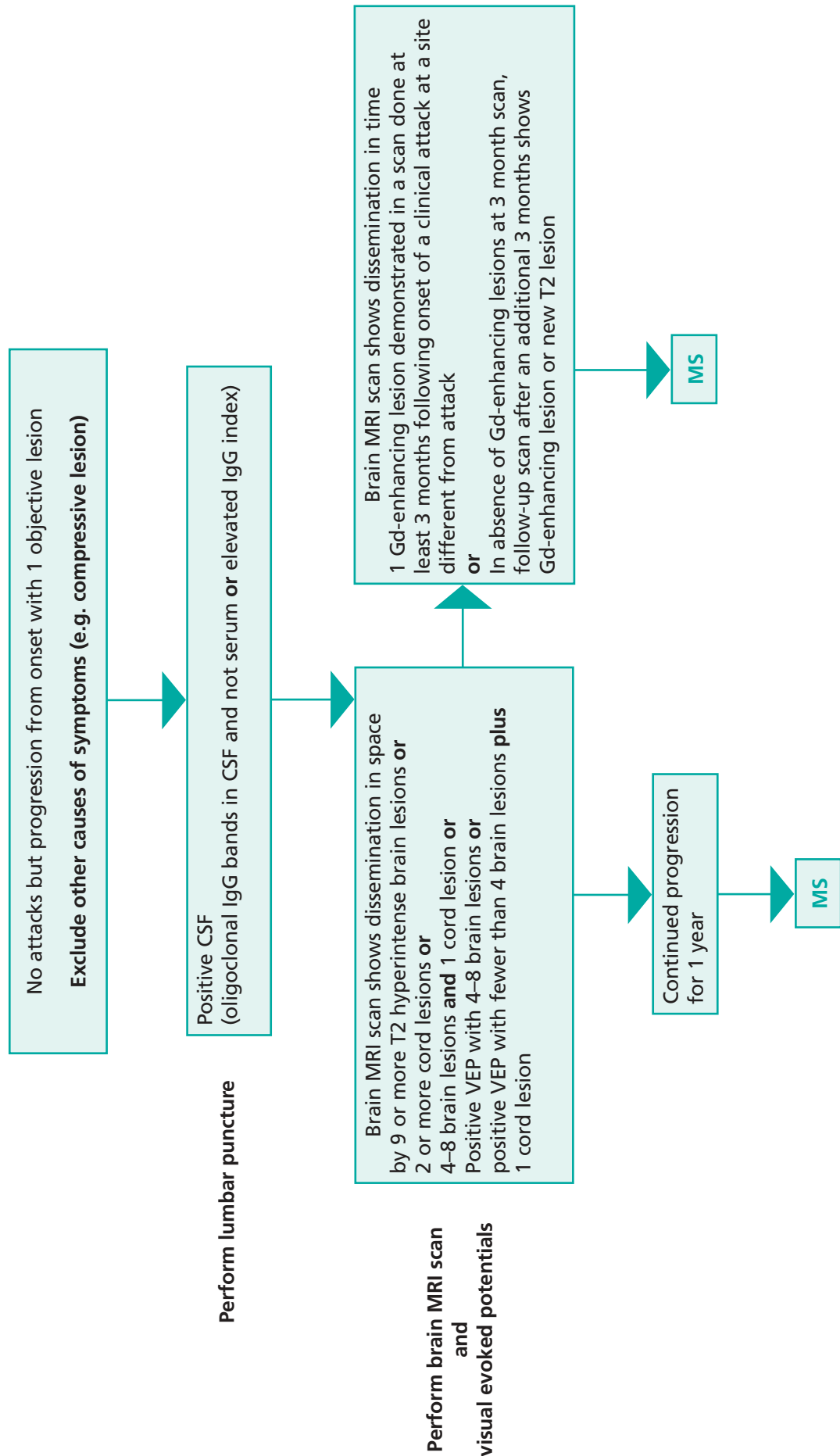
Guidelines for the accurate diagnosis of MS according to the McDonald criteria

Some general points
1. The diagnosis should be made by an experienced clinician with expert knowledge of MS and similar neurological conditions. 2. The prior probability that the individual has MS depends on factors such as age, ethnicity and geographical location. 3. Objective evidence of dissemination in time and space of lesions typical of MS is mandatory, as is the exclusion of other, better explanations for the clinical features. 4. Historical reports of symptoms may suggest previous episodes of demyelination, but cannot be used without objective evidence to satisfy the requirement of lesions disseminated in time and space. 5. MS can be diagnosed on purely clinical evidence of lesions separated in time and space. 6. Radiological (MRI) and laboratory evidence is desirable and may be essential where clinical evidence is insufficient for a secure diagnosis. 7. The choice of investigation will be determined by the clinical situation – for example, a delayed visual evoked potential is of value in a person with a spinal cord lesion but is of little value in a person with optic neuritis. 8. MRI is less useful in older people and in other inflammatory conditions such as acute encephalomyelitis where its specificity is lower. MRI is not applicable in people with metallic foreign bodies, pacemakers, etc. or in those who cannot tolerate the procedure. McDonald et al. (2001) Recommended diagnostic criteria for MS. <i>Annals of Neurology</i> 50:121–7

Relapsing–remitting MS



Primary-progressive MS



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MULTIPLE SCLEROSIS

National clinical guideline for diagnosis
and management in primary and secondary care

With joint leadership from

The Royal College
of Physicians 

The Chartered Society
of Physiotherapy 

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Preface

It is a pleasure to welcome you to this guideline on the management of multiple sclerosis (MS). It describes best practice for the health care management of a complex disorder that affects individuals and their carers in many and varied ways. This variability has made it hard to plan a cohesive or effective NHS service, and the challenge now is for all those involved in health care (those that commission care, those that deliver care, and the patient and carer groups) to ensure that these guidelines are used.

We would particularly direct readers to the six key messages set out in the Executive Summary at the front of the document and to the audit/implementation criteria (Section 7) for measuring the implementation process. If these are acted upon, then service provision will be improved and those with MS will enjoy a better quality of life and less disability in the future.

The guideline has been developed by National Collaborating Centre for Chronic Conditions (NCC-CC) with a commission from the National Institute for Clinical Excellence (NICE). The commission stipulated that the guideline should concentrate on the health (ie NHS) aspects of multiple sclerosis, and that while it would include the interface with other agencies including social services, it would not discuss their detailed provision. An additional stipulation was that topics already covered by an existing NICE appraisal report would be incorporated without further assessment.

For many areas of MS there is little evidence upon which to base recommendations, and the gaps between the evidence have been filled with recommendations, based on a formal consensus of the experts on our guideline groups. In each section of the document the level of supporting evidence is made clear on the understanding that the stronger the evidence the greater likelihood that the recommendations based on it are sound. However the reader should not equate level of evidence with strength of recommendation – some of the most important recommendations, with the greatest consequences for the health service or for people with MS, have been made by group consensus because there was inadequate evidence. This is what the experts believe to be best practice – what they would recommend for their patients or relatives.

While the detail of local implementation of this guideline may vary (according to local facilities and geography), the main aims ought to be common across England and Wales, and if adopted should lead to better standards of care and thus better outcomes from this often distressing condition. There may be some readers who will find particular recommendations, especially those reached by consensus, hard to accept, and to them the challenge is to go out and produce and publish evidence to either confirm or refute what this guideline sets out. This additional research and thought applied to multiple sclerosis could make future versions of this guideline even stronger.

Mike Pearson FRCP

Director, National Collaborating Centre for Chronic Conditions

Executive summary

Multiple sclerosis (MS) is diagnosed in 3.5 to 6.6 people per 100,000 of the population each year, equivalent to about 1,800 to 3,400 people each year in England and Wales. Prevalence is between 100 to 120 per 100,000 of the population, equivalent to about 52,000 to 62,000 people with MS in total in England and Wales.

Some people with MS develop few symptoms, but for others the disease and society's interactions with them lead to problems affecting all aspects of their lives. The disease often has an impact upon the family.

Many people with MS need to make extensive use of primary and secondary health care, and social services. This guideline suggests how clinical services for people with MS can be improved both in terms of delivery and in terms of specific interventions. The needs of people with MS are similar to those of many other patients with long-term conditions, and this guideline will have general lessons which can be applied more widely than just MS.

The following recommendations have been identified as priorities for implementation.

▷ Specialised services

MS is a relatively rare condition often leading to complex problems that require expert services. We recommend that *specialist neurological and neurological rehabilitation services should be available to every person with MS when they need them, usually when they develop any new symptom, sign, limitation on activities or other problem, or when their circumstances change*. We have made suggestions about what this might mean for commissioners in the audit criteria section of the guideline (Section 7).

▷ Rapid diagnosis

Once a patient has experienced symptoms suggestive of MS, a rapid diagnosis is needed. This ensures that any required treatments are started, and reduces anxiety and uncertainty. We recommend that *an individual who is suspected of having MS should be referred to a specialist neurology service and seen rapidly within an audited time. The individual should be seen again after all investigations necessary to confirm or refute the diagnosis have been completed (also rapidly within an audited time).**

▷ Seamless services

People with MS often have complex problems requiring input from many different groups both within and outside the NHS. Many find that bureaucracy and border disputes lead to stress and

* The Guideline Development Group debated the meaning of the word 'rapidly'. In this context, it is taken to mean that the exact time will vary according to clinical need but should, in the opinion of the development group, be no longer than six weeks from referral to being seen by a neurologist, and a further six weeks until any necessary investigations are completed.

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delays in even the simplest of actions. Current policies should lessen this, but still we recommend that *every health commissioning organisation should ensure that all organisations in a local health area agree and publish protocols for sharing and transferring responsibility for and information about people with MS, so as to make the service seamless from the individual's perspective.* We recommend that these protocols are publicly available and that the timescales involved are audited to ensure that unnecessary delays do not occur.

▷ A responsive service

People with MS can experience one or more of a wide variety of symptoms and difficulties. Each person's needs are unique, and a flexible response is required from the NHS. We recommend that *all services and service personnel within the health care sector should recognise and respond to the varying and unique needs and expectations of each person with MS. The person with MS should be involved actively in all decisions and actions.* In other words, services should be patient centred. A patient-led system of audit can help address some of the difficulties in monitoring this.

▷ Sensitive but thorough problem assessment

The great variety of possible problems that people with MS may have can make it difficult for health care professionals to detect all relevant changes. We have recommended that *health service professionals in regular contact with people with MS, should consider in a systematic way whether the person with MS has a 'hidden' problem contributing to their clinical situation, such as fatigue, depression, cognitive impairment, impaired sexual function or reduced bladder control.* The main text of the guideline details the various problems that a person with MS may have and appropriate ways of treating these problems.

▷ Self-referral after discharge

There is no predictable pattern or progress of the condition in any individual with MS, but problems may arise quickly at any time. Some people therefore have routine appointments 'to keep in touch', which is wasteful and perpetuates a dependent approach, while many others 'fall out' of the system until a crisis occurs. We have strongly recommended that *every person with MS who has been seen by a specialist neurological or neurological rehabilitation service should be informed about how to make contact with the service when he or she is no longer under regular treatment or review. The individual should be given guidance on when such contact is appropriate.* This recommendation should mean that each specialist service (neurology, and neurological rehabilitation) has in place a mechanism for accepting and responding to direct contact by someone with MS, even when they are no longer under regular treatment or review by that service.

Conclusion

The full document gives specific advice to clinical staff on a huge range of issues such as the management of bladder problems, the treatment of spasticity, therapy for reduced walking ability and the identification and management of difficulties in swallowing. One strong message

[Executive summary](#)

is that clinical staff need to be systematic in their approach to each person with MS so that all remediable problems are identified and managed effectively. This depends upon a well-trained body of staff working in a team with appropriate support from information systems.

Finally, the document emphasises the importance of prevention of ill health, which is a vital function of the NHS. Prevention is especially important in people with long-term conditions because they are often at risk of many specific secondary conditions. For example people with MS may experience infections, contractures, and falls. However, the occurrence of a pressure ulcer is perhaps the most serious and the best marker of service quality. We have suggested that the occurrence of a pressure ulcer in someone with MS should be considered an adverse event worthy of formal investigation.

If the NHS can deliver a good service to people with MS then it will also be delivering a good service not simply to other people with neurological disability but to all people with long-term conditions. This guideline should help set the NHS on course for this.

Glossary

Activities of daily living (ADL)

This phrase refers to activities or tasks undertaken as part of day-to-day life such as getting dressed, cooking or shopping. They can be subdivided into personal ADL, domestic (household) ADL, and community ADL.

Adverse events

Sometimes known as side effects. Adverse events are any event that is not to the benefit of the person. Some are predictable, and some are only rare and unexpected. Adverse events from drugs might include, for example, rashes, feeling fatigued and being depressed. Adverse events can also follow rehabilitation treatments and might include falling while learning to walk and pain from stretching a joint.

Allied health professionals

Health care professionals, other than doctors and nurses, directly involved in the provision of health care. Includes several groups such as physiotherapists, occupational therapists, dieticians, etc. (Also known as professions allied to medicine or PAMs.)

Alternative therapies

A term that is difficult to define because the classification of therapies is not fixed. This usually refers to treatments of any type which are not prescribed or recommended by doctors, or are not given by health care professionals practicing within the NHS.

Applicability

The extent to which the results of a study or review can be applied to the target population for a clinical guideline.

Appraisal of evidence

Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.

Area under curve (AUC)

See *receiver operating curve (ROC)*.

Association of British Neurologists (ABN)

The professional body to which all neurological specialist physicians belong.

ATG

Anti-thymus globulin.

Bias

Systematic errors in the design and execution of a study which may lead to an over- or underestimation of the 'true' effect of a treatment or intervention.

Blinding

The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned or of the population from which the subject has come. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' is to protect against bias.

British National Formulary (BNF)

The BNF is the recognised authoritative source of up-to-date information on drugs and pharmaceutical products for health care professionals. The emphasis is on those that are prescribed in the UK, rather than over-the-counter medicines. It is a joint publication of the British Medical Association (BMA) and the Royal Pharmaceutical Society of Great Britain (RPSGB).

CAM

Complementary and alternative medicine, eg acupuncture, homeopathy.

Cardiorespiratory fitness

The extent to which the heart and lungs are able to respond to demand. Fitness depends upon a) muscles, primarily in the legs and b) the heart and lungs.

Case-control study

A study that starts with the identification of a group of individuals sharing the same characteristics (eg people with a particular disease) and a suitable comparison (control) group (eg people without the disease). All subjects are then assessed with respect to other factors, such as things that happened to them in the past, eg things that might be related to getting the disease under investigation.

Ceiling effects

See *floor and ceiling effects*.

Cerebro-spinal fluid (CSF)

Fluid produced in hollow structures within the brain that circulates around the outside of the brain and also down the spinal canal. CSF is removed when a lumbar puncture is undertaken.

Clinical audit

A systematic process for setting and monitoring standards of clinical care. Patients' notes and other clinical records are examined as part of the

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audit process. Clinical audit should cover the practice of all relevant health care professional groups, as opposed to medical audit which only looks at the doctor's role in patient care.

Whereas 'research' defines what the best clinical practice should be, 'audit' investigates whether best practice is being carried out.

Clinical effectiveness

How well a drug, treatment or package of care works to produce good outcomes for patients.

Clinical importance

The importance of a particular guideline recommendation compared with other aspects of clinical management that may be under consideration.

Clinical trial

Research study conducted with patients, usually to evaluate a new treatment or drug. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. See also *randomised controlled trial*.

Clinician

A health care professional providing patient care, eg a doctor, nurse or physiotherapist.

Cochrane Library

The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). The Cochrane Library is available on CD-ROM and on the Internet.

Cognitive status

Cognition refers to the processes involved in thinking, concentrating, planning, solving problems, learning, analysing sensations and remembering. A person's cognitive status is the extent to which they can use their brain to undertake these processes.

Cohort study

A cohort study takes a group of patients and follows them forward in time and measures their outcome (eg disease or mortality rates). Patient subgroups are then identified from information collected about patients and these groups are compared with respect to outcome, eg comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent cohort study') or identified from past records and followed forward from that time up to the present (a 'historical cohort study'). Because patients are

not randomly allocated to the two groups, the groups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Competence

In legal terms, this refers to the ability of someone to make an informed judgement and it depends upon being able to understand written or spoken material sufficiently, hold the information in the memory and use the material to make a considered judgement.

Complementary therapies

See *alternative therapies*.

Computerised tomography (CT)

A technique whereby X-rays are used to map the inside of the body, especially the brain.

Confidence interval

This helps us assess the likely effect of a clinical intervention by describing a range of possible effects that are consistent with the results of a study (or of a combination of studies). A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. We usually interpret a 95% confidence interval as the range of effects within which we are 95% confident that the true effect lies.

Confounding factor

Something that introduces uncertainty and bias into an observed outcome, complicating interpretation.

Consensus methods

A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.

Consistency

The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also *homogeneity*.

Control group

A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group

receiving an experimental treatment, such as a new drug.

Controlled clinical trial (CCT)

A study that includes some form of control that is not randomised.

Correlation

A measure of the strength of association between two or more variables. For example in children height, weight and age are all correlated because older children tend to be taller and heavier. A positive correlation indicates that one variable has been observed to increase as the other increases, a negative correlation indicates that one decreases as the other increases.

Cost-benefit analysis

A type of economic evaluation where both costs and benefits of health care treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost-effectiveness

How expensive treatment and care are compared to how much benefit they offer to patients. In cost-effectiveness analysis, the outcomes of different interventions are converted into health gains for which a cost can be associated, for example, cost per additional heart attack prevented.

Crossover study design

The administration of two or more experimental treatments one after the other in a specified or random order to the same group of patients.

Decision analytic model

A method, in health economics, of establishing the best course of action when evidence, both clinical and cost, is uncertain.

Department of Health

A generic term for four UK government departments responsible for the health and well-being of people in England, Wales, Scotland and Northern Ireland, and having specific responsibility for the National Health Service (NHS) and Social Services Inspectorate (SSI).

DGH

District general hospital (non-teaching hospital).

Diagnostic odds ratio (DOR)

DOR is used as a summary measure of the accuracy of a diagnostic test. It is calculated as the odds of a correct positive result, divided by the odds of a false positive result. When a test provides no diagnostic evidence then the DOR is 1.0, but a valuable diagnostic test will tend to have a high DOR.

Diagnostic study

Any research study aimed at evaluating the utility of a diagnostic procedure. The methods employed are generally different to those in a *clinical trial* aimed at evaluating an *intervention*.

Diagnostic work-up

The process of making a diagnosis through tests, clinical history and clinical judgement.

Disease modifying therapies (DMTs)

Any treatment that slows down, stops or reverses the processes that damage the nervous system in MS.

Disease progression

This specifically refers to increasing damage to the nervous system. There is only a weak relationship between damage to the nervous system and increasing symptoms or signs. And some episodes of worsening are simply due to another illness (eg bladder infection) and not progression of the damage to the nervous system.

Dominant

An economic term for an intervention which is cheaper and clinically more effective than the alternative(s).

Dysarthria

Difficulty of articulating words caused by disease of the central nervous system, typically characterised by slurred speech, imprecise articulation and disorders of intonation.

Economic evaluation

Comparative analysis of alternative courses of action in terms of both their costs and consequences.

Effectiveness

The extent to which a specific treatment or intervention, when used under usual or everyday conditions, does what it is intended to do, eg control or cure an illness. (Clinical trials that assess effectiveness are sometimes called 'management trials'.)

Efficacy

The ability of a drug or other treatment to control or cure an illness. In research terms, 'efficacy' refers to the extent to which a specific intervention produces the intended (beneficial) result under ideally controlled conditions, eg in a laboratory.

Episode of care

A technical, Department of Health term that refers to the whole of a treatment episode from hospital admission to discharge or from starting to stopping a course of treatment.

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Evidence-based

The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.

Evidence table

A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Evoked potentials

Electrical changes in the brain that follow stimulation of the nervous system. The commonest example is to flash lights in the eyes, when an electrical change will occur over the occiput (back of the head) about 1/10th of a second later. They can only be detected using computers and many repeated stimulations because the potentials are so small.

Experimental study

A research study designed to test if a treatment or intervention has an effect on the course or outcome of a condition or disease.

Extrapolation

The application of research evidence based on studies of a specific population to another population with similar characteristics.

Floor and ceiling effects

Problems encountered in some *outcome* measures where there are limits to how low or high a numerical value they can assume, eg it is impossible to measure more than 100%. These can make it difficult to assess the true effect of an *intervention*.

Focus groups

Method of group interview or discussion of between 6 and 12 people focused around a particular issue or topic. The method explicitly includes and uses the group interaction to generate data.

Functional status

An individual's ability to continue normal social and physical activities.

Grade of recommendation

A code (eg A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.

Guideline

A systematically developed tool which describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available, rather than opinion. It is used to assist clinician and patient decision making about appropriate health care for specific clinical conditions.

Guideline recommendation

Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.

Health technology

Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion (eg the role of diet *vs* medicines in disease management) and other therapeutic interventions.

Health technology appraisal (HTA)

A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost-effectiveness of a *health technology*. NICE health technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.

Heterogeneity

Or lack of *homogeneity*. The term is used in *meta-analyses* and *systematic reviews* when the results or estimates of effects from separate studies seem to have different magnitude or even different sign or direction. Differences in the patient populations, outcome measures, definition of variables and duration of follow-up of the studies included in the analysis create problems of non-compatibility. See also *homogeneity*.

Hierarchy of evidence

An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions of a well-conducted study. Well-conducted randomised controlled trials (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than, say, one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence. See also *randomised controlled trial*.

History, clinical

The information collected and considered by a health care professional regarding an individual's previous health-related experiences.

Homogeneity

This means that the results of studies included in a systematic review are similar and there is no evidence of *heterogeneity*. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also *consistency*, *heterogeneity* and *systematic review*.

HTA

See *health technology appraisal*.

Iatrogenic

Caused by a health care treatment.

Incidence

The rate of new occurrences of a condition or disease, often given as people per year or episodes per year.

Inclusion criteria

See *selection criteria*.

Intention to treat analysis

An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment.

Intervention

Health care action intended to benefit the patient, eg prescribing drugs, surgical procedures, psychological therapy, etc.

Intervention groups

In a *clinical trial*, groups to which participants are allocated. Typically, these groups will receive different *interventions* or a *placebo*.

Level of evidence

A code (eg 1a, 1b) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles. See also *hierarchy of evidence*.

Literature review

A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.

Local protocols

See *protocol*.

Low vision service

Any local health service provided to cater for people experiencing visual problems.

Magnetic resonance imaging (MRI)

An imaging technique which uses powerful magnetic fields rather than radiation to obtain accurate images of soft tissue inside the body. Some people cannot safely be scanned with MRI, for example those with pacemakers.

Meta-analysis

Results from a collection of independent studies are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. A systematic review may or may not include a *meta-analysis*. It is always appropriate and desirable to systematically review a series of results but it may sometimes be inappropriate, or even misleading, to

statistically pool results from separate studies. See also *systematic review* and *heterogeneity*.

Methodological quality

The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.

Methodological weakness

Any problem in the way in which a study has been conducted, which throws doubt on the conclusions. See *methodological quality*.

Methodology

The overall approach of a research project, eg the study will be a randomised controlled trial, of 200 people, over one year. See also *randomised controlled trial*.

Multimodal intervention

An *intervention* comprised of more than one aspect which can affect outcomes for the patient.

Musculo-skeletal pain

Pain arising from the muscular and skeletal systems, as distinct from neurogenic pain.

National Institute for Clinical Excellence (NICE)

NICE is a special health authority responsible for providing patients, health professionals and the public with authoritative, robust and reliable guidance on current 'best practice'. NICE commissioned and funded the development of this guideline.

Neurogenic

Arising from the nervous system.

Neuropathic

Pertaining to disorders of the nervous system.

Non-experimental study

A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.

Objective measure

A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and study participants.

Odds ratio

Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in medical reports. They provide an estimate (usually with confidence interval) for the effect of an intervention. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks

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and not odds) will be very similar. See also *control group, relative risk*.

Oligoclonal banding

A phenomenon which can be detected by testing *cerebro-spinal fluid*. It can help to diagnose MS.

Optic neuritis

Inflammation of the optic nerve, which carries visual information from the eye to the brain.

Orthodox therapies

See also *alternative therapies*. Any medical or physical therapy which is usually used or recommended by health care professionals working within the NHS

Outcome

The end result of care and treatment and/or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers decide what outcomes to measure before a study begins. Outcomes are then assessed at the end of the study.

Palliative care

Care aimed at alleviating symptoms, pain and distress, and hence improving quality of life, rather than at curing or slowing progression of a disease or condition. It is often associated with, but is actually not limited to, the end of life.

PCT

See *primary care trust*.

Pilot study

A small scale 'test' of the research instrument. For example, testing (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.

Placebo

A pill, medicine, or other treatment that has no physiological effect and is used as a dummy treatment. A placebo may be used as a comparison (control) in tests on new drugs etc.

Placebo effect

A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself. See *placebo*.

Pooled estimate

An estimate of the effect of a treatment, arrived at through a *meta-analysis*.

Postpartum

After childbirth.

Pre-post study

A study design which measures outcomes in one group of people, first before, and then after, an intervention is given or initiated.

Prevalence

The proportion of a population of people who are experiencing a condition or disease at a given time.

Primary care

Health care delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other health care professionals, dentists, pharmacists and opticians.

Primary care trust

A primary care trust is an NHS organisation responsible for improving the health of local people, developing services provided by local GPs and their teams (called primary care) and making sure that other appropriate health services are in place to meet local people's needs.

Prior probability

In a *diagnostic study*, the proportion of the population which has the condition in question, regardless of what the test result subsequently is.

Probability

How likely an event is to occur, eg how likely a treatment or intervention will alleviate a symptom.

Prognostic factor

Patient or disease characteristics which influence the course of a particular condition. In a randomised trial to compare two treatments, chance imbalances in variables (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis these prognostic factors become confounding factors. See *confounding factor*.

Prospective study

A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. Prospective studies may be of several types, including cohort or randomised controlled trials. See *cohort study* and *randomised controlled trial*.

Protocol

A policy or strategy which defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, at both national and local levels.

P-value

If a study is done to compare two treatments then the P-value is the probability of obtaining the results, or something more extreme, if there really was no difference between treatments. Suppose $P = 0.03$. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of P is below 0.05 (ie less than 5%) the result is seen as *statistically significant*. Where the value of P is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the *confidence interval*.

Qualitative methods

Research techniques used to describe life's experiences and give them meaning, using a systematic, subjective approach. This type of research is conducted in order to describe and promote understanding of people's experiences, feelings, motivations and behaviour. Examples of qualitative methods include focus groups, in-depth interviews and participant observation. These techniques generate non-numerical data, eg a patient's description of their pain rather than a measure of pain.

Quality-adjusted life years (QALYs)

A measure of health outcome. QALYs are calculated by estimating the total life-years gained from a treatment and weighting each year with a quality of life score.

Quantitative methods

Research techniques that generate numerical data or data that can be converted into numbers. For example, census questions such as the number of people living in a household.

Quasi-experimental study

This is a study in which the treatment comparison groups are not assigned by randomisation.

Randomised controlled trial

A trial in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment.

The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was.

Receiver operating curve (ROC)

A mathematical method of comparing diagnostic procedures involving their *specificity* and *sensitivity*. The closer the area under the curve (AUC) is to 1, the better the test.

Reference standard

In *diagnostic studies*, the test being evaluated is often compared to the best known diagnostic procedure, which is known as the reference standard or gold standard.

Rehabilitation

Rehabilitation is a process that focuses on ability and aims to optimise social participation and to minimise distress and stress for both the person with MS and any carers involved, mainly through a problem-solving approach that will involve multi-focal interventions from a specialist team over time.

Relative risk

A summary measure which represents the ratio of the risk of a given event in group of subjects compared to another group. When the 'risk' of the event of interest is the same in the two groups the relative risk is 1. Relative risk is sometimes used as a synonym for *risk ratio*. In a treatment comparison study a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment.

Relative risk-benefit ratio

A method of comparing two interventions, balancing the risk and benefit of each to a defined population.

Reliability

Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession – and if their assessments tend to agree then the method of assessment is said to be reliable.

Review

Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.

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Sample

A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.

Sampling

Refers to the way participants are selected for inclusion in a study.

Secondary

Conditions and symptoms which are brought about by an existing disease or condition are described as secondary. For example, secondary pain can result from restrictions in mobility because of MS. The pain in this case is secondary to the MS.

Secondary care

Care provided in hospitals.

Selection criteria

Explicit criteria used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

Self-report measure

An outcome measure which uses the views and experience of the person with MS rather than clinical measurements.

Sensitivity

The sensitivity of a diagnostic test is the proportion of people with MS who, when tested, have a true positive result.

Sensitivity analysis

A mathematical process, often employed in good quality health economics studies, which assesses the sensitivity of the conclusions to inaccuracy in the estimates regarding cost, clinical effectiveness of the treatments, and the structure of the health service.

Sequelae

A condition occurring as a consequence of a disease.

Significance, statistical

Also 'significant difference' or 'significant effect'.

Specialist

Health care professional with relevant qualifications, necessary knowledge and skills.

Specificity

The specificity of a diagnostic test is the proportion of people without MS who, when tested, have a true negative result.

Stakeholder

Any national organisation, including patient and

carers' groups, health care professionals and commercial companies with an interest in the guideline under development.

Standard deviation

A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean to describe numerical data.

Survey

A study in which information is systematically collected from people (usually from a random sample within a defined population).

Systematic

Methodical, according to plan; not random.

Systematic review

A review in which evidence from scientific studies has been identified, appraised, and synthesised in a methodical way according to predetermined criteria. May or may not include a *meta-analysis*.

Systemic

Involving the whole body.

Tertiary centre

A major medical centre providing complex treatments, which receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre. See also *primary care* and *secondary care*.

Transverse myelitis

Inflammation with neurological symptoms, caused by lesions on the spinal cord.

Trial of treatment

A planned period during which a person with MS receives a treatment to find out if it will be of benefit to them as individuals.

Trust

A trust is an NHS organisation responsible for providing a group of health care services. An acute trust provides hospital services. A mental health trust provides most mental health services. A primary care trust buys hospital care on behalf of the local population, as well as being responsible for the provision of community health services.

Validity

Assessment of how well a tool or instrument measures what it is intended to measure. See also *external validity*, *internal validity*.

Well-being

A concept combining an individual's health, their quality of life, and their satisfaction. There is no universally agreed definition that is useful in the context of health care.

DEVELOPMENT OF THE GUIDELINE

1 Introduction

1.1 Guideline aim

Multiple sclerosis (MS) is a condition of the central nervous system (brain and spinal cord) that usually starts in early adult life. Once present the disease never goes; there is no cure and the person lives with the condition for life but a significant proportion of people have few or no problems. The impact of MS on the individual is variable but one constant feature is uncertainty. The condition also has an impact on family members

Many people with MS may need to make extensive use of health services and social services. Consequently, the aim of this guideline is to ensure that people with MS benefit from a coherent and consistent response from services, to minimise their problems as far as can be achieved.

1.2 Who is the guideline intended for?

A guideline has been defined as 'a systematically developed statement that assists clinicians and patients in making decisions about appropriate treatment for a specific condition'.¹

These guidelines are aimed at helping health care professionals provide optimal services for those with MS by:

- providing individual clinicians with a set of explicit statements on the best way to manage most common clinical problems to maximise the effectiveness of the service
- providing commissioning organisations and provider services with specific guidance on the best way to organise complex services, to maximise efficiency and equity.

Others, including the general public, may find the guideline of use in understanding the clinical approach to MS. Separate short-form documents for a) the public and b) clinical staff are available which summarise the recommendations without full details of the supporting evidence.

1.3 Clinical context

MS is diagnosed in 3.5 to 6.6 people per 100,000 of the population each year, equivalent to about 1,820 to 3,380 new people being diagnosed each year in England and Wales (population 52 million). Life expectancy in the majority is more or less normal. The prevalence (frequency in the population) is between 100 to 120 per 100,000, equivalent to two people for each general practitioner or 52,000 to 62,400 people in total in England and Wales.²⁻⁴ In comparison, the incidence of stroke is 240 per 100,000 each year, equivalent to about 124,800 new cases each year in England and Wales. The prevalence is about 700 per 100,000, equivalent to about 14 per GP or 364,000 people in England and Wales in total.

Multiple sclerosis is usually diagnosed between the ages of 20 and 50 years. Once diagnosed, people often recognise that they have had the condition for many years. It affects two women for each man affected. The cause is unknown, but it is thought to have several different 'causes' because the evidence suggests that there are both genetic (inherited) and environmental factors at play.

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The disease process involves episodes where white matter within the brain or spinal cord becomes inflamed and then damaged by the person's own immune system. These inflamed areas become scarred, giving the disease its name: *multiple* areas of hardening (*sclerosis*) within the brain and spinal cord. Many episodes do not cause any symptoms, but when sudden symptoms occur the person is said to have had a relapse. In some people there is simply a slow progressive increase in symptoms.

Although there is no cure, there are positive roles for the health service. These include making the correct diagnosis, trying to reduce the disease progression, and trying to help the person (if necessary) experience as few symptoms and functional problems as possible.

1.4 The challenge

The challenge facing both organisations and individual clinicians is major. MS is an extremely variable condition. The specific symptoms or signs experienced by an individual can vary. Each person will have a unique combination of symptoms, signs, personal circumstances and wishes. Furthermore, the prognosis for an individual patient is unpredictable. Through their disease pathway people with MS may present to any one of a wide range of health care professionals in any one of a wide range of specialist services. They also present to a wide range of non-health care professionals with their problems, and these professionals may know little or nothing about the condition and yet need to make decisions. Moreover, the evidence needed by a professional to make an informed decision is often difficult to find. Consequently many people with MS are seen by individuals who have relatively little expertise or knowledge, and who cannot find relevant advice easily, and who often are working in isolation away from co-ordinated services, and the service is suboptimal both for the patient in terms of effectiveness and for society in terms of efficiency and equity.

Several studies have highlighted the poor provision of services to people with MS in the UK. Freeman and Thompson surveyed an opportunity sample of 150 patients in contact with the NHS, and found many people with significant disability failed to receive services.⁵ An audit of services in Oxfordshire showed the extent of the disorganisation, and the problems faced by individual patients.⁶

Large resources are needed to help people with MS. A recent survey of people with MS at three specialist centres in England estimates a mean total cost per patient of £17,000 per year, suggesting a total burden to society of around £1.34 billion per year.⁷ Informal care accounts for 26% of this total, and direct medical cost only 16%. A cost of approximately £3,400 per patient per year falls on the NHS, and the remainder is borne by patients and their families and carers. As well as this financial cost, the quality of life of people with MS is affected by the physical limitations imposed by the disease, and also by the social limitations that follow from this and the emotional problems that may also arise.

1.5 Underlying guideline principles

The main principles behind the development of these guidelines were that they should:

- consider all issues that are important in the health care of people with MS
- use published evidence wherever this is available
- be useful to and usable by all professionals

- take full account of the perspective of the person with MS and their family
- indicate areas of uncertainty or controversy needing further research.

The problems presented by people with MS are complex, covering many aspects of illness and lifestyle. As any set of hospital notes will illustrate dramatically, it is difficult to describe their problems in a simple way. This complexity also makes it difficult to construct a set of guidelines.

The solutions to address this complexity in terms of the guidelines are:

- to use a systematic model of illness, the World Health Organization (WHO) International Classification of Functioning (ICF) model
- to consider the different aspects of the management processes separately
- to recognise that
 - people with MS have different needs
 - many people with MS will have very complex needs at different stages of their disease
 - many people may have few or no needs.

The model of illness used is the WHO's International Classification of Functioning, Disability and Health (ICF) framework (see Appendix A).⁸ This allows the description of a person with MS's situation at four levels – disease, symptoms and signs, behaviour, and social situation. It also recognises three different environmental or contextual factors – the social environment, the physical environment, and the person's own internal environment (ie their beliefs, wishes and expectations). It has a specific terminology that has been preferred throughout this document, but the older terminology is also used in places for two reasons: it is sometimes simpler, and it may be more familiar to some readers. More details are given in Appendix A.

1.6 How to use this document

The document is large, covers many topics and gives much background information. The reader is strongly recommended to use the contents page to find his or her way to the relevant part and a glossary is provided at the back of the book to clarify terminology. **The recommendations made in Section 3 apply to all other recommendations, and should be read first.**

Once the relevant part has been found, the reader will probably first look at the recommendations. Generally these follow a logical order from problem identification through simple interventions suitable in most cases, on to complex interventions that will only be used rarely. If the reader wants, he or she can then read the evidence statements above and look at the tables to understand more about why the recommendation was made.

1.7 The structure of the document

The document is divided into sections, each of which covers a set of related topics. For each topic the layout is similar.

The **background** to the topic is described in one or two paragraphs which simply set the recommendations in context.

Then the **evidence statements** are given and these summarise the evidence given in the **evidence tables**, which are Appendix I. In addition, there may be an evidence statement about the health

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economic evidence where this is available. In many parts there is a brief statement explaining how recommendations relate to the evidence.

The main **recommendations** follow. These are graded to indicate the strength of the evidence behind the recommendation.

The main recommendations are followed by **local implementation points**: these are specific areas where local clinicians need to develop local policies or guidelines to facilitate the implementation of national guidelines at the local level. They often require collaborative working between NHS services and other local statutory and voluntary sector agencies.

1.8 Guideline limitations

The document and recommendations are subject to various limitations.

The commissioning authority, NICE, is primarily concerned with health services, and so these recommendations only indirectly refer to social services, housing and so on. Nonetheless, the importance of other agencies cannot be overstated and in each locality they should become actively involved.

Not all evidence used comes from MS-specific studies. A systematic approach was used to locate and appraise the evidence. Due to the magnitude of the literature potentially relevant to MS specific inclusion or exclusion criteria were applied. The inclusion/exclusion criteria aimed to limit the included studies to those of a higher quality conducted primarily in people with MS. Where these were not available, well-conducted studies outside MS, or lower-level studies in people with MS, were included.

A general principle behind the search strategy was the use of studies relevant to the clinical situation. Where the situation was specific to MS, for example diagnosis, then the study population was limited to those with MS. However, where the situation was an impairment arising from neurological damage then the search is usually focused upon that impairment when it arose from other neurological diseases causing similar damage. Variation between people with MS is far greater than the variation between people with the same impairment arising from different neurological conditions. Therefore this was not deemed to be extrapolation and the evidence was graded directly.

In areas which primarily relate to organisational matters or general principles such as communication, full systematic searching was not undertaken because priority was given elsewhere. In these areas, existing reviews and other information readily available was considered.

The evidence base was current as of October 2002. Since then additional research findings have become available. However, it is unlikely that these would have a significant impact upon the recommendations.

Using a systematic approach coupled with the grading of evidence used means that some relevant evidence may be omitted. It also means that some recommendations appear without evidence because the recommendation seems self-evident and good practice; no one will consider researching into the area (and ethical considerations might also preclude it). We recognise that much current practice without evidence may in fact be ineffective, but we also recognise that much current practice without evidence may be highly effective and may never

acquire evidence. Consequently, we must emphasise that the lack of evidence cannot be used alone to justify a reduction or withdrawal of resources.

Finally it must be emphasised that these guidelines refer to recommended best clinical practice. It is not the purpose of these guidelines to specify what resources are needed or how appropriate resources are devoted to any particular recommendation.

1.9 Plans for guideline revision

The process of reviewing the evidence is expected to begin four years after the date of issue of this guideline. Reviewing may begin earlier than four years if significant evidence that affects the guideline recommendations is identified.

2 Methodology

2.1 The developers

The National Collaborating Centre for Chronic Conditions (NCC-CC) is housed by the Royal College of Physicians (RCP) but governed by a multi-professional partners board inclusive of patient groups and NHS management. The collaboration was set up in 2000 to undertake commissions from the National Institute for Clinical Excellence (NICE), to develop clinical guidelines for the National Health Service. NICE originally commissioned the RCP and the Chartered Society of Physiotherapy (CSP) to develop this guideline. When the NCC-CC was formed, it assumed the management responsibility, but with continuing leadership from the executive leads of the CSP and RCP.

Editorial responsibility for the guideline rests solely with the development group.

Each commission is systematically developed from the current evidence base. Two multi-professional groups, supported by a technical team from the NCC-CC, were involved in the development of the guideline:

- a small **Guideline Development Group** (GDG) that met monthly and undertook the detailed evidence assessment and recommendation drafting
- an enlarged group, the **Consensus/Reference Group** (CRG), which met early in the development to ensure the clinical questions and aims were appropriate. At the end of the process, the CRG met again to review the recommendations drafted by the GDG and to consider clinically important areas where there was insufficient evidence, and where formal consensus techniques were required to develop recommendations.

Membership details can be found on page iii of this document. The groups were formed by inviting nominations from stakeholder organisations selected by the NCC-CC to ensure an appropriate mix of clinical professions and patient groups. Each nominee was expected to serve as an individual expert in their own right and not as a mandated representative, although they were encouraged to keep their parent organisation informed of the process. All group members made a formal 'declaration of interests' at the start and provided updates during the development. The NCC-CC and the group leader monitored these.

2.2 The scope of the guideline

The scope for this guideline (see Appendix J) was developed utilising the NICE stakeholder consultation process. In summary, the guideline is required to be relevant to adults of all ages with MS, and to consider the full range of care that should be routinely available from the NHS. This includes appropriate use of mainstream pharmacological, physical therapy, rehabilitation and psychosocial treatments. Existing NICE guidance relating to interferon beta and glatiramer acetate is to be incorporated into the guideline. Since this is a guideline for the NHS, it should comment on the interface with other sectors but will not consider them in detail.

2.3 Involvement of people with MS

The NCC-CC was keen to ensure that the guideline development process was informed by the views of people with MS and their carers. This was achieved in two ways:

- by securing patient organisation representation on the guideline development groups
- by carrying out focus groups and interviews to ensure that the views of people directly affected by MS informed the guideline development process.

The Multiple Sclerosis Society and the Multiple Sclerosis Trust had a representative each on the development groups. They were therefore involved at every stage of the guideline development process and were able to consult with their wider constituencies throughout the process.

Before the first meetings of the development groups, focus groups were held to identify issues that people with MS consider important when describing the impact of MS on their lives. The study had three stages:

- focus groups with people with MS (one for people with mild to moderate MS and one for people with moderate to severe MS)
- focus group with carers of people with MS (one group)
- one-to-one interviews with people with severe MS who were fully dependent.

The patient organisation representatives helped to recruit people with MS to participate in each of the groups. Trained facilitators from the NICE Patient Involvement Unit based at the College of Health ran the groups and interviews.

Further information about this study can be found in a separate document (to be issued later). A summary of the key findings from the study and how these have informed the guideline recommendations can be found in Appendix B.

2.4 Searching for the evidence

There were three stages to this process.

- 1) First, the technical team set out a series of specific clinical questions that covered the issues identified by the project scope. The CRG met to discuss, refine and approve these questions as suitable for identifying appropriate evidence within the published literature.
- 2) The information scientist then developed a search strategy to identify the evidence for each question. Identified titles and abstracts were reviewed for relevance to the agreed clinical questions and full papers obtained as appropriate. Full papers were assessed for inclusion according to predefined criteria (Appendix C).
- 3) Finally, the full papers were critically appraised and the relevant data entered into evidence tables (see Table 1) which could be reviewed and analysed by the GDG as the basis upon which to evaluate recommendations.

Limited details of the searches with regard to databases and constraints applied can be found in Appendix C. Grey literature was searched for using the System for Information on Grey Literature in Europe (SIGLE) database. Stakeholder evidence identified via the NICE process⁹ was incorporated where appropriate.

In some sections systematic searches were not undertaken because the issue under consideration was not MS specific. Non-systematically retrieved supporting information for these sections is presented.

Evidence on cost-effectiveness was extracted from the main searches wherever it existed, this was rare but was necessary to undertake a separate search for information on the potential costs and benefits of the interventions and management strategies considered in this guideline. This search was carried out by the information resources section in the School for Health and Related Research at the University of Sheffield, and was designed in collaboration with the health economist. The GDG realised that few formal cost effectiveness analyses would be identified, therefore the search for economic evidence was very broad and designed to identify information about the resources used in providing a service or intervention and/or the benefits that can be attributed to it. No study design criteria were imposed *a priori*, ie the searches were not limited to randomised controlled trials (RCTs) or formal economic evaluations. Further details of the searches for economic evidence are given in Appendix D.

Identified titles and abstracts from the economics searches were reviewed by the health economist, and full papers obtained as appropriate. The health economist critically appraised the full papers and the relevant data was conveyed to the group alongside the clinical evidence for each question. Given that the economics searches were so broad and that no standard measure of assessing the quality of economic evidence is available, careful consideration was given to each study design and the applicability of the results to the guideline context.

A further important aim of the economics searches was to identify the key gaps in evidence on potential costs and benefits; hence the titles and abstracts were mapped to the clinical questions at an early stage, so that the GDG could decide which areas to prioritise for further work (see below).

Identifying relevant literature and evidence, evaluating the strength of that evidence, and collating it into a usable form required great efforts. It has to be recognised that:

- Relevant, often important evidence is scattered very widely, often in sources that are not easily available and sometimes not indexed.
- Much of the relevant evidence is not specific to MS (for example, evidence on the management of neuropathic pain is of great relevance but few studies are exclusively based on MS). This applies to most impairments and activities.
- Much of the evidence on costs and benefits comes from the US health care system and is therefore of limited applicability to a UK guideline.
- The scope of the topic is such that there is a great volume of evidence that the GDG considered to be of very variable quality.

2.5 Synthesising the evidence

Each paper was assessed for its methodological quality against pre-defined criteria (based upon CRD report 4 for RCTs and systematic reviews (SRs)¹⁰ and the QUADAS tool for diagnostic accuracy studies¹¹ (full details are available on request)).

Papers that met the inclusion criteria were then assigned a level according to Table 1 (overleaf).¹²

The clinical question dictated the appropriate study design that should be sought and the level was then assigned as above. RCTs were the most appropriate study design for a number of clinical questions and RCTs lend themselves particularly well to research into medicines.

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Table 1 Grading scheme and hierarchy of evidence*

Recommendation grade	Evidence
A	Directly based on category I evidence.
B	Directly based on category II evidence, or extrapolated recommendation from category I evidence.
C	Directly based on category III evidence, or extrapolated recommendation from category I or II evidence.
D	Directly based on category IV evidence, or extrapolated recommendation from category I, II or III evidence.
DS	Evidence from diagnostic studies.
HSC	Health service circular 2002/2004.
Evidence category	Source
Ia	Evidence from meta-analysis of randomised controlled trials.
Ib	Evidence from at least one randomised controlled trial.
IIa	Evidence from at least one controlled study without randomisation.
IIb	Evidence from at least one other type of quasi-experimental study.
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

*Adapted from Eccles M, Mason J.¹²

However, they were not the most appropriate study design for some other questions, particularly in the area of rehabilitation where interventions are often tailored to the needs of the individual. The result is that evidence on pharmaceutical interventions tended to receive higher levels than for other equally valid interventions. This should not be interpreted as a preference for a particular type of intervention nor as a reflection on the quality of the evidence for questions where non-RCT evidence is valid and appropriate.

2.6 Health economics evidence

The mapping exercise, based on the titles and abstracts identified in the broad search for economic evidence, confirmed that very little information on cost effectiveness was available; of the 464 papers identified there were only nine economic evaluations based on RCTs. In general the economic information came from studies that considered either costs or outcomes but not both. In addition the majority of studies did not investigate specific interventions or services, but rather considered the overall cost of MS to society and/or the individual with the condition, or they dealt with measuring quality of life in general in MS. This evidence could only be of limited use in informing the recommendations.

The health economics input was therefore distinguished according to whether or not formal economic evaluations were available. Where this type of evidence did exist it was presented alongside the clinical evidence with advice on the quality of the evidence and its applicability to the recommendations. However, in the majority of areas there was no formal economic evidence and this problem was exacerbated by a lack of systematic and readily available information on:

- the potential costs and benefits of any of the specific interventions or models of service delivery considered – this is particularly problematic in relation to benefits, as costs can often be estimated from other sources
- the current resource use associated with MS both in the NHS and wider society
- the current range of clinical practice within the NHS.

While health economic analysis can provide a framework for collating information from a variety of sources in order to estimate, and systematically compare, costs and benefits, this is a complex and labour intensive process and it does require a level of clinical evidence that is not readily available in MS. As a result the group prioritised those areas, which they believed would benefit most from additional information on costs and benefits. Priorities were assessed on the basis of:

- potentially large health benefits
- a potentially large effect on NHS resources (positive or negative)
- considerable uncertainty surrounding the benefits and resources
- potentially large service impact
- important equity considerations.

A number of areas were suggested by the health economist and the clinical advisor, and the GDG identified three priorities: the use of magnetic resonance imaging (MRI) scans in the diagnosis and continued management of MS; the delivery of high dose corticosteroids for acute relapse; and the issue of specialist *vs* generalist services for the provision of care. This third area was not explored in detail due to time constraints. Details of the work carried out in the first two areas are included in Appendices E and F.

2.7 Drafting the recommendations

Evidence for each topic was extracted into tables and summarized in graded evidence statements. The clinical advisor used this evidence to draft recommendations that were provided to the group prior to the meetings. The GDG reviewed the recommendations and their grading at their meetings and reached a group opinion. Recommendations were explicitly linked to the evidence that supports them and then graded according to the level of the evidence upon which they were based. Although the grade given to a recommendation reflects the level of evidence on which it is based, it does not necessarily reflect the importance attached to the recommendation. Furthermore, the level of evidence is based on a single hierarchy of research design, but in reality different designs are appropriate for different types of research problem. Specifically in research into rehabilitation and research involving people with long-term conditions, other designs and methodology such as single case studies, quasi-experimental designs, qualitative studies and correlational studies based on prospective observational cohorts will often be stronger than randomised controlled studies. Consequently many of the recommendations that received a grade D were nonetheless those that the GDG felt were the most important.

2.8 Agreeing the recommendations

A one-day meeting of the CRG was held after the evidence review had been completed and when an early draft of the guideline produced by the GDG was available. The CRG considered the draft guideline in two stages using a Rand modified nominal group technique,¹³ first via a pre-meeting vote and again in a formal meeting:

- 1) Are the evidence-based statements acceptable and is the evidence cited sufficient to justify the grading attached?
- 2) Are the recommendations derived from the evidence justified and are they sufficiently practical so that those at the clinical front line can implement them prospectively? There were three types of recommendation to be considered:
 - a) A recommendation from the GDG based on strong evidence – usually non-controversial unless there was important evidence that had been missed or misinterpreted.
 - b) A recommendation that was based on good evidence but where it was necessary to extrapolate the findings to make it useful in the NHS – the extrapolation approved by consensus.
 - c) Recommendations for which no evidence exists but which address important aspects of MS care or management – and for which a consensus on best practice could be reached.

The formal consensus methods that have been established within the NCC-CC, drawing on the knowledge set out in the health technology appraisal,¹³ and practical experience. It made full use of electronic communication and voting techniques and will be fully described in separate publications

2.9 Writing the guideline

The guideline was drawn up by the technical team in accordance with the decisions of the guideline development groups. The draft guideline was circulated to stakeholders according to the formal NICE stakeholder consultation and validation phase⁹ prior to publication, and modifications, approved by the GDG, were made as a result.

THE GUIDELINE

3 General principles of care

An effective, efficient and high quality service depends as much upon its organisation and style as it does upon individual competence. For example, there is little point in having an excellent service for people with continence problems if less than 20% of that group are ever seen in the service or have the problem identified. There is much evidence that patient dissatisfaction with services is primarily focused on organisational matters and communication.¹⁴ Consequently this section covers various topics that apply to the overall management of MS.

This section is divided into five main interlinked areas:

- 1) Interaction between the professional and person with MS
- 2) Interactions between the team and the person with MS
- 3) Service organisation and inter-relationships between services
- 4) Within-team communication – a conceptual framework
- 5) Provision of services over time.

Evidence on the areas covered in this section is generally scant and difficult to synthesise, and with little of it specific to MS. For example, the evidence supporting specialist stroke services could be used to support some of the recommendations.¹⁵ Systematic searching was not undertaken for this section, but supporting evidence is provided.

These guidelines cannot cover all general aspects of good patient care; this section will emphasise those areas that specifically concern people with MS. Specific aspects have been given specific recommendations, and important general aspects that apply to all patients with any condition are found in the accompanying tables.

The recommendations made in this section stress the importance of patient-centred teamwork and the need to consider all aspects of a person with MS's situation.

3.1 Interaction between the professional and person with MS

Most studies of the experience of service users¹⁴ show that many professionals appear to have an inappropriate attitude towards people with MS, who often feel deprived of the information and support they want. There are also discrepancies in perception between people with MS and professionals concerning health care needs.¹⁶ These findings suggest the need for improvements in:

- style and manner of communication, especially of initial diagnosis
- accuracy and detail of information given
- recognition of the emotional consequences of the information given
- acknowledgement that people with MS have expertise and have views that should be taken into account
- encouragement of self-management by people with MS.

3.1.1 Communicating and giving information

Many studies have emphasised the importance of good communication between individuals and health care professionals.

Anyone can now access vast amounts of information on any topic using the Internet, and there are books available in public libraries on almost any topic. However much of this information is of low quality, inaccurate, and/or difficult to understand. Therefore it is vital for health care professionals to take seriously the provision of accurate, relevant and appropriately presented information to people with any disease.

Many people with MS have some impairment of cognitive skills, and some have visual impairment. These are two important factors to consider in all communication. All the basic principles of good practice apply (see Table 2) and information provided in the section on 'Encouraging autonomy/self-management' (3.1.3) is also of relevance.

▷ Health economic statements

It is not possible to say anything certain about the economic implications of improved information provision and communication. It is not clear what NHS resources are currently devoted to this, but they are unlikely to be substantial. Improvements in co-ordination of information could potentially result in savings through increased efficiency, and this is particularly true of the interface between primary and secondary care and between the NHS and social services. Good information provision may directly improve patient well-being by reducing uncertainty, relieving stress and contributing to empowerment if the patient is more involved in decisions about care. This may also have subsequent effects in terms of functional status. In addition, information may change the pattern of service use and this will also have the potential to benefit patients, carers and their families. However, if current provision is very poor, then substantial resource increases may be required in order to improve the situation. A significant part of this will be required to equip health professionals with the necessary skills to assess individual patient needs for information.

RECOMMENDATIONS

R1	All communication with all people with MS should comply with the general principles of good communication, shown in Table 2.	D
R2	Some people with MS may not be able to follow everything fully or remember complex details. This includes people who have no obvious disability. So, when talking to the person with MS, the health care professional should: ● be straightforward ● check the person has understood ● back up what was said with written (and other) material ● reinforce as necessary.	D

LOCAL IMPLEMENTATION POINTS

Local services will need to:

- provide leaflets and other information for the people with MS detailing local NHS, social care and voluntary sector resources

3 General principles of care

- ensure that information is accurate and up to date and takes into account local ethnic and language needs
- ensure that there are mechanisms for disseminating information to those who need it.

Table 2 Principles of good communication in health care

Principle (what the health care professional should do in any communication)	Comment
Communicate in a suitable environment, usually a quiet area or room free from distraction or interruption.	Privacy and quiet are important.
Seek agreement from the person with MS that anyone present can be there and ensure that as far as possible anyone she or he wants present is there.	Consider especially students and family.
Start by asking what the person knows or believes already.	Establishes expectations.
Establish the nature and extent of the information that the person wishes to receive.	Establishes expectations.
Consider carefully the balance between the benefits and the risks associated with giving each item of information.	Once given information cannot be withdrawn.
Tailor the communication to the person's: • specific situation • communicative and cognitive abilities • culture.	Makes information relevant.
Limit information given to that within your own knowledge, referring on to others as necessary for more detailed information.	Do not give information if uncertain about it.
Clarify specifically any options and choices the person may need to choose, specifying: • likely outcomes of each choice • benefits and risks of each choice.	Both in diagnosis and treatment.
Offer back-up with information being given: • in different ways (eg written leaflets, tapes) • by different people (eg specialist nurse) • at another time (eg follow-up appointment).	Information is often forgotten.
Inform the person with MS about any recommended local or national sources of further information including employment and voluntary sector sources.	Allows person with MS to follow-up and take more control.
Consider need for emotional support during process, especially if the information might be stressful, and arrange emotional support if needed.	Should be considered an intrinsic part of the process (see R3).
Document in notes and inform other healthcare staff closely involved what has been communicated, especially to the general practitioner.	Ensures consistency over time and across settings.

Failure in communication between health care professionals and people with MS was a common theme in the focus groups. The development group there felt it was essential to have recommendations on communication, and indeed took this as the first topic to consider. The development group reviewed the evidence summarised in 4.2 and took into account all the evidence of factors (such as poor memory and visual disturbance) that might affect communication. During several long discussions and debates, a series of specific recommendations were derived, primarily through consensus. In the interest of brevity and clarity, these were then converted to this table of recommendations.

3.1.2 Giving emotional support to people with MS

MS is a disease that causes emotional distress in many ways:

- it often starts at a young age when individuals are anticipating marked life development
- it is unpredictable and causes much uncertainty
- it has a bad 'reputation' and expectations are often worse than reality
- it can lead to many cumulative losses over many years
- feelings of control can be lost
- the effects on family members and changing interactions between family members can also increase emotional distress.

The management of anxiety and depression is covered in Section 6. Here we consider the emotional support that may be required by any person, at any time, and which is frequently requested by people with MS, especially in the early stages.¹⁷ When reading the evidence and considering the recommendations, we have taken the following into account. *Counselling* is a word used both in relation to giving information, and in relation to giving emotional support. *Emotional support* may take two forms: a formal therapeutic process (eg psychotherapy) that usually requires training and expertise, and an informal process that, although it may be improved by training, is part of many personal interactions which occur between the person with MS and both professionals and non-professionals.

This section is primarily concerned with informal emotional support. Within the process of informal emotional support given by knowledgeable professionals there is also inevitably a component of giving information (another aspect of 'counselling'), which may itself reduce emotional distress.

► Evidence statements

Three RCTs that assessed the utility of neuropsychological compensatory training, psychotherapy and coping skills training for persons with MS were identified (Ib). The first RCT assessed the effectiveness of traditional psychotherapy compared to participation in a 'current affairs' topic group or no intervention. The results showed psychotherapy to be superior on two of the four outcome measures assessed, namely depression and locus of control. However, it had no significant effect on either anxiety levels or levels of self-esteem.¹⁸ The second RCT examined a coping skills group compared to non-directive peer telephone support. The coping skills group entailed formal therapist support and considerable contact time, whilst the telephone support group was informal and only entailed one hour a month. No overall differences between the groups were observed on any of the five outcome measures.¹⁹ The last RCT compared neuropsychological compensatory training to supportive psychotherapy. The results indicated beneficial effects on measures of social aggression, but no difference between the groups on measures of depression or personality change.²⁰

One controlled clinical trial (CCT) compared client-centred psychotherapy to a no-treatment control in patients with MS. The results indicated beneficial effects on four of the seven outcome measures assessed, with all of these being within inter- or intra-personal domains²¹ (IIa). Two further CCTs were identified that examined therapeutic groups for persons with either MS or spinal cord injury. However, both of these studies reported only within subject results and therefore no comparison could be made as to the efficacy of the interventions between the groups.^{22,23}

3 General principles of care

Two uncontrolled pre-post studies examining coping skills training and stress management instruction were also included. The first study assessed coping skills training in patients with MS. The results showed an overall beneficial effect on measurements of depression, physical mobility and emotional reaction.²⁴ The second study examined the efficacy of stress management instruction in patients with disease of mixed aetiology. The results showed a positive effect on two of the four outcome measures assessed^{24,25} (III).

▷ Economic statements

The current resources devoted to emotional support are not known. Any recommendation to increase assessments for psychological symptoms and offer various types of counselling will result in increased resource use. However, savings may result from increased efficiency if counselling is being used inappropriately at present, and also if counselling reduces the need for other health interventions. The benefits for patients, carers and their families are potentially very large, including reduced stress and anxiety and improved functional status. Good quality cost effectiveness analyses of psychological support for people with MS, including the different ways in which this support could be provided, are required.

▷ From evidence to recommendations

Formal psychotherapy may require many resources, and we felt that the evidence reviewed was insufficient to allow any firm recommendations to give formal therapeutic intervention. However the evidence suggests some possible benefits for giving emotional support in some way which leads to our consensus recommendations.

RECOMMENDATION

- R3 A person with MS may benefit from emotional support; this should be considered by each individual and team in contact with the individual. Where possible, that emotional need should be met directly or through referral to a suitable resource. D

LOCAL IMPLEMENTATION POINT

Local services will need to agree which individual people or services locally, both within the NHS and elsewhere, are sufficiently expert and knowledgeable about MS to provide emotional support to people with MS who have particularly great need.

3.1.3 Encouraging autonomy/self-management

People with MS have their disease for life, and may only see any individual professional for a short time. Moreover, the person with MS has to live with the consequences of any decisions made and in the absence of firm evidence for most decisions, it is especially appropriate to involve the individual in all decisions as far as they wish. Encouraging self-management is consistent with recent moves towards the 'expert patient',²⁶ which aims to use patients to give other patients the skills, knowledge and confidence to participate actively in all aspects of their own health care.

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▷ Evidence statements

One RCT assessed the effect of a self-care program for patients with MS living in the community. Overall, the results showed no positive benefit with significant changes only on two out of six of the items assessed.²⁷

▷ Health economic statements

The economic implications of encouraging patient autonomy are uncertain. An intensive patient education programme for self-management in people with asthma resulted in improved outcomes in the intervention group with no significant difference in costs.²⁸ However, the patient group and the geographical location (Finland) undermine the relevance of these to the population of people with MS in the UK. The balance of resource burden between the NHS and the patient and their family is an important factor in any move towards self-management.

▷ From evidence to recommendations

The evidence specific to MS is sparse. However, the GDG also took into account emerging evidence in other areas of health care, and the move from NHS towards encouraging greater patient autonomy. It therefore reached strong consensus behind the recommendations made.

RECOMMENDATIONS

R4 People with MS should be enabled to play an active part in making informed decisions in all aspects of their MS health care by being given relevant and accurate information about each choice and decision. **D**

R5 As far as possible, people with MS should be helped to manage their own general health through the following information and advice provided in written, audio or other media on: **D**

- specific activities that promote health maintenance and prevent complications
- changes in their health that may require them to take further action
- the condition and its management, including both local and national sources of further information and support in clear and accessible language.

This function should be fulfilled by working in conjunction with local voluntary organisations and through acquiring the skills needed to:

- seek, evaluate and use advice and help available
- communicate effectively with health care professionals (for example, through participation in the Expert Patient Programme (<http://www.doh.gov.uk/cmo/progress/expertpatient/index.htm>)).

LOCAL IMPLEMENTATION POINTS

Local services will need to discuss and specify:

- who is responsible for providing information on self-management for people with MS
- who is responsible for providing access to self-management programmes (such as the Expert Patient Programme) for people with MS
- making all screening and disease-prevention programmes accessible to people with long-term illness.

3.1.4 Support to family and informal carers

Family members, and sometimes close friends, of a person with MS may play three roles, related to the MS, and often need help with these.

- 1) They may provide physical assistance or supervision. While many families will do this willingly, there is a risk that a normal family relationship may change to a patient-carer relationship.
- 2) They may become the main social contact for the person with MS, making the relationship increasingly intense. This may then lead to significant interpersonal strains, and distress both the person with MS and the family member(s).
- 3) They may take over responsibility for family roles once held by the person with MS, such as earning money, running the household or being a parent. This may cause stress on the family member if other roles are not relinquished, may upset the person with MS and may stress family relationships.

Such informal supporters and carers often live under the same roof, but some may perform these roles at a distance. Children (sometimes of a young age) are often involved in one or more of these roles and the effects of having a parent with a disabling condition can be severe.

The recognition of these factors and the provision of assistance where possible may benefit both the person with MS and the family itself. Sometimes the needs and wishes of family members may conflict with those of the person with MS, and this must be acknowledged. One must bear in mind that a) the person with MS and the family member(s) may have different general practitioners and social workers and b) the primary responsibility of the health care team is usually to the person with MS.

► Evidence statements

Three studies assessed the effectiveness of support for caregivers of people after stroke. One RCT and one CCT assessed the benefits of an educational group for patients who had suffered a stroke and their main caregiver. The RCT that compared a stroke educational program to the use of standard stroke unit information leaflets showed beneficial effects only in terms of the patient and carer's knowledge about stroke. No differences were observed between the groups on any measure of either patients' or carers' health status, activities of daily living (ADL) or levels of anxiety and depression²⁹ (Ib). The CCT compared a group educational program to home visits or no intervention for patients caregivers. The results showed beneficial effects for both programs compared to no intervention on two of the four outcome measures, but no significant difference between the different program groups³⁰ (IIa). The last RCT examined the utility of Stroke Association family support compared to normal care. The results showed beneficial effects on two out of the four measures assessed for carers, but no difference between groups on any outcome measures for the patients³¹ (Ib).

► From evidence to recommendations

Consensus was used to agree recommendations as the evidence available neither supported nor refuted the benefits of providing carer support.

RECOMMENDATION

- R6** Family members (including any school children) living in the same house as a person with MS, and family members delivering substantial support (even if living elsewhere), should be supported by: **D**
- asking about their physical and emotional health and well-being, especially in the case of children aged 16 years or less, and offering advice and referring on for additional support if necessary
 - providing them with general factual information about MS; this should only be extended to include more specific information related to the person with MS with the permission of that person
 - ensuring that they are willing to undertake support of personal activities of daily living (such as dressing and toileting), are safe and competent at such tasks, and that the person with MS is happy for them to provide such assistance
 - informing them about social services and their entitlement to carer assessment and support procedures.

LOCAL IMPLEMENTATION POINTS

Local services should:

- identify services able to assess and support children of people with MS
- collate and publicise information about statutory and non-statutory support services available for families and carers locally and how to access them.

3.2 Team approaches to rehabilitation

3.2.1 Interactions between the team and the person with MS: approaches to rehabilitation

Specific aspects of rehabilitation are covered in later sections; here we consider the general approach to rehabilitation. Because few of these issues are specific to MS, no systematic review has been undertaken.

▷ Assessment and measurement

The process of assessment refers both to the collection and to the interpretation of data needed to identify problems (screening) and to inform the solutions. The process of assessment may or may not include measurement, which is the quantification of data against some metric. In other words, an assessment procedure may be considered to have two purposes which may be distinct or combined:

- the **detection** of a phenomenon (ie diagnosis); and,
- the **measurement** of a phenomenon.

Evaluation of a diagnostic tool in one setting is not necessarily transferable: a measure for use in one context, such as research with a small, homogenous group, may be unsuitable for day-to-day clinical practice. Few studies have evaluated measures in different settings or in comparison with each other. Consequently we have not systematically reviewed the evidence and cannot make any specific recommendations about which measures to use (see Table 4 and Appendix H).

3 General principles of care

A common approach across all services will make assessment more efficient, less repetitious for the person with MS, and provide an impetus towards an integrated delivery of services.

The specific issues relating to the detection (diagnosis) of specific problems arising in people with MS are that the person:

- may have or develop one or more of a large range of specific problems
- may have problems that are not always obvious, and which may come on insidiously so that even the person with MS is unaware
- may be unaware that something can be done to alleviate problems and so may not mention them
- may be in touch with someone who focuses on only one problem, and who may fail to detect or know about others, consequently not referring the patient on to appropriate services for further treatment.

Consequently it is important to have systems in place that:

- check at appropriate intervals whether the person with MS has common problems
- do not waste the time of the person with MS or the health care professional.

The specific issues relating to the measurement of problems arising in people with MS are that:

- the person with MS may have many problems that could be measured, and each measure may take considerable time and effort that may waste resources unless each measurement has a clear and relevant purpose
- many measures are available for almost every single phenomenon but there is minimal data available to guide the choice of measure, and none may be appropriate
- the presence of multiple impairments in one person may make the measurement of some phenomena either difficult or impossible, and also may complicate interpretation of the data.

One solution in many clinical situations is for the team members to identify and specify their goals as a method for evaluating an intervention. This is often referred to as 'goal attainment scaling' which has become well recognised as a useful method for evaluating complex and varied interventions.^{32–34}

The recommendations made here are intended to ensure that the person with MS has any difficulties detected as soon as possible so that the difficulty is managed, often by referring on to the appropriate service for expert further assessment and management. The recommendations are also intended to give general guidance on measurement. Because the clinical situation and time course of people with MS can vary so greatly, this section uses an 'episode of care' to mean any series or programme of interactions with health care staff or teams concerned with the same underlying problem. It is trying to ensure that problems are not overlooked without overloading the health care system or the person with MS.

The guidelines have not recommended any specific, named measures for use in any specific situation. A quick review of the evidence tables will show that over 60 different measures have been used in research and apart from the Expanded Disability Status Score (EDSS) few have been used on more than 10 occasions (see Appendix H). There is very little research comparing the utility of different measures in different situations. Indeed, relatively few measures have any evaluative data published at all. Systematically reviewing the available evidence would be a major undertaking, and because the number of measures supported by different people and

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organisations is large, consensus will not be achieved. Therefore we agreed not to recommend any specific measures.

RECOMMENDATIONS

R7	The review checklist shown in Table 3 should be used each time a person with MS starts a new 'episode of care' (including initial diagnosis), and whether or not the presenting issues relate to the MS. The health care professional should:	D
	● record the information for future comparison ● refer to the specific recommendations made in this document if any problem is identified.	
R8	Health care staff who frequently undertake MS-specific assessments or treatments should:	D
	● be familiar with simple methods for detecting impairment and limitations on activities ● be trained in their use and interpretation (if used).	
R9	All health care staff within a local health community should use the same simple methods for common assessments.	D
R10	When initially assessing a person, and when undertaking any treatment, health care staff should consider the characteristics of a measure (see resource pack on the NICE website: www.nice.org.uk/pdf/cg008_msresourcepack.pdf) recognising that:	D
	● formally evaluated measures may not exist or be practical ● personalised measures should be considered, including comparing the outcome against goals agreed (goal attainment scaling).	
R11	Before embarking on any course of treatment, the health care professional should be satisfied that the individual fully understands the implications of the treatment, and is able to participate in it as necessary.	D
- Further guidance may be found at the Department of Health consent website at www.doh.gov.uk/consent/index.htm

LOCAL IMPLEMENTATION POINTS

Local services will need to set guidelines on:

- the specific measures and assessment procedures to be used locally for common problems
- training of all staff in the use of simple screening methods for impairment, and in the use of simple measures of activities.

3.2.2 Teamwork and goal setting

People with MS often have several problems that need resolution and consequently will usually need actions from more than one person. Co-ordination of interventions, often delivered by several people over time, requires teamwork from a group of individuals working together towards a single goal or set of goals. A group of individuals who happen to work with one person with MS is not a team but a workgroup;³⁵ a team must communicate and work jointly. The difficulties and weaknesses of community teams in the UK have been discussed^{36–38} and clinical standards have been produced for rehabilitation teams both in hospitals and in the community.^{39,40}

Table 3 Review checklist***Initial question**

It is best to start asking an open-ended question such as, *Since you were last seen or assessed has any activity you used to undertake been limited, stopped or affected?*

Activity domains

Then, especially if nothing has been identified, it is worth asking questions directly, choosing from the list below those appropriate to the situation based on your knowledge of the person with MS.

Are you still able to undertake, as far as you wish:

- ☐ vocational activities (work, education, other occupation)?
- ☐ leisure activities?
- ☐ family roles?
- ☐ shopping and other community activities?
- ☐ household and domestic activities?
- ☐ washing, dressing, using toilet?
- ☐ getting about (either by walking or in other ways) and getting in and out of your house?
- ☐ controlling your environment (opening doors, switching things on and off, using the phone)?

If restrictions are identified, then the reasons for these should be identified as far as possible considering impairments (see below), and social and physical factors (contexts).

Common impairments

It is worth asking about specific impairments from the list below, again adapting to the situation and what you already know.

Since you were last seen, have you developed any new problems with:

- ☐ fatigue, endurance, being over-tired?
- ☐ speech and communication?
- ☐ balance and falling?
- ☐ chewing and swallowing food and drink?
- ☐ unintended change in weight?
- ☐ pain or painful abnormal sensations?
- ☐ control over your bladder or bowels?
- ☐ control over the movement?
- ☐ vision and your eyes?
- ☐ thinking, remembering?
- ☐ your mood?
- ☐ your sexual function or partnership relations?
- ☐ how you get on in social situations?

Final question

Finally, it is always worth finishing with a further open-ended question. *Are there any other new problems that you think might be due to MS that concern you?*

*This is not a list of questions to be asked of every person with MS on every occasion. It is a list to remind clinicians of the wide range of potential problems that people with MS may face, and which should be actively considered as appropriate. A positive answer should lead to more detailed assessment and management

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Table 4 Characteristics of a useful measure

When considering measuring the effect of a treatment or the extent of some aspect of a person's situation, any potential measure should be considered against the following characteristics.

Domain	Questions
Feasibility	- Can the measure be used in this situation? - Will the process be acceptable to the person with MS?
Utility	- Is this measure going to be useful? - Will the time and effort required be worthwhile?
Validity	- Is this measure going to measure whatever it is I am interested in? - Does this measure also include unrelated phenomena that reduce its validity?
Reliability	- How much variation occurs from time to time when there is no 'real' change? - How much variation occurs between observers?
Sensitivity	- Will this measure detect the change or difference that I am looking for? - Does the measure cover the whole range of possible change?
Communicability	- Can I communicate this result? - Will other people involved understand the result?

The agreeing of goals is one way of facilitating effective teamwork. Goal setting refers to the identification of, and agreement on, an outcome or group of outcomes that the person with MS and family, therapist or team will work towards over a specified period of time. The important characteristics of goal setting in a rehabilitation service have been the subject of a non-systematic review.⁴¹

Recommendations are needed to ensure that efficient and effective teamwork occurs.

RECOMMENDATIONS

R12	When several health care and other professionals are involved with a person with MS, they should work together with the person and his or her family, as a team:	D
	- towards common agreed goals - using an agreed common therapeutic approach.	
R13	The goals set should:	D
	- be agreed as relevant and important by the person with MS - cover both short-term specific actions and longer-term outcomes - be challenging or ambitious but achievable - be set both at the level of individuals and at the level of the team as a whole - be formulated in such a way as to leave no doubt as to when they have been met.	
R14	Goal attainment scaling should be considered as one way of setting goals and evaluating progress.	D

LOCAL IMPLEMENTATION POINTS

Local services need to discuss and agree common:

- approaches to therapies to be used within and between teams
- terminology to be used within and between teams
- documentation to be used within and between teams.

3.3 Service organisation

Specific recommendations made in later sections can only be successful if a) services are organised so that they can be used efficiently by the person with MS, and b) service staff have appropriate knowledge and skills to advise on the specific problem. An audit in Oxfordshire documented the long and tortuous routes people traversed to resolve specific problems,⁶ suggesting that people with MS are often seen by people without appropriate skills to solve specific problems.

In terms of service organisation, effectiveness and efficiency depend upon two separate matters:

- the *grouping* of people with different skills into named services, and
- the *timing* of actions undertaken by the organisation.

This section makes recommendations concerning specialisation and timing.

Expertise is a key issue here. For this document the following definitions will apply:

- a *specialist* is a health care professional with the necessary knowledge and skills in managing people with the problem concerned, usually evidenced by having a relevant further qualification, and keeping up to date through continuing professional development
- a *specialist team or service* is a group of specialists *who work* together regularly managing people with a particular group of problems, and who between them have all the necessary knowledge and skills to assess and resolve over 90% of all problems faced.

In practice, the person with MS will rarely present with a new problem to a specialist, and so it is important that clear and unhindered routes of referral exist, but at the same time it must be recognised that many problems can be resolved by clinicians and services with less MS-specific expertise. In other words, all health staff should work within their level of competence:

- *competence* is defined as the sufficient knowledge and skills to assess and resolve the problem and to recognise when further, more specialist help is needed.

A single service will be unlikely to cover all problems presented to it. Many problems will be simple, only peripherally related to MS, or well within the competence of the service first approached. Specialist services, on the other hand, can only retain expertise if they are not overwhelmed by simpler problems. Consequently it is inevitable that some people will need to be referred on from one service to another (or even to two or more others). Recommendations need to take this into account.

Lastly, services will be developed over time, and it is important that people with MS are involved in discussions about the development of services used by them.

3.3.1 Specialist services

The evidence in support of specialisation in general, and relating to specialisation in the management of people with MS in particular, has not been searched systematically. It is widely accepted that specialisation can deliver many benefits in terms of effectiveness and efficiency, for example to patients with conditions such as cancer or vascular disease.

The benefits of specialist services have been well demonstrated in stroke where specialised stroke units are effective in research settings¹⁵ and also have better processes in practice.⁴² Similarly, specialist neurological rehabilitation teams can improve outcome after head injury.^{43,44} The Health Select Committee, in its report on Rehabilitation after Traumatic Brain Injury,⁴⁵ drew attention to the inefficiencies resulting from the fragmented management structure for rehabilitation in most NHS trusts, and recommended that the best single way to avoid such fragmentation of NHS rehabilitation services would be for every NHS trust providing rehabilitation to appoint a named general manager to be responsible for all elements of the rehabilitation services operated by the trust.

At least five studies have investigated the effect of a specialist neurological rehabilitation team specifically in the management of MS, and found benefits.^{46–51}

The evidence is given in more detail later (4.5, 5.2). In summary, one study has shown that the input of a specialist rehabilitation team was associated with improved outcome three months after an acute relapse; one study showed that a two week inpatient specialist rehabilitation was associated with sustained benefits at six months; one study showed that outpatient specialist rehabilitation was associated with sustained benefits; one study showed that specialist rehabilitation lead to positive change at 15 weeks; and two controlled clinical trials have demonstrated sustained benefits after input from a specialist neurological rehabilitation team. This must be set in the context of a much greater volume of evidence for specialist neurological rehabilitation services in other neurological conditions such as stroke and head injury.

This section makes general recommendations concerning specialist services, without detailing the model of service delivery or resource implications. There are particular difficulties in specifying a 'core team' because people with MS may need help from almost any profession or service at some point. The recommendations are based on consensus informed by the existing studies, studies in other areas, and the logical consequences of the many recommendations made elsewhere in this guideline.

► Health economics statements

Many of the recommendations made in this section and elsewhere in this guideline imply an increase in the number of specialists and specialist centres that can diagnose and treat people with MS. At present, the provision of services is inadequate and geographically variable. It is well established that there is a shortage in the required number of consultant neurologists in the UK. There are currently around 350 consultant neurologists, giving a population ratio of 1:177,000 – much lower than other European countries. In some areas, like the South East, the ratio is 1:100,000, whereas in less well-served areas it is 1:250,000. An Association of British Neurologists (ABN) survey in 2001 revealed that the average waiting time to see a consultant neurologist from GP referral varied from 13 weeks in North West Thames to 51 weeks in Wales.⁵²

3 General principles of care

Anecdotal evidence suggests that for specialist MS services the situation is worse, but there is no formal evidence to back this up. The vast majority of people with MS are treated as outpatients so they will suffer from the long waiting times reported here. In addition they are adversely affected by the lack of specialist centres where multidisciplinary team-based care can be provided. Preparatory work for the UK health departments risk-sharing scheme (see Section 4.6) shows that 66 centres in the UK have self-nominated as 'specialist' centres, but the number of centres that can actually provide multidisciplinary team-based care is probably around half of this number. The result is that only the minority of people with MS have access to a specialist centre and many do not even have access to a neurologist.

We have not attempted to estimate the resource increase that will be needed to provide these improved services, and neither do we have appropriate evidence to make judgements on the cost-effectiveness of using NHS resources in this way; this is an important area for future research. It is not simply a matter of making finance available, as the implications for the training of health professionals are also important. As a minimum, the ABN, for example, suggests that the number of consultant neurologists must be doubled to provide an acceptable service. They have estimated that this could be achieved by 2008 if the number of trainees was increased by two per year (from the current figure of around 158). Future research should investigate the need for improved services, the potential benefits to the NHS, people with MS and their families, and the resources involved, including any potential resource savings that might accrue elsewhere in the health care system.

RECOMMENDATIONS

R15	Every health care commissioning authority should ensure that all people with MS have ready access to a specialist neurological service for:	D
	● diagnosis of MS initially, and of subsequent symptoms as necessary ● provision of specific pharmacological treatments, especially disease-modifying drugs, and enacting the risk-sharing scheme for interferon beta and glatiramer acetate.	
R16	The health care commissioning authority should also ensure that its population has ready access to a specialist neurological rehabilitation service. This should be available to all people with MS when the presenting problem is outside the competence of the first point of contact, for:	D
	● undertaking assessment (that is, diagnosis) when the person has complex problems ● undertaking specific pharmacological or other therapies ● providing an integrated programme of rehabilitation when the person has complex problems ● monitoring change, especially when the person with MS has more severe impairments or limitations on activities ● giving advice to other services.	
R17	As a minimum, the specialist neurological rehabilitation service should have as integral members of its team, specialist:	D
	● doctors ● nurses ● physiotherapists	

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- occupational therapists
- speech and language therapists
- clinical psychologists
- social workers.

The team should either have as team members, or through agreed mechanisms, ready access to other local relevant specialist services with expertise in treating neurologically disabled people, to cover: D

- dietetics
- liaison psychiatry
- continence advisory and management services
- pain management services
- chiropody and podiatry
- ophthalmology services.

LOCAL IMPLEMENTATION POINTS

Local services will need to discuss and agree on:

- which specialist services are available to each primary care trust (PCT), or GP
- the most appropriate point of referral into each service in different circumstances
- specific referral pathways and mechanisms
- which health workers are in the local core team and which are additional to the team
- how health care workers who are additional to the team should be contacted.

3.3.2 Interfaces

People with MS present to any one of a large number of people within any one of a large number of organisations, and may in turn be referred on to many different people.⁶ One of the main complaints made by people with MS is that they are constantly referred on to other services and have to start from the beginning each time. Referral between services and organisations is inevitable, given the nature of the condition and the organisation of statutory services. Therefore it is vital that the interfaces are made as seamless as possible for the person with MS.

People with MS have stressed the importance of having access to a single contact point to provide on-going information and support, and to provide advice and sign-posting to other services. This coordinating and advising role is important both to the person with MS and to the various health and social service professionals involved.

The roles that are needed include:

- service coordinator with wide local authority and voluntary sector links, eg housing
- information signposter
- resources coordinator
- facilitator for an individual person with MS.

RECOMMENDATIONS

- R18** All parts of the health care system, social services and other statutory services should have agreed protocols that specify: **D**
- how responsibility for people with MS is shared with other groups or organisations
 - what agreed descriptive information (that is, a common dataset) about the person with MS should always be shared
 - the point of contact within any service or organisation, and how contact should be made.
- R19** People with MS should be able to identify and contact: **D**
- a named person in their health area who is responsible for all NHS services for local people with MS (including coordination and collaboration with other statutory services)
 - a named person in their health area with clinical expertise who is able to respond to any inquiry on clinical problems (and to guide the person to the most appropriate local service)
 - a named person within any health care team with which they are involved.

LOCAL IMPLEMENTATION POINTS

Services should discuss and agree:

- referral and funding mechanisms between the following agencies; GPs, PCTs/LHGs, specialist neurological services, the specific neuro-rehabilitation services, social services departments, local authority housing department
- standardised data to be shared across each interface
- who will fulfil the specific roles identified in R19 within the area.

3.3.3 Timing of actions

To be useful (that is, to be effective and efficient) it is important that any intervention is timely. Setting a target time for every recommendation would be both wordy and difficult to base on evidence. There is no evidence on appropriate timing, but the government has set targets for some services. Therefore, we have made some general recommendations about timeliness that reflect government targets, the concerns of people with MS and consensus.

RECOMMENDATIONS

- R20** Any action recommended within these guidelines should be undertaken within a time that takes into account: **D**
- risk of direct harm associated with any delay
 - distress or discomfort being experienced or likely to occur
 - risk of secondary complications associated with delay
 - risk of harm to others (for example, carers) associated with delay
 - any nationally recommended targets for timing
 - action being taken by any other person or service.

LOCAL IMPLEMENTATION POINT

The local commissioners and service providers should agree a set of timed targets which should include, at a minimum, those time targets contained within this guideline.

3.3.4 Involvement with service development

The involvement of service users in service development and research is government policy within the clinical governance framework, so no specific evidence has been sought concerning these issues. Good guidelines have been produced by the Department of Health in relation to the involvement of patients in research.

People with MS will have several important contributions to make to health service planning and development. First, there will be some services where the issues concern specific MS-related matters. The service responsible for making the original diagnosis and for managing acute relapses and the prescription and monitoring of disease-modifying drugs is the most obvious. However, in practice people with MS probably make more use of, and will be more concerned about an increase in, generic services such as neurological rehabilitation services, continence services, and wheelchair services. Lastly, people with MS should be able to use any other services, with particular attention to health promotion and disease prevention services.

In the first case it is obviously important that people with MS are specifically involved. In the second and third cases it would certainly be appropriate for people with MS to be involved and they are likely to have much to contribute but people with other neurological disabilities could also be involved in addition to, or in place of, people with MS.

It should be emphasised that particular efforts are needed to involve any group of people with disabling conditions, and that their involvement is important because they are active users of most services over most of their lives. However, no specific recommendations will be made because this applies to all patient involvement and is not specific to people with MS.

3.4 Within-team communication

A common vocabulary is fundamental to the success of any complex organisation or service. This will usually depend upon an agreed, comprehensive framework that will facilitate the development of common understanding, and encourage the use of a shared vocabulary that helps communication. This will also increase the likelihood of effective teamwork through the setting of common goals. Although there is no evidence comparing models of illness, the increasing prominence of the World Health Organisation's International Classification of Functioning (see Appendix A) suggests that it should be used, especially as much work has already been devoted to its development. The recommendations made are intended to facilitate cohesive teamwork.

RECOMMENDATION

- R21** All individual clinicians, professional groups and organisations involved in the care of those with MS should use WHO's International Classification of Functioning (WHO ICF) model of illness, and its vocabulary. **D**

LOCAL IMPLEMENTATION POINT

The local services will need to agree a vocabulary that is shared across all organisations including social services.

3.5 Provision of services over time (rehabilitation, maintenance, prevention and palliative care)

It is important to consider the management of MS over time, accepting that the disease is inherently unpredictable. Four time phases have been suggested,⁵³ but only a minority of people with MS will pass through all four and many only experience the first two:

- 1) *Diagnostic phase*: initial symptoms, and diagnosis (with disease modifying drugs now used).
- 2) *Minimal disability*: relapsing-remitting phase with episodes of sudden worsening with partial or complete resolution; some disability; probably stops work and becomes dependent upon others for some aspects of community or household activities.
- 3) *Moderate disability*: progressive increase in limitation on activities at a slower or faster rate; becomes dependent on others for personal activities of daily living.
- 4) *Severe disability*: more-or-less totally dependent upon others at all times; sometimes in residential care; higher rate of complicating medical illnesses such as chest infection.

In the first phase a service that focuses on diagnostic and disease treatment is appropriate. However, it is never too early to apply general rehabilitation principles: for example, the diagnosis of MS may sometimes call for measures relevant to the person's future family, occupational or financial situation. These considerations apply more urgently in the second phase, when therapeutic interventions may also be indicated, often with a preventive as well as a remedial rationale. In the third phase, services maximising activity and participation are more likely to be involved in adapting the social and physical environment, in addition to continuing therapy interventions. In the fourth phase, service delivery will be centred on the provision of support and of a suitable environment, while still aiming to maintain social participation. Health services have an important role to play in all four phases, but social services will become increasingly involved as the person moves into the third and fourth phases.

Neurological rehabilitation services will be used by many people, and factors which apply specifically to people with MS include:

- people with MS are probably the largest single group of people needing specialist neurological rehabilitation aged under 65 years (with people with stroke and head injury being the next two groups)
- the unpredictable, fluctuating, but generally progressing nature of the disease is different from most diseases
- people with MS also fluctuate on a day-to-day basis
- the disease starts in young adult life.

Services, especially but not only neurological rehabilitation services, therefore need to be able to respond flexibly to the specific situations of individual people with MS and their family and carers. When care needs are extensive, the needs of the carers become especially important.

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People with MS are at increased risk of many specific additional pathologies such as pressure ulcers, contractures, osteoporosis and deep vein thrombosis. Services should always try to reduce the risk of these. There is evidence that pressure ulcers and contractures are common, and some evidence is available on how to reduce the risk and treat these complications, discussed in sections 6.5 and 6.17. The significance of other complications such as deep vein thrombosis and osteoporosis is difficult to establish in the absence of evidence, and so most other complications have not been mentioned specifically in this guideline. However, individual clinicians should always consider whether the risk of any person with MS suffering a particular complication can be reduced.

▷ Health economic statements

Little is known about the health economics of long-term health support. The provision of this type of care is complex because it must respond to a broad range of needs and is likely to be provided in a variety of different settings. There is no good evidence on the effects of palliative care on quality of life of people with MS. On the cost side it is important to bear in mind that a significant proportion of the burden of long-term care will fall on the patient and their family and carers. One RCT of the cost-effectiveness of a district coordinating service for people who were terminally ill with cancer in South London revealed no difference in outcomes between the two groups but showed that the service could be delivered with lower resource use than standard care. In particular, savings accrued from reduced inpatient days in acute hospital wards.⁵⁴ The authors argue that since people with cancer appear to want to remain at home as long as possible, reductions in hospital stays may generate benefits to patients. It is difficult to know the extent to which these findings are relevant to the population of people with MS. If palliative care is to be provided in residential or nursing homes, this is a particularly expensive type of provision but can produce enormous benefits for patients and their families and carers. More information on the cost-effectiveness of residential care is required.

RECOMMENDATIONS

R22	Services should cater for the varying needs of people with MS over time, by: ● responding in a timely and flexible way to the intermittent acute needs of people with MS, especially in the early phases ● identifying and reducing the risks of complications that might develop in the individual ● making fully available, to people with MS, population-based programmes of health promotion and/or disease prevention (such as screening for cervical carcinoma), specifically taking into account an individual's possible impairments and activity limitations.	D
R23	When any 'episode of care' (medical or rehabilitation treatment programme) ends (that is, when no further benefit is anticipated), the health care team should: ● ensure that any necessary long-term support needs are met ● ensure that the person with MS knows whom to contact and how to contact them, in the event that the person with MS experiences a change in his/her situation ● discuss with the person with MS whether they want a regular review of their situation and, if so, agree on a suitable and reasonable interval and method of review (for example, by phone, by post or as an outpatient).	D

3 General principles of care

- R24 Health services should ensure that there are mechanisms to allow good communication between health and social services at all times. D
- R25 Individuals who are severely impaired and markedly dependent should have their support needs reviewed at least yearly, and they should have these needs met as necessary and in accordance with their wishes, through one or more of the following: D
- additional support in the home
 - respite care in the home
 - respite care in another age-appropriate setting
 - moving into a residential or nursing home.

LOCAL IMPLEMENTATION POINTS

Local service commissioners and providers need to agree:

- which specialist rehabilitation service will be responsible for maintaining function and for long-term support
- what local social opportunities exist for people with a range of impairments and limited activities and how they are accessed
- which residential and nursing homes are suitable for younger people
- clear mechanisms for agreeing funding for complex, expensive care home support packages and/or respite support and/or residential care.

4 Disease diagnosis and specific treatment

MS is a disease affecting the white matter of the central nervous system (CNS; brain and spinal cord). It is defined clinically by accumulating evidence from the history, examination or investigations that the individual has lesions within the CNS that are scattered in time (ie two or more separate episodes) and space (ie in two or more separate locations). Histological proof (ie under the microscope) is rarely available in life, and there is no single test or investigation that can 'prove' the diagnosis. Consequently, people who may or may not have MS and clinicians advising them need to live with uncertainty; the diagnosis is never proven '100%' and the prognosis is always uncertain.

This section covers the management of MS at the level of pathology (ie the disease process). It deals with the diagnosis of the disease and all treatments that may affect the disease process itself (in contrast to the secondary symptoms and signs). Within this section the term *acute episode* is used in place of *relapse* in many instances because the first episode, which cannot logically be called a relapse, will usually require the same management in terms of diagnosis and treatment. When used, the term 'relapse' refers to a clinically presumed episode of acute demyelination.

The topics covered are:

- making the diagnosis of MS
- involving the person with MS in the diagnostic process
- diagnosis of acute episodes
- treatment of acute disease episodes (including optic neuritis and transverse myelitis)
- treatments to modify the course of the disease (prevention of relapses using drugs, and drugs to slow down progression*)
- other actions that may influence relapse rate.

4.1 Making the diagnosis of MS

In medicine the process of diagnosis may include:

- confirming (or determining the probability) that a diagnosis is true
- making or excluding an alternative diagnosis
- classifying the disease further, to help determine prognosis and/or responsiveness to specific treatments.

All three aspects of diagnosis will be considered here. While the diagnostic process is most important when the person first presents with symptoms or signs, the diagnosis should always be considered when the person presents with completely new or unexpected problems. The principles will be similar.

* This section includes the treatment of MS with interferon beta or glatiramer acetate but has not reassessed the evidence for them as this was excluded from the scope of this guideline by NICE see note on p 59 (Section 4.6).

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The diagnosis of MS is made clinically.⁵⁵ It depends upon obtaining evidence of characteristic neurological lesions:

- located in different parts of the CNS
- that have occurred at different points in time.

MS may cause potentially almost any neurological symptom. There is no definitive diagnostic test for MS and confirmation of the diagnosis may require several neurological tests and clinical evaluation over a period of time (see algorithm). In many instances, even with all available investigations, it is not possible to reach a definite diagnosis in the early stages and it is important to explain this to anxious patients.

In practice, an accurate diagnosis can sometimes be reached either on clinical grounds alone, or by following a clinical diagnostic strategy using appropriate investigations. However, even among specialist neurologists there may be disagreement.⁵⁶

The algorithm in Appendix G explains how investigations such as MRI can be used to reduce the stressful delay which can result while the required clinical evidence is obtained over a period of time. An international panel, meeting in 2000, published recommended criteria to utilise MR in this way.⁵⁵ Although these criteria are not above criticism, they are probably the best currently available. The criteria were developed by consensus using an internationally renowned group of experts. Initial evidence supports the McDonald criteria (see below) and we have agreed to follow their recommendations. When considering the recommendations it must be remembered that making a diagnosis is a process that logically depends as much on excluding reasonable alternative diagnoses as it does on confirming a diagnosis, especially in MS where there is no confirmatory test. Consequently in practice when faced with an individual the clinician must:

- have a diagnostic strategy, and not depend upon a single feature (eg investigation)
- recognise that no single feature can confirm or refute the diagnosis
- consider which investigation is most likely to help given the specific prior likelihood of a diagnosis.

The classification of MS is likewise controversial. Although commonly used, there is little firm epidemiological evidence to validate any of the categorisation schemes used and there are no studies of the reliability of the classification. Nonetheless, classifications may be useful both in research and in clinical practice, not least in relation to trials of new drugs.

The categorisation most commonly used is a subset of that published in 1996.⁵⁷ This categorisation was based on an international survey of 215 people actively involved in research in MS, of whom 125 (58%) replied. Several clinical types were recognised, with the first three remaining in common use:

- **relapsing-remitting:** clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between relapses characterised by a lack of disease progression. About 80% have relapsing-remitting disease at onset
- **secondary progressive:** initial relapsing-remitting course followed by progression with or without occasional relapses, minor remissions and plateaux. About 50% of people with relapsing-remitting MS develop secondary progressive MS during the first 10 years of their illness
- **primary progressive:** disease progression from onset with occasional plateaus and temporary minor improvements allowed. About 10–15 % have primary progressive disease at onset.

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In addition this group recognised other categories which are not widely used:

- **progressive-relapsing:** progressive from onset with clear acute relapses but with progression in between relapses (this is probably comparable to primary progressive disease)
- **benign:** disease in which the patient remains fully functional in all neurologic systems 15 years after onset
- **malignant:** disease with a rapid progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset.

One other category was put forward, 'relapsing progressive', but no consensus was achieved.

Several points need emphasis. This classification reflects the person's history up to that point and it is not a classification that can be made prospectively. It has been used as a way of selecting or excluding patients for clinical trials of disease-modifying agents, and for the application of some of these treatments in clinical practice. There is evidence that the classification changes over time.⁵⁸ It is also important to stress that these categories do not reflect pathologically different types of disease and are poor predictors of subsequent behaviour of the disease in any one individual.⁴

► Evidence statements (all diagnostic studies)

A total of 33 studies met inclusion criteria. These studies assessed the diagnostic accuracy of 143 tests or test combinations. Of these studies, nine used a diagnostic case control design and the remainder were diagnostic cohort studies. The reference standard (the method to determine whether patients truly had MS) used was based upon clinical examination in all studies. For the diagnostic cohort studies patients were generally followed up for a period of time to determine if they developed MS. Only three of the studies^{59–61} followed up patients for five years or more and were determined to have used an appropriate reference standard. The introduction of the McDonald criteria (see the algorithm in Appendix G) potentially changes matters because the reference standard may have changed.

All but one⁶² of the studies reported sufficient data to construct a 2×2 table of test performance, although one additional study did not report sufficient data to construct a 2×2 table for one of the tests investigated.⁶³ These studies reported areas under the receiver operating curve (ROC). The 2×2 table data was extracted and used to calculate sensitivity, specificity and the diagnostic odds ratio (DOR) for each of the tests evaluated.

The DOR gives an overall (single indicator) measure of the diagnostic accuracy of a diagnostic test (see the appendices). It is calculated as the odds of positivity among diseased persons, divided by the odds of positivity among non-diseased. The DOR combines sensitivity and specificity into one measure. When a test provides no diagnostic evidence then the DOR is 1.0. The higher the DOR, the better the test and, generally speaking, a DOR greater than 100 provides convincing diagnostic evidence, and a DOR greater than 25 provides strong diagnostic evidence. In studies of diagnostic accuracy there is a trade off between having a high sensitivity (correctly identifying those people who have the condition), and having a high specificity (ie not diagnosing people as having the condition when they don't have the condition). For MS the use of this measure can be misleading. The proportion of confirmed MS patients with an abnormal visual evoked potential is about 90% but in suspected cases, at the time when you need such

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tests, it may be less than 70%. However, it is a very reliable test of optic nerve disease and, in the appropriate case, can allow a confident diagnosis of MS. It is as important to detect all patients with MS as it is to avoid mistakenly diagnosing someone as suffering from MS.

The tests evaluated were grouped into four categories – clinical criteria, imaging, cerebrospinal-fluid tests, evoked and event related potentials – and combinations of tests. DORs varied considerably, both overall and within categories, either for technical reasons or more usually because of differences in the mix of patients being submitted to the test. Overall, DORs ranged from less than 1 to 2,091. They were generally higher in studies that did not include an appropriate range of patients. An appropriate range of patients was defined as a group of patients in whom the test would be used in practice, ie patients suspected of having MS but in whom the diagnosis had not been confirmed

Clinical criteria

One study evaluated the accuracy of the McDonald criteria applied at three months and one year after initial presentation. This study used the Poser criteria at three year follow-up as the reference standard.⁶⁴ The McDonald criteria use a combination of clinical features and MRI findings to make a diagnosis of MS, these are detailed in Appendix G. This study found that the McDonald criteria was an average diagnostic test at three months with a DOR of 24 and a good diagnostic test at one year with a DOR of 82. Both these figures were obtained when the diagnosis was made using a combination of clinical signs and MRI findings. When MRI evidence of dissemination in time and space alone were used to make the diagnosis, the diagnostic performance dropped to a DOR of 19 at three months and 24 at one year. When interpreting these figures it should be noted that the reference standard is unlikely to have correctly classified all patients, and so these figures may be biased.

Imaging

Twenty four studies assessed the accuracy of imaging in the diagnosis of MS, including a total of 61 test evaluations.^{59–82} The majority of these assessed MRI (59), two assessed the diagnostic accuracy of computerised tomography (CT).

The DOR for magnetic resonance imaging (MRI) showed great variation, ranging from less than 1 to 2091. In 29 of the comparisons the DOR was less than 25, suggesting poor overall test performance. The DOR ranged from 25–50 in a further 16 evaluations, suggesting good diagnostic performance, and was greater than 100 in nine evaluations, suggesting excellent test performance. One study reporting two evaluations of MRI (different cut-off points) reported the area under the receiver operating curve (ROC) and reported an area under the curve (AUC) of 0.96.⁶² This suggested excellent diagnostic performance, but this study did not include an appropriate spectrum of patients.

The wide variations in the DORs estimated from these studies makes it difficult to draw conclusions regarding the accuracy of MRI for the diagnosis of MS. The variations appear related to a number of factors, mainly the spectrum of patients included in the study and the cut-off point used to determine a positive test result. Generally speaking, the studies which reported the higher estimates of test performance did not include an appropriate spectrum of patients, suggesting that estimates of test performance obtained from such studies are likely to

4 Disease diagnosis and specific treatment

be biased. Of the 29 studies in which the DOR was less than 25, five (17%) did not include an appropriate spectrum. Of the 17 studies that reported a DOR between 25 and 100, nine (52%) did not include an appropriate spectrum of patients. Only one of the eight comparisons with a DOR greater than 100 included an appropriate spectrum of patients.

In summary, although difficult to draw conclusions from these results given the large variation in DORs, it would appear that MRI is a reasonable although not excellent investigation when making the diagnosis of MS. In addition, the studies used many different definitions of a positive test result. Due to time limitations however, it was not possible to investigate the influence of this.

CT using X-rays was found to be a poor predictor of MS in both studies in which it was investigated.^{63,66} The first found a DOR of 2.4 which corresponded to a sensitivity of 38% and specificity of 80%.⁶⁶ The other did not report data to construct a 2×2 table but instead reported the area under the receiver operating curve (ROC). This was found to be 0.5 which indicates that CT was no better than chance alone at diagnosing MS. This study also assessed the diagnostic accuracy of MRI and found this to be significantly higher than that of CT (AUC was 0.82 for MRI and 0.52 for CT).⁶³ Both studies were of reasonable quality.

Evoked potentials and event-related potentials

Evoked potentials (EPs) and event-related potentials (ERPs) were assessed in eight studies,^{66,72,78–80,83–85} including 40 test evaluations. Generally, ERPs were found to be less accurate than MRI with DORs ranging from 0.6 to 90. The majority of the evaluations (28) reported DORs less than 25, suggesting poor diagnostic performance. The remaining evaluations suggested good diagnostic performance. As with the evaluations of MRI, studies which did not include an appropriate range of patients tended to produce higher estimates of test performance. Of the 28 evaluations which reported DORs less than 25, 15 (53%) included an appropriate range of patients. This compares to one (8%) of the 12 evaluations which reported DORs greater than 25.

The studies assessed a variety of different EPs/ERPs including: visual evoked potentials (VEP) ($n = 18$), auditory event-related potentials (AERP) ($n = 1$), brainstem auditory evoked potentials (BAEP) ($n = 4$), long latency auditory evoked potentials (LLAEP) ($n = 2$), middle latency auditory evoked potentials (MLAEP) ($n = 2$), motor-evoked potentials (MEP) ($n = 2$), somatosensory evoked potentials (SEP) ($n = 6$), sympathetic skin response (SSR) ($n = 1$), and various combinations of these ($n = 4$). Overall, VEPs appeared to be the most accurate in diagnosing MS. Six of the eight included studies assessed more than one ERP.^{66,72,78–80,85} These studies varied in terms of which ERP was found to be most accurate in diagnosing MS. Three of the studies found that the VEP was the most accurate,^{66,72,79} one found that MEP was the most accurate,⁷⁸ one MLAEP⁸⁵ and the other BAEP.⁸⁰ Two of the studies which found that VEP was the most accurate did not assess MEPs.^{66,79} In summary, there is disagreement regarding which EP is the most accurate for the diagnosis of MS. Overall, ERPs do not provide strong diagnostic evidence for the diagnosis of MS.

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Cerebrospinal fluid

Various cerebrospinal fluid (CSF) tests were evaluated in 15 studies^{60,66,68–70,78–80,86–92} reporting a total of 37 test evaluations. The DORs ranged from 0 to 378.8. In 26 (70%) of evaluations, the DORs were less than 25, in seven (20%) the DOR was between 25 and 100 and in four (10%) evaluations the DOR was greater than 100. Of the evaluations reporting a DOR less than 25, 20 (77%) included an appropriate range of patients. In comparison only half of the studies with DORs between 50 and 100 included an appropriate range of patients. However, in contrast to the studies included in the other sections, three of the four studies reporting DORs greater than 100 included an appropriate range of patients.

The tests evaluated in the studies varied. The most commonly investigated test was the presence of oligoclonal bands. This was assessed in 15 test comparisons, including all four comparisons which found convincing diagnostic evidence.^{70,86,88,89} A further three of these studies reported DORs between 25 and 100,^{89,90,92} two of these included an appropriate range of patients.^{89,92} The remaining studies, all of which included an appropriate range of patients, reported DORs between 0 and 24. This illustrates a wide discrepancy in the estimates of diagnostic performance for the presence of oligoclonal banding. The reasons for the heterogeneity in estimates are unclear. There appears to be some evidence from reasonable quality studies that the presence of oligoclonal bands may be an accurate test for the diagnosis of MS, although this is not supported by all studies. Other tests which provided strong diagnostic evidence (DOR >50) were the IgG index^{91,92} and the IgG synthetic rate.⁹¹ However, the study which investigated both tests did not include an appropriate range of patients.⁹¹ The IgG index was investigated in a further two studies which reported DORs of 4.0⁷⁹ and 12.2.⁸⁹ The value of this test in the diagnosis of MS using CSF is therefore unclear. Other evaluated tests which did not provide strong or convincing evidence included: IgG synthesis ($n = 3$); level of IgG in CSF ($n = 4$); the presence of antibodies to various disease in CSF ($n = 1$); CSF total protein ($n = 1$); CSF/serum albumin ratio ($n = 1$); IgG albumin ratio ($n = 1$); the presence of myelin basic protein in CSF ($n = 1$). There is no evidence to suggest that these tests are accurate for the diagnosis of MS. Five comparisons included various combinations of tests.^{68,78,90} For all of these the DOR was less than 25.

Test combinations

Two studies, reporting four evaluations, assessed the accuracy of combinations of tests.^{68,69} All four evaluations assessed the effectiveness of combined measures based on oligoclonal bands and MRI. For three of the evaluations the DOR was less than six, suggesting that this combination is not accurate for the diagnosis of MS.^{68,69} The fourth evaluation reported a DOR of 42.2 (sensitivity 96%, specificity 63%) for the presence of at least two oligoclonal bands only in CSF and an MRI diagnosis based on the presence of three quarters of Barkhof's criteria.⁶⁹

Economic evidence

There were no economic studies of CSF, EPs or ERPs.

4 Disease diagnosis and specific treatment

MRI

Magnetic resonance imaging (MRI) is a relatively expensive diagnostic technology (costing approximately £200 per scan), and a relevant question is whether the benefits of MRI are worth the additional cost. Unfortunately this is a difficult question to answer as there is a large amount of uncertainty around the diagnostic accuracy of MRI in MS and the influence of a MRI-backed diagnosis on disease management.

Benefits from MRI in diagnosis of MS may arise from the medical information it provides (which in turn informs disease management), and also from the potential psychological value of the information to the patient. In addition, MRI may reduce the need for other tests, and in particular the need for EPs and CSF examination has diminished in recent years.

In MS the majority of interventions are targeted at symptoms rather than the disease itself, and the extent to which symptom management is influenced by diagnosis is unclear. The availability of the disease-modifying therapies (DMTs) interferon beta and glatiramer acetate under the risk sharing scheme (see section 4.6 for further details) may have implications for the use of MRI in diagnosing MS. The ABN criteria, which determine the eligible population for DMTs, are not dependent on diagnosis using MRI and it is unclear how many of the eligible population would require an MRI scan to confirm diagnosis before access to treatment (the majority of people will already have had an MRI scan before this point). Nevertheless, in countries where DMTs have been more commonly used than the UK, MRI is often used to aid the decision on whether to start, stop or modify therapy. This may mean that the risk sharing scheme does increase the requests for MRI scans.

Only two relevant existing studies were identified.^{93,94} These looked at the targeting and cost-effectiveness of MRI for people with equivocal neurological symptoms who may have MS. Both studies employ decision analytic models, which are particularly valuable in evaluating diagnostic technologies since they enable modelling of alternative scenarios with their associated costs and benefits given available information. They also allow the identification of key areas of uncertainty around clinical utility and cost-effectiveness which can guide future research. The two studies are by the same authors and represent developments of the same piece of work; only the latest study is included in the evidence tables.⁹³

This study made good use of information available at the time (the early 1990s) and also employed comprehensive sensitivity analysis to deal with the large amount of uncertainty surrounding the key model parameters. The study concluded that MRI was not cost effective in people with low prior probability of MS (unless the diagnostic information has a very high psychological value to patients). As the probability of disease increases, further MRI use becomes cost effective. Given the fact that this study is relatively old (and in an area where the technology is developing) and that it is based in the US, there is little value in citing specific cost-effectiveness ratios. Nevertheless, the results do question the usefulness of the routine use of MRI in people where the probability of MS being present is low unless there is a reasonable probability of an alternative diagnosis that can also be diagnosed using MRI being present.

The results from both studies illustrate that the key areas of uncertainty are the diagnostic accuracy of MRI and the value of the diagnostic information to patients; both of these factors will have an important influence on the cost effectiveness of the technology. While evidence on the former may have improved since this study was published, evidence on the latter is virtually

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non-existent. In addition, these studies were carried out before the availability of the DMTs interferon beta and glatiramer acetate, so they do not take account of any additional benefit arising from speeding up access to these therapies.

For more detail see Appendix I.

▷ From evidence to recommendations

Linking these evidence statements to recommendations depends upon a clear understanding of the diagnostic process. When making a diagnosis a doctor will start with a reasonable estimate of the probability that someone has a particular disease, and may have a list of other diagnoses that might also be present. Consequently, investigations are used as much to exclude alternative diagnoses as to confirm the suspected diagnosis, and most diagnostic studies do not evaluate this two-pronged approach. The doctor will (or should) also use a strategy appropriate to the particular situation, choosing the test most likely to clarify matters before undertaking further tests.

In practice, neurologists will often use an MRI scan first for three reasons.

- 1) To rule out other disorders, eg spinal cord compression in a patient with a spinal cord lesion.
- 2) To establish the presence of clinically-silent lesions in other parts of the CNS, and/or
- 3) To demonstrate new lesions appearing since the last clinical episode. However other considerations, such as the need to exclude a disease through examining CSF or a patient's claustrophobia, may dictate an alternative strategy. The recommendations made draw on the evidence, but also draw on the strategy implied.⁵⁵ They should give a useful clinical diagnostic strategy.

RECOMMENDATIONS

There is no single specific diagnostic test available, but in practice, the diagnosis can be made clinically in most people.

R26	When an individual presents with a first episode of neurological symptoms, or signs suggestive of demyelination (and there is no reasonable alternative diagnosis), a diagnosis of MS should be considered.	D
R27	When an individual presents with a second or subsequent set of neurological symptoms, which are potentially attributable to inflammatory or demyelinating lesions in the central nervous system (and again, there is no reasonable alternative diagnosis), the person should be referred to an appropriate expert for investigation.	D
R28	A diagnosis of MS should be made clinically: • by a doctor with specialist neurological experience • on the basis of evidence of CNS lesions scattered in space and time • primarily on the basis of the history and examination.	D
R29	When doubt about the diagnosis remains, further investigation should: • exclude an alternative diagnosis, or • find evidence that supports the potential diagnosis of MS. (Dissemination in space	D

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should usually be confirmed, if necessary, using an MRI scan, interpreted by a neuroradiologist if possible, using agreed criteria such as those described by McDonald and colleagues⁵⁵ (see Table G1 in Appendix G). Dissemination in space may also be confirmed using evoked potential studies. Visual evoked potential studies should be the first choice. Dissemination in time should be confirmed clinically, or by using the MRI criteria described (in Table G1 in Appendix G).

R30	Other tests supportive of the diagnosis of MS, such as analysis of CSF, should only be used either when the investigation is being undertaken to exclude alternative diagnosis or when the situation is still clinically uncertain.	D
R31	The diagnosis of MS is clinical and an MRI scan should not be used in isolation to make the diagnosis.	DS
R32	A CT brain scan should only be used to exclude alternative diagnoses that can be diagnosed using that investigation.	DS
R33	Any CSF samples taken from individuals who may have MS should be tested for the presence of oligoclonal bands and should be compared with serum samples.	DS
R34	The evidence supporting the diagnosis and its degree of certainty should always be documented formally in the medical notes and letters discussing the diagnosis. This allows the diagnosis to be reviewed critically and reinvestigated if necessary.	D

LOCAL IMPLEMENTATION POINT

Local guidelines will need to consider and define how urgent referrals of potential cases of MS should be made from primary care trusts (PCTs) and local health groups (LHGs) to a specialist neurological service.

4.2 Involving the person with MS in the diagnostic process

This covers the involvement of the patient in the diagnostic process from first presentation to a doctor to confirmation of the diagnosis and being informed of the diagnosis. It must be emphasised that making and telling the diagnosis is a process that may extend over some time, and that recommendations made elsewhere concerning communicating with the patient (see Section 3) should also be consulted. It is known that people with MS often have strong views about the process of making and telling the diagnosis, usually feeling that it could have been done better.¹⁴ Two comments from people with MS attending the focus groups (for further details see Section 2.3 and Appendix B) exemplify this:

‘Every test you go for no one tells you the results – you have to go back to the neurologist and go back to the GP – he didn’t know anything ... In the end it’s a relief just to be told you have it.’

‘The diagnosis was handled particularly badly by a particular junior doctor who was doing his neurology rotation in the hospital – in a very matter of fact manner as if the diagnosis was made. Go away to your GP and he will sort it out from there, was almost the attitude.’

► Evidence statements

Diagnosis

Two SRs were identified that assessed communication at the time of diagnosis of a potentially chronic or fatal disease, not MS^{95,96} (Ia). A review of 21 studies assessing the effect of physician-patient communication found that the quality of communication in both the history taking segment and during discussion of the management plan influenced patient health outcomes.⁹⁵ Positive effects were observed in patients' emotional health, symptom resolution, general functioning, physiological measures and pain control. The results indicated that patients should be involved in the consultation and in decisions about care. A review of different strategies for communicating 'bad' news to newly diagnosed patients showed mixed result.⁹⁶ Overall the use of an information package, follow-up telephone call or provision of a consultation summary only influenced patients' knowledge and satisfaction levels in half of the trials. No differences were seen in patients' psychological adjustment between the control and intervention groups.

Four studies were identified that examined patients' response to the diagnosis of MS⁹⁷⁻¹⁰⁰ (III). Two studies assessed patients' responses to undergoing a diagnostic work-up.^{97,100} The first study assessed the effect of diagnostic information on patients' sense of well-being.⁹⁷ The results indicated that most patients felt better having received diagnostic information, although this varied according to sub-groups of patients. Those in whom no definitive diagnosis emerged tended to be more anxious, whilst individuals with 'positive' work-ups became less anxious and expressed favourable feelings about the diagnosis despite now facing a chronic disease. The second study assessed the effect of diagnostic testing on patients' health perceptions.¹⁰⁰ Overall, the results indicated a significant and generally beneficial change in patient health perceptions with the neurological 'work-up' in suspected MS, irrespective of the final diagnosis. Two further studies explored patients' reaction to being diagnosed as having MS.^{98,99} The first of these focussed upon whether patients wish to know their disease status and how they had been informed of this.⁹⁹ The results showed that 83% favoured knowing the diagnosis, 13% were indifferent and less than 4% preferred not to know the diagnosis. Almost a quarter of patients had discovered the diagnosis for themselves, and all respondents thought that the consultant was the person who should convey the diagnosis. The second study explored the individual's experience of having symptoms and then being told they had MS.⁹⁸ The narrative synthesis indicated that diagnosis disclosure had been a painful and unexpected event for participants, but also viewed by some as a relief.

Information and education

Three reviews evaluated the effectiveness of information strategies in patient care, not especially MS¹⁰¹⁻¹⁰³ (Ia). The first review of nine studies assessed the provision of lectures, leaflets, booklets or manuals for stroke patients and their caregivers.¹⁰¹ The results provided some evidence that information combined with educational lectures improved knowledge and was more effective than providing information only. However, information only had no effect on mood, perceived health status or quality of life for patients or carers. The second review evaluated the use of audio-taped interviews, audio-visual aids, individual patient care records and written information for patients with cancer.¹⁰² The review showed positive effects on patient outcomes such as recall and knowledge, symptom management, satisfaction,

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preferences and health care utilisation. The interventions had no effect on psychological indices, and there was an interaction between disease prognosis and intervention. Where prognosis was poorer added information was detrimental. The last review of eight studies assessed the effects of providing recordings or summaries of their consultation to people with cancer.¹⁰³ The results support the use of recordings or summaries as an aid to information recall. However, they had little effect upon the level of patients satisfaction with the information provided and no effect upon patients' level of anxiety or depression.

Two RCTs were identified that assessed patient support through education or the provision of information in people with MS^{104,105} (Ib). The first study examined the effectiveness of an educational program for newly diagnosed patients with MS.¹⁰⁵ The results indicated no significant differences between the groups on measures of physical and occupational functioning, emotional well-being and general contentment, nutrition and health or family and social relationships. A positive effect was observed for levels of patients' self-worth. However, the sample size was too small for any robust conclusions to be drawn. The second study assessed the provision of an information booklet to aid medication compliance.¹⁰⁴ The results showed that the booklet had a positive effect on patients' understanding of medication information, but had no effect on either correct medication usage or their level of medication compliance.

A further three studies in patients with MS examined patient information needs at the time of initial diagnosis and during periods of disease exacerbation^{106–108} (III). The first study explored information needs and sources of information.¹⁰⁷ Biological information was prioritised by patients as information they personally required, whilst they advised encouragement and supportive information for others recently diagnosed. The most common sources of information besides the neurologist were other patients, patient-authored books and the MS society. Another study examined the information needs and information seeking behaviours of patients within the context of an acute exacerbation.¹⁰⁶ The results indicated gaps in patients' knowledge about physical symptoms experienced, emotions and treatments. Generic information on MS was not seen as being helpful and the major barrier identified was the dearth of current, realistic and up-to-date information. The last study assessed the utility of an information pack on symptoms and treatments, dietary advice and local and national resources for individuals with MS.¹⁰⁸ The results showed that 90% of the participants would have liked the information pack within six months of being diagnosed, and that usage of the pack was dependent upon the individuals' experience of managing their symptoms.

▷ From evidence to recommendations

The evidence reviewed is difficult to use directly because the research rarely explored explicit questions or gave answers that translate into recommendations. However, the focus groups and much written descriptive research emphasise that people with MS attach great importance to involvement in and clear communication throughout the diagnostic process. Additionally, the evidence did not suggest any harmful effects. The GDG reached strong consensus on the recommendations made, which reflect the main areas of concern expressed by people with MS.

RECOMMENDATIONS

R35	An individual should be informed of the potential diagnosis of MS, as soon as a diagnosis of MS is considered reasonably likely (unless there are overwhelming patient-centred reasons for not doing so). This should occur before undertaking further investigations to confirm or refute the diagnosis.	C
R36	Throughout the process of investigating and making the diagnosis of MS, the health care professional should: ● find out what and how much information the individual wants to receive (this should be reviewed on each occasion) ● discuss the nature and purpose of all investigations, especially the likely outcomes and their implications for the individual.	C D
R37	If a diagnosis of MS is confirmed, the individual should be told by a doctor with specialist knowledge about MS (usually a consultant or experienced specialist registrar). See also the recommendations for good communication (Table 2).	C
R38	After the diagnosis has been explained, the individual should be: ● offered in the near future* at least one more appointment to see wherever possible the doctor who gave the original diagnosis ● put in touch with, or introduced to, a skilled nurse or other support worker, ideally with specialist knowledge of MS and/or other neurological conditions and counselling experience ● offered written information about local and national disease-specific support organisations, including details of local rehabilitation services ● offered information about the disease, preferably in the form of an information pack, specific to the newly diagnosed.	D D C D A
R39	Within six months of diagnosis, the individual should be offered the opportunity to participate in an educational programme to cover all aspects of MS.	B

LOCAL IMPLEMENTATION POINTS

Local services should establish:

- a mechanism for keeping an up to date register of which doctors (consultants and trainees) should confirm and give the diagnosis
- a list of all relevant local and national organisations involved with MS, with a mechanism of keeping it up to date
- an agreed mechanism for putting a person newly diagnosed with MS in touch with a nurse or other support worker with knowledge of MS
- develop a set of information suitable for newly diagnosed people, including information on local services, and ensure that it is kept up to date.

* The GDG debated the meaning of the words 'in the near future'. In this context, it is taken to mean that the exact time will vary according to clinical need but should be, in the opinion of the development group, no longer than four weeks.

4.3 Acute episodes: diagnosis

An acute episode, often referred to as a relapse, is a neurological event that occurs in people diagnosed with MS that lasts more than 24 hours. It has no better explanation, and is assumed to be due to an episode of acute inflammation within the CNS. Consequently, treatments designed to reduce CNS inflammation have been tried.

Two specific acute clinical syndromes are recognised, optic neuritis and transverse myelitis. Each is particular a) because it is often the first manifestation of MS in the person concerned and b) because only a proportion of patients presenting with the syndrome have or go on to develop MS itself. Nonetheless they share many features with other acute relapses, and may occur in someone known to have MS, and so are considered within this section.

Establishing whether a recent change in a patient's state is due to an episode of demyelination is important. First, it may determine specific treatment such as steroids. Second, it may determine the need (and eligibility) for preventative treatments. Third, there may be another treatable reason for the apparent decline in neurological function.

However, there are major difficulties in defining and diagnosing a relapse, given the natural variability of the condition. First, it is well known that many new lesions seen on MRI scans are clinically silent.^{109,110} Second, incidental illnesses such as influenza and possibly other stressors may cause marked neurological deterioration that clinically cannot be distinguished from a relapse. Third, if access to specific treatment depends upon the diagnosis (or otherwise) of a relapse, bias is inevitable.

This section considers the diagnosis of people with MS who present with symptoms suggestive of an acute episode with onset within the previous four weeks (a time chosen because most studies have this time limit).

4.3.1 General diagnosis

▷ Evidence statement

There were no studies on the validity or reliability of the diagnosis of a relapse that fulfilled the inclusion criteria.

▷ From evidence to recommendations

The absence of any studies on the validity and reliability of the clinical diagnosis of a relapse concerned the GDG. However it was essential to make some recommendations, if only because the Department of Health risk sharing scheme depends absolutely on the diagnosis of relapses. Therefore a clinical consensus was reached, without difficulty, on the recommendations that follow.

RECOMMENDATIONS

- R40** If a person with MS has a relatively sudden (within 12–48 hours) increase in neurological symptoms or disability, or develops new neurological symptoms, a formal assessment should be made to determine the diagnosis (that is, the reason for the change). This should be recorded clearly. **D**

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- R41 This diagnostic assessment should: D
- be undertaken within a time appropriate to the clinical presentation
 - consider the presence of an acute infective cause
 - involve a GP or acute medical/neurological services.
- R42 Further neurological investigation should not be undertaken unless the diagnosis of MS itself is in doubt. D

LOCAL IMPLEMENTATION POINTS

Local clinicians will need to set out protocols for:

- which specialists should be approached by GPs and how
- agreed local criteria for further neurological investigation.

4.3.2 Optic neuritis: diagnosis

Optic neuritis is an acute demyelination of the optic nerve. Optic neuritis is often the first manifestation of MS. Many attacks of optic neuritis are asymptomatic, but symptoms may include pain in or around the eye and altered visual acuity, presenting as blurring, or altered colour perception. It is one of two specific clinical diagnoses that often but not always indicate an acute attack of MS (the other is transverse myelitis, discussed next). In the context of an already established diagnosis of MS the management is little different from that of any other acute relapse. However if this is the first clinical attack then there are specific considerations relating to the likelihood of eventually developing further clinical evidence of MS. The risk can be estimated using MRI brain scanning, and people with no abnormalities on MRI scanning are at low risk of developing MS within five years.^{111,112} This section covers the approach to optic neuritis as the first neurological manifestation in a patient, but the guidelines will apply even in the context of a known diagnosis.

▷ Evidence statement

Two diagnostic accuracy studies examined the effectiveness of different tests for the diagnosis of optic neuritis. The first assessed the use of the Aulhorn Flicker Test in which the luminance of a visual field varies at flicker rates between 0–50 Hz and subjective ratings of this are recorded. The results showed that a decrease in the brightness sensation at medium frequencies and a brightness enhancement at 1–3 Hz, the ‘late maximum’, gives a sensitivity of 98% and a specificity of 86% for the diagnosis of florid optic neuritis. Overall this gives a DOR of 300, indicating that the test provides strong diagnostic accuracy, being able to differentiate between patients in the florid stage of optic neuritis and those in the recovery phase.¹¹³ The second study examined the utility of three different optotype contrast sensitivity charts in the diagnosis of optic neuritis. The results indicated that the 3% chart with a cut-off point of 2.25 lines was best able to discriminate between patients with optic neuritis and normal controls. At this cut-off point the test yielded a DOR of 873, which is indicative of a test with convincing diagnostic accuracy. However as the patient range was composed of patients with unilateral/bilateral optic neuritis and normal healthy controls this is highly likely to have inflated the diagnostic accuracy of the test.¹¹⁴

4 Disease diagnosis and specific treatment

▷ From evidence to recommendations

The main issues to be considered are ensuring that people with potential optic neuritis are seen by a specialist for diagnosis of MS and deciding on what actions to take following the diagnosis. The recommendations therefore reflect the clinical issues, and were made by consensus without difficulty

RECOMMENDATIONS

R43	Every individual presenting with an acute decline in visual acuity, with or without associated pain, should be seen by an ophthalmologist for diagnosis.	D
R44	If the diagnosis is confirmed as optic neuritis, without any other specific cause and possibly due to MS, the ophthalmologist should discuss the potential diagnosis with the individual (unless there are overwhelming patient-centred reasons for not doing so; see R35). A further referral to a neurologist for additional assessment should be offered.	D

LOCAL IMPLEMENTATION POINTS

These will need to cover:

- which local ophthalmologists are interested in neuro- or medical ophthalmology
- how urgent referrals are made both to the ophthalmologist and, if necessary, to the neurologist.

4.3.3 Transverse myelitis: diagnosis

Transverse myelitis is a reasonably rapid (several hours to a few days) onset of impairment of motor control, sensory function, and control over bladder, bowel and sexual functions that has a specific spinal cord level and no demonstrated structural cause (eg herniated disc). It may be the first manifestation of MS, although about a third of patients have no further attacks.¹¹⁵

▷ Evidence statement

No diagnostic accuracy studies were identified.

▷ From evidence to recommendations

As with optic neuritis, the main clinical concerns are that people with potential transverse myelitis are diagnosed correctly, especially to ensure that there is no alternative treatable diagnosis, and that appropriate actions then taken. Evidence concerning investigations of acute spinal syndromes and prognosis was not sought. The recommendations were made by consensus without difficulty

RECOMMENDATIONS

R45	Every person presenting with symptoms and signs of acute spinal cord dysfunction should be investigated urgently, especially to exclude a surgically treatable compressive lesion.	D

- R46** If a diagnosis of transverse myelitis is made (and there is no previous history of neurological dysfunction), the individual should be informed that one of the possible causes is MS. **D**

4.4 Treatment of acute episodes

Acute episodes of neurological symptoms that lead to first presentation or to the recognition of a relapse are thought to be secondary to an episode of demyelination. Hence treatments that affect the inflammatory process and immune system are used, especially corticosteroids. Currently, the use of corticosteroids is recommended as the standard treatment of acute MS relapses but clinical practice varies widely.¹¹⁶ Several preparations of steroids exist, and the recent trend has been away from adrenocorticotrophic hormone (ACTH) (no longer available) and oral prednisolone to more potent preparations such as methylprednisolone and dexamethasone. Although there are many studies, they often address different questions making a synthesis of the evidence difficult. Furthermore many doctors use (and many patients prefer) oral corticosteroids and again the evidence about the efficacy or otherwise of this is simply absent. Lastly it should be recognised that both acute short-term and longer-term use of steroids may have side effects but, again, evidence on the clinical importance of this risk, and relative risk-benefit ratios is absent.

This section will consider optic neuritis and transverse myelitis as acute episodes, and will review the evidence for all three conditions and make one set of recommendations. This approach has been taken to reduce repetition.

4.4.1 General treatment

► Evidence statements

The effectiveness of treatments for patients suffering an acute worsening of symptoms was evaluated in three systematic reviews (**Ia**) and 14 RCTs (**Ib**).

Steroids

Three systematic reviews^{117–119} assessed the effectiveness of steroids in the treatment of acute worsening (**Ia**). The first review of six RCTS, reported that both methylprednisolone and ACTH showed a protective effect against the disease getting worse within five weeks of treatment.¹¹⁹ The review found no significant difference in terms of drug (methylprednisolone or ACTH), route of administration or treatment duration (five days *vs* 15 days). Only one study reported data for long-term follow-up, and reported no significant effect of treatment in terms of improvement or the number of new exacerbations between the methylprednisolone and placebo groups. All of the studies included in the second review of five studies were included in the first review.¹¹⁷ The third review performed two separate analyses.¹¹⁸ The first of these analyses involved the evaluation of studies which compared high dose methylprednisolone with placebo. The studies included for this section of the review were also included in the other two reviews. All three reviews reported similar results.

4 Disease diagnosis and specific treatment

A further two RCTs,^{120,121} not included in any of the reviews compared the effects of ACTH (combined with bed rest in one study) to control (placebo in one RCT and bed rest in the other) (Ib). One RCT¹²¹ only reported a beneficial effect for three of the seven outcomes assessed, and these effects were only observed in the first six weeks. The second¹²⁰ reported within rather than between group differences and so it is not possible to draw any conclusions from this study.¹²⁰ Both studies reported significantly more minor adverse effects in the ACTH group including rounding of the face, ankle oedema and mood elevation, which occurred in most of the patients treated with ACTH.

One review¹¹⁸ also included studies comparing high and low dose methylprednisolone (Ia). No differences were found in Expanded Disability Status Score (EDSS) scores among patients treated with high and low dose methylprednisolone. An additional RCT, not included in the review, also compared high (2g/day) and low dose (1g/day) intravenous methylprednisolone (IVMP). No differences were seen on any of the outcome measures assessed at three week follow-up.¹²² One further RCT compared the effects of high dose (2g/day) and low dose (0.5g/day) methylprednisolone combined with 300mg ranitidine daily (Ib). This study found no significant differences between groups in terms of EDSS scores, but did find a positive effect in favour of the high dose treatment group for two MRI measures.¹²³ Minor side effects were reported in both groups. Two RCTs compared intravenous and oral methylprednisolone (500mg). Both studies found no significant differences between the two treatment groups.^{124,125} One study¹²⁴ reported more withdrawals in the oral treatment group and both groups reported similar minor side effects.

Two RCTs^{126,127} compared short-term treatment (15 days) with ACTH and methylprednisolone (Ib). These studies reported no significant differences in the effects of the two treatments either in the short-term or at long-term follow-up (18 months). Adverse events were relatively minor and were similar between the two groups in one study,¹²⁶ while in the other all side effects were reported in the ACTH group and included ankle oedema and glycosuria.¹²⁷ A third RCT compared intravenous ACTH, intravenous dexamethasone (8mg daily maximum) and methylprednisolone (40mg daily maximum) in the short-term treatment of patients suffering an acute relapse. The average EDSS score improved significantly more in patients treated with dexamethasone compared to those receiving ACTH or methylprednisolone. Significantly more patients showed a lowering of the EDSS score of at least one point in the groups treated with ACTH and dexamethasone compared to those receiving methylprednisolone.¹²⁸ Adverse events were not reported.

One RCT compared the effectiveness of intrathecal triamcinolone acetonide crystal suspension and oral methylprednisolone. No significant differences were found between the two treatment groups in EDSS scores.¹²⁹

Side effects were reported in two of the systematic reviews and two RCTs. These included herpes simplex, herpes zoster, severe ankle oedema, fractured neck of femur, acute anxiety and severe depression;¹¹⁷ weight gain, oedema, gastrointestinal symptoms and psychological symptoms;¹¹⁹ raised blood glucose;¹²⁶ infection and raised blood pressure.¹²¹ One review reported that the major side effects were significantly more frequent in the intervention group compared to the control group. The frequency of minor side effects was high in all the studies.

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Other interventions (all Level Ib)

One RCT¹³⁰ assessed the effects of plasma exchange combined with ACTH and oral cyclophosphamide to a control group receiving ACTH, oral cyclophosphamide and sham plasma exchange. This study found no significant differences between the two treatment groups.

Ciclosporin A was compared to prednisolone in one RCT. At the end of treatment there were no significant differences between the two groups but after three month follow-up there was a significant improvement in EDSS score in the prednisolone group compared to the ciclosporin group.¹³¹ There were reports of side effects including nausea and paraesthesia of the extremities all in the ciclosporin group.

ATG combined with ACTH was compared to treatment with ACTH alone. The RCT¹³² reported a significant improvement in DSS score in those in the combined treatment group compared to those receiving ACTH alone. Side effects occurred in both groups and so the treatment period was reduced from 28 to 14 days.

One RCT assessed the efficacy of ginkgolide B at different doses compared to placebo. This study found no significant differences between the treatment groups for any of the three outcomes assessed.¹³³ Adverse effects were similar between the groups although hiccups were reported more commonly in the ginkgolide group.

▷ Economic evidence on methylprednisolone in the treatment of acute relapses in MS

The use of high-dose steroids to manage acute relapse in MS was deemed an important area for economic analysis; in particular the group was interested in the potential costs and benefits of different methods of administering high-dose steroids.

Clinical practice varies greatly and the only formal clinical evidence comes from two RCTs comparing oral methylprednisolone with intravenous administration as a hospital day case;^{124,125,134} these show equal efficacy. This evidence is of limited relevance as a recent survey of consultant neurologists suggested that only 7% could offer administration as a day case.¹¹⁶

Formal economic modelling was not deemed worthwhile given the lack of relevant clinical data. Instead a 'think piece' was prepared which attempted to itemise the potential costs and benefits of alternative methods of administration in a way that facilitates comparisons.

The three alternative methods of administration considered were:

- hospital IV (inpatient or day case)
- home IV
- oral.

The potential costs and benefits were classified under six headings:

- effectiveness
- NHS resources
- quality of life
- patient and carer costs
- side effects and tolerability
- NHS delivery issues.

Details are given in Appendix E.

4 Disease diagnosis and specific treatment

One may conclude that many factors should be considered when comparing alternative methods of methylprednisolone delivery and that there is little formal evidence on any of these. As a result there is no clearly dominant treatment in terms of clinical effectiveness or resource use, and the group was unable to make a recommendation for the preferred method of administration of high dose steroids.

▷ From evidence to recommendations

There was much evidence available. However, each study investigated a separate question. The questions were rarely related to each other. They used different steroids at different doses and had different outcome measures at different times. Direct synthesis of an answer to the question 'What treatment should I give, in what dose, by what route, for how long, and how infrequently?' was not possible. The GDG debated the issue several times, over several hours in total, and eventually agreed the recommendations unanimously

4.4.2 Optic neuritis: treatment

Many patients with optic neuritis are asymptomatic, and do not even approach their GP. However in those people presenting with symptoms treatment may be considered, either to reduce current problems or to prevent later problems.

▷ Evidence statement

One systematic review of three placebo-controlled RCTs assessed four comparisons of the effects of steroids on short- and long-term functional improvement.¹¹⁷ Two studies assessed ACTH, one assessed prednisone and one intravenous methylprednisolone. The overall results showed that there were no beneficial effects on functional improvement at eight days, but a small significant beneficial effect at thirty days. However, there was no long-term effect on functional improvement or on relapse occurrence. A number of the studies also reported both major and minor side effects associated with steroid treatment¹¹⁷ (Ia). Two further studies, one RCT and one CCT, not included in the review also examined the effects of methylprednisolone. The RCT compared intravenous methylprednisolone against mecobalamin. No overall beneficial effects on any of the six outcomes measures assessed were observed at one year follow-up¹³⁵ (Ib). The CCT compared methylprednisolone against vitamin B1. The results showed no significant beneficial effects on any of the three outcome measures assessed¹³⁶ (IIa).

A further four placebo-controlled RCTs met the inclusion criteria. The first examined intravenous immunoglobulin and was terminated at one year follow-up due to lack of efficacy of the intervention. No beneficial effects were observed for any of the four outcome measures assessed and the incidence of both major and minor side effects in the treatment group was high.¹³⁷ The second RCT evaluated the use of corticotrophin gel in patients with unilateral optic neuritis. The results showed no significant benefits for treatment on any of the six outcome measures assessed.¹³⁸ The last two RCTs both examined the use of a single injection of triamcinolone. The first trial reported a significant beneficial effect for overall visual improvement at three-month follow-up.¹³⁹ However, the second trial reported no significant differences between the groups on any of the outcome measures at six months¹⁴⁰ (Ib).

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▷ From evidence to recommendations

The evidence, although extensive, is difficult to use because the research has not considered many of the questions such as the relative effectiveness of different doses, different durations of treatment, different preparations, or different routes of administration. The guideline developers discussed the matter extensively and the recommendations below draw upon the evidence, experience and evidence in other areas of medicine, and current practice. We agreed that a single set of recommendations covering acute episodes including optic neuritis (and transverse myelitis, where there was no evidence) would be appropriate.

RECOMMENDATIONS

- R47 Any individual who experiences an acute episode (including optic neuritis) sufficient to cause distressing symptoms or an increased limitation on activities should be offered a course of high-dose corticosteroids. The course should be started as soon as possible after onset of the relapse and should be **either**:
- intravenous methylprednisolone, 500mg – 1g daily, for between three and five days **A**
 - or
 - high-dose oral methylprednisolone, 500mg – 2g daily, for between three and five days. **A**
- R48 An individual should be given a clear explanation of the risks and benefits involved in taking corticosteroids. **D**
- R49 Frequent (more than three times a year) or prolonged (longer than three weeks) use of corticosteroids should be avoided. **D**
- R50 Other medicines for the treatment of an acute relapse should not be used unless as part of a formal research protocol. **D**

LOCAL IMPLEMENTATION POINTS

The local services will need to set guidelines on:

- who may prescribe or recommend methylprednisolone
- where and how intravenous methylprednisolone is to be administered if used
- how patients are linked in to appropriate disability services (see next section).

4.5 Acute episodes: rehabilitation

An acute episode will usually cause some increased limitation on activities, and the increased disability will itself often require urgent intervention, if only the provision of additional support to the person with MS. Sometimes hospital admission is the only way to manage the increased dependence. The general aspects of the management of increased dependence are covered later. The specific features of increased dependence associated with an episode are its relatively sudden onset and the likelihood that recovery will occur over three to six months, albeit not necessarily complete recovery.

4 Disease diagnosis and specific treatment

▷ Evidence statements

One RCT¹⁴¹ compared the efficacy of planned multidisciplinary team assessment and intervention combined with IVMP (1g/day for three days) to standard ward routine care combined with IVMP for acute relapse. The results showed significant beneficial effects on four of the five outcome measures at three-month follow-up in favour of the group who had received the multidisciplinary team intervention.

▷ From evidence to recommendations

Although there was only one trial that specifically considered rehabilitation after acute relapse, the additional evidence (reviewed elsewhere in this document) confirming the benefits of specialist neurological rehabilitation coupled with the strong evidence supporting rehabilitation after stroke (which is similar in presenting with sudden onset complex neurological disability) meant that the GDG had no difficulty in supporting the recommendations made.

RECOMMENDATION

R51 When a person with MS experiences a sudden increase in disability or dependence the individual should be:

- given support, as required and as soon as practical, both in terms of equipment and personal care D
- referred to a specialist neurological rehabilitation service. The urgency of the referral should be judged at the time, and this referral should be in parallel with any other medical treatment required. A

LOCAL IMPLEMENTATION POINTS

Local services will need to specify and agree:

- arrangements for swift access to a neurological rehabilitation service for post-relapse support
- how equipment and home care should be provided for relapse and post-relapse support
- arrangements for accessing neuro-ophthalmology and low vision services.

4.6 Interventions affecting disease progression

The primary aim of medical intervention is generally to cure pathology, by preventing disease progression and/or removing or stopping the disease process. In MS therefore it is to prevent relapses and progressive demyelination once a diagnosis of MS is confirmed. Demyelination has an inflammatory component, and therefore most treatments target the immune system.*

* NB There are three interferon beta products: Avonex (manufactured by Biogen) and Rebif (Serono) are interferon beta-1a products licensed only for the treatment of relapse-remitting MS (RRMS). Betaferon (Schering) is interferon beta-1b and is licensed for the treatment of both RRMS and secondary progressive MS.

The evidence relating to interferon beta and glatiramer acetate has not been reviewed for this document. The National Institute for Clinical Excellence (NICE) reviewed the clinical and cost-effectiveness evidence and concluded that, 'On the balance of their clinical and cost-effectiveness neither interferon beta nor glatiramer

continued

► Evidence statements

Steroids

The studies in this part are distinguished by taking patients who were *not* in an acute relapse.

The effectiveness of steroids in the long-term treatment of MS was investigated in one systematic review (Ia), six RCTs (Ib) and one CCT (IIa). The review¹¹⁷ included four placebo-controlled RCTs comparing the effects of ACTH ($n = 1$), prednisolone ($n = 1$) and methylprednisolone ($n = 2$) given for 9–18 months. It reported no significant effect on long-term functional improvement or on relapse occurrence. The review also reported the occurrence of both major and minor side effects including herpes simplex, herpes zoster, severe ankle oedema, femur fracture, acute anxiety and severe depression.¹¹⁷ Four of the controlled trials also compared steroids to placebo. Two RCTs, one of ACTH and the other of two different doses of zinc hydroxide corticotrophin, found no effect of treatment on any of the outcomes investigated.^{142,143} One reported a greater incidence of adverse effects including steroid diabetes, increased blood pressure, oedema, acne and hirsutism in the intervention groups.¹⁴² A placebo-controlled RCT¹⁴⁴ of methylprednisolone daily for five days followed by oral prednisone for a further four days reported beneficial effects for four (pyramidal function, cerebellar symptoms, sensitivity disorders and overall EDSS scores) of the eight outcomes investigated. This study only included patients with primary progressive MS. A second placebo-controlled RCT investigated a combination treatment of prednisolone, azathioprine and anti-lymphocyte globulin. This study found no effects on relapse rate or EDSS score but did report a positive effect on VEP latency.¹⁴⁵ One RCT and one CCT compared the regular administration of intravenous methylprednisolone to treatment with methylprednisolone during relapses.^{146,147} Both studies included only patients with relapsing remitting MS, and both reported positive effects of treatment. It should be noted that the CCT was of very poor quality,¹⁴⁶ and the RCT was only of average quality.¹⁴⁷ The CCT reported only mild side effects, however, the RCT reported two serious adverse effects (acute glomerulonephritis and severe osteoporosis) in the group receiving regular steroid treatment.

Aminopyridines

The effectiveness of aminopyridines was assessed in one systematic review (Ia), three placebo-controlled crossover RCTs and one pragmatic crossover RCT (Ib). The systematic review, which included five crossover trials, reported significantly greater improvements in a variety of outcomes in those receiving 4-aminopyridine or 3,4-diaminopyridine.¹⁴⁸ It reported that six

acetate is recommended for the treatment of multiple sclerosis (MS) in the NHS in England and Wales'. The guidance also invited the Department of Health and National Assembly for Wales 'to consider the strategy outlined in Section 7.1 [of TA 32] with a view to acquiring any or all of the medicines for this guidance in a manner that could be considered to be cost effective'.

Subsequently the Department of Health and National Assembly for Wales set up a risk sharing scheme with the pharmaceutical companies concerned (see HSC 2002/004 and WHC 2002/016) so that these drugs will be funded for use in selected people with MS. Selection is undertaken using the guidelines developed by the Association of British Neurologists (see www.theabn.org/downloads/msdoc.pdf), both for starting and stopping the drugs. A subset of people with MS, who agree, will be monitored using a standard protocol.^{141a,141b,141c}

It is worth noting that there is no evidence relating to the validity or reliability of making the diagnosis of the type of multiple sclerosis or the occurrence of a relapse, both important components of the current policy.

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major side effects occurred in the 144 treated patients included in the review. These included acute encephalopathy, confusion and seizures. All three of the placebo-controlled studies not included in the review found no overall significant differences between the treatment groups, 4-aminopyridine in two and 3,4-diaminopyridine in the other, and those receiving placebo.^{149,150} The study using 3,4-diaminopyridine reported that over half the participants experienced side effects when in the active treatment group compared to around 10% when receiving placebo.¹⁴⁹ The studies were of good quality. One reasonable quality crossover RCT compared the effects of 3,4-diaminopyridine and 4-aminopyridine.¹⁵¹ This study reported that 4-aminopyridine appeared more effective than 3,4-diaminopyridine. More patients withdrew during treatment with 3,4-diaminopyridine as they believed their condition had deteriorated.

Cytotoxics

The effects of cytotoxics were investigated in one systematic review (**Ia**), two RCTs (**Ib**) and three CCTs (**IIa**).

The review included two RCTs which compared the effects of cladribine to placebo, and an additional placebo-controlled RCT of cladribine also met inclusion criteria. The review reported that one study reported a beneficial effect of cladribine but the other did not.¹⁵² The RCT reported no difference in the two treatment groups in terms of clinical outcomes but reported a beneficial effect of cladribine on MRI outcomes.¹⁵³ The review highlighted the cladribine is a potentially toxic immunosuppressive agent.

Mitoxantrone was compared to placebo in two RCTs included in the review, and two RCTs and one CCT not included in the review. An additional RCT compared mitoxantrone to methylprednisolone. The review found that both RCTs reported significant delays in progression and reductions in relapse rate, although one trial was of short duration.¹⁵² Both studies not included in the review supported these findings. The first RCT included a large number of participants and was of reasonable quality.¹⁵⁴ It reported a beneficial effect of treatment for all five outcomes investigated.¹⁵⁴ The second RCT compared high (12mg/m) and low-dose (5mg/m) mitoxantrone to placebo. The results showed a significant beneficial effect of high-dose treatment compared to placebo on EDSS scores, AI scores and the number and severity of relapses. There were no significant differences between the placebo and low-dose groups.¹⁵⁵ The CCT reported a beneficial effect on mean exacerbation rate in those receiving mitoxantrone, although it found no significant effects on EDSS score.¹⁵⁶ This study was of poor quality and only included 20 patients. Mitoxantrone has significant cardiac side effects and cannot be given for more than two years. The pragmatic RCT found no difference between treatment with mitoxantrone and methylprednisolone in terms of EDSS score, disease progression or the number of patients with clinical improvement. However, mitoxantrone was more effective than methylprednisolone in terms of the number of relapses and MRI lesions.¹⁵⁷

Cyclophosphamide was investigated in the review and also in two CCTs.* The review included five placebo-controlled RCTs of cyclophosphamide, in four of these it was combined with corticosteroids.¹⁵² Delays in progression were reported in two trials but this was not confirmed

* A Cochrane review – La Mantia, Milanese C, Mascoli N, Incorvaia B *et al.* Cyclophosphamide for multiple sclerosis. Cochrane Library, Issue 4, 2002 – also met the inclusion criteria. The review however did not include any trials not already included.

by the other three, a wide range of side effects were reported in all studies.¹⁵² An additional poor quality placebo-controlled CCT was identified which was not included in the review. This study compared two different regimes of cyclophosphamide compared with corticotrophin and also included a no-treatment group. Both cyclophosphamide groups showed beneficial effects on time to progression and there were no differences between the two intervention groups.¹⁵⁸ The second poor quality CCT compared three different treatment regimes. It found no significant differences between the groups in terms of EDSS score but found that time to progression was improved in those receiving a slightly higher total mean dose of cyclophosphamide than those receiving the lowest dose.¹⁵⁹

Immunoglobulin

One systematic review which included three placebo-controlled trials of intravenous immunoglobulin (IVIg) (Ia), and three further placebo-controlled trials not in the review met inclusion criteria, two of which were randomised (Ib) and one of which was a controlled trial (IIa). An RCT of gamma-globulin (Ib) and a controlled trial of anti-lymphocyte globulin also met the inclusion criteria (IIa). The review reported that two of the three trials reported no effect on disease progression, although the third small trial did report an effect. Relapse rate was reduced in all three trials. A wide range of side effects including headache were reported in all trials.¹⁵²

The remaining three placebo-controlled studies all reported some beneficial effects of treatment. The RCT reported a beneficial effect on disease progression (as assessed by the EDSS score) and on the number of relapses, but found no effect on muscle strength or depression.¹⁶⁰ The randomised crossover trial found a beneficial effect on the period of no exacerbation but not on any of the other four outcomes assessed, during IVIg treatment.¹⁶¹ This study also reported a high number of common adverse events during the IVIg phase. The CCT reported a positive effect on both the number of exacerbations and the severity of exacerbation and reported no side effects during treatment.¹⁶² The second CCT which investigated a combination of interventions including anti-lymphocyte globulin (with combinations of azathioprine, prednisolone and thoracic-duct drainage), did not report appropriate results and so it is not possible to draw conclusions from this study.¹⁶³ One small placebo-controlled RCT investigated the effects of gamma-globulin and found no difference between the intervention and control group.¹⁶⁴

Immunostimulants

Two reasonable quality placebo-controlled RCTs investigated the effects of **levamisol**. The first reported no effect on disability or neurological function,¹⁶⁵ while the second reported a reduction in the number of patients experiencing an exacerbation.¹⁶⁶ Both studies reported that side effects, although minor, were more common in the intervention group.

Immunosuppressives

One systematic review (Ia), nine RCTs (Ib) and two CCTs (IIa) met inclusion criteria. The review, which included one systematic review of seven studies and two RCTs, assessed the effectiveness of **azathioprine**.¹⁵² Three additional RCTs and one CCT also assessed the effectiveness of azathioprine.^{167–170} The review found that both RCTs and the review reported non-

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significant delays on progression, and that the placebo-controlled studies reported a reduction in relapse rate of one-third or more. It also reported that azathioprine has unpleasant side effects with around 10% of patients suffering intolerable vomiting.¹⁵² None of the other trials of azathioprine reported an overall beneficial effect of treatment. Three studies found no beneficial effect of treatment^{167–169} and one reported a beneficial effect on MRI lesion load and MEP but not on any of the other outcomes investigated.¹⁷⁰ All studies reported side effects of azathioprine treatment, some of which were severe.

Two placebo-controlled RCTs assessed the effectiveness of **cyclosporin**. One reported no beneficial effect of treatment,¹⁷¹ the other reported a positive effect on three of the five outcomes investigated.¹⁷² Both studies reported adverse effects associated with cyclosporin. Renal function was adversely affected in almost all patients receiving cyclosporin in both trials, with significant nephrotoxicity occurring in around one fifth of patients in one of the trials.¹⁷² An additional RCT compared cyclosporin with azathioprine and found no significant differences between the two treatment groups.¹⁷³ Side effects occurred in both groups but more severe in the azathioprine treated group.

Other immunosuppressives investigated included 6-mercaptopurine combined with methotrexate,¹⁷⁴ mizoribine,¹⁷⁵ and lenercept,¹⁷⁶ each in one RCT, and antegren in two RCTs.^{177,178} None of these interventions showed an overall beneficial effect of treatment compared to placebo. The systematic review also included two RCTs of methotrexate.¹⁵² There was a significant beneficial effect in one trial when assessed using a composite measure of treatment failure; the other trial, however, reported no effect on relapse rates.

Interferons (excluding interferon beta)

Seven RCTs assessed the effectiveness of **α-interferon**.^{179–185} None of the RCTs reported a beneficial effect on clinical outcomes, but four of the RCTs did report positive effects on MRI parameters including the number of new and active lesions.^{180,182,183} Adverse events were significantly more common in the interferon-treated groups.

Antiviral

A number of different antiviral treatments have been investigated in the treatment of disease progression. A total of eight RCTs (**Ib**) and two CCTs (**IIa**) met inclusion criteria. These studies investigated the effects of valaciclovir ($n = 1$),¹⁸⁶ isoprinosine ($n = 3$),^{187–189} aciclovir ($n = 1$),¹⁹⁰ influenza vaccine ($n = 3$),^{191–193} tuberculin ($n = 1$),¹⁹⁴ and amantadine ($n = 1$).¹⁹⁵ None of these studies reported an overall beneficial effect of treatment, and the RCT of tuberculin reported a harmful effect of treatment with a greater incidence of exacerbations in the treatment group.¹⁹⁴ One RCT of amantadine¹⁹⁵ reported a positive effect of treatment on two (time to first relapse and number of relapses) of the seven outcomes investigated. All but one of these studies were placebo controlled. The study without placebo control compared isoprinosine with prednisolone and found no difference between the two treatment groups.¹⁸⁸

Anti-inflammatory

Two RCTs (**Ib**) and one CCT (**IIa**) assessed the effectiveness of anti-inflammatory agents; all were placebo controlled. The CCT¹⁹⁶ which investigated D-penicillamine and metacycline, and

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one of the RCTs¹⁶⁴ which investigated chloroquine and soluble aspirin, both reported no beneficial effects of treatment. The second good quality RCT investigated the effects of sulfasalazine and reported a beneficial effect of treatment for three (progression rate, relapse rate and MRI T2 lesions) of the six outcomes investigated.¹⁹⁷ Treatment was stopped permanently in eight patients treated with sulfasalazine due to adverse effects including neutropenia, hepatitis, allergy and depression.

Transfer factor

The effectiveness of transfer factor was investigated in three RCTs (Ib) and one CCT (IIa). None of the RCTs reported any beneficial effect of treatment.^{198–200} The CCT reported a beneficial effect for one of the three outcomes investigated.²⁰¹ This study was of very poor quality.

Irradiation

Four placebo-controlled RCTs (Ib) investigated the effects of treatment with total lymphoid irradiation (TLI). One good quality small RCT found no beneficial effects of treatment,²⁰² one reported an initial beneficial effect which was no longer significant after 18 months follow-up,²⁰³ one reported a beneficial effect for one of the two outcomes investigated²⁰⁴ and the other reported an overall beneficial effect of treatment.²⁰⁵ The study which reported an overall beneficial effect of treatment was stopped prematurely due to decreased patient entry because of the availability of β -interferon.²⁰⁵ All studies reported a greater incidence of adverse events in the TLI treated groups. These included nausea, hair loss, amenorrhoea, infections, thrombocytopenia and pancytopenia.

Hyperbaric oxygen

A systematic review (Ia) and one additional RCT (Ib) met the inclusion criteria. The review included 14 RCTs but the results were restricted to eight studies which were judged to be of reasonable quality.²⁰⁶ The review reported that only one of eight trials reported results in favour of hyperbaric oxygen therapy, the others found no clear positive effects. Side effects were generally minor with ear and visual problems predominating. The additional RCT, which was of good quality, reported a positive effect of treatment for all five outcomes investigated and reported only minor adverse events associated with treatment.²⁰⁷

Linoleic acid

One systematic review (Ia) met the inclusion criteria. The review included three RCTs and found that the severity and duration of relapses was reduced in those treated with linoleic acid. It also found that patients with very low disability at trial entry ($\text{EDSS} \leq 2$) treated with linoleic acid showed a significantly smaller increase in disability than those in the control group, however, this was not observed in those with higher disability at trial entry.²⁰⁸

Linomide

Three RCTs and two CCTs assessed the efficacy of linomide. The first RCT reported no beneficial effect of treatment,²⁰⁹ the second reported a beneficial effect for a number of MRI

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measures but not for any clinical measures,²¹⁰ and the third investigated the effects of two different doses of linomide compared to placebo.²¹¹ This study found no beneficial effect of the lower dose (2.5mg/day) of linomide compared to placebo, but reported a positive effect for this higher dose (5mg/day) for two of the three outcomes investigated.²¹¹ Two of the RCTs^{209,211} were ended prematurely due to an increase in serious adverse events including death (IIb). Both of the CCTs reported overall beneficial effects of treatment with linomide. However, both also support a high number of minor adverse effects in the intervention groups.^{212,213}

Myelin basic protein

Six RCTs (Ib) assessed the effectiveness of various forms of myelin basic protein; all studies were placebo controlled. Five of these reported no beneficial effects of the intervention for any of the outcomes investigated.^{214–218} Interventions investigated in these trials were: HBC,²¹⁴ AG284 (human leukocyte antigen with myelin base protein),²¹⁵ altered peptide ligands at three different doses,²¹⁶ T-cell receptor peptide,²¹⁷ and bovine myelin.²¹⁸ One of these studies was stopped prematurely due to the appearance of a systemic hypersensitivity reaction in 13/142 patients.²¹⁶ One reasonable quality RCT of myelin basic protein reported a significant beneficial effect of treatment for patient self report of various symptoms, no other outcomes were assessed.²¹⁹ This study reported that no adverse effects were observed during the study.

Plasma exchange

One systematic review (Ia) and one CCT (IIa) examined the effects of plasma exchange. The review,²²⁰ which included six RCTs comparing various treatment combinations including plasma exchange to the treatment combination without plasma exchange, found that plasma exchange significantly reduced the proportion of patients who experienced neurological decline at 12 months follow-up. The CCT,²²¹ which only included 16 patients and was of very poor quality, found no beneficial effects of treatment. It reported transient hypotension in one patient in the intervention group but reported no other adverse effects.

Thymectomy

The effects of thymectomy were investigated in two poor quality controlled trials (IIa). Both included three treatment groups, one receiving azathioprine combined with thymectomy, the second receiving thymectomy alone, and the third receiving no intervention. One study reported no beneficial effects of the thymectomy, either alone or combined with azathioprine.²²² The second reported a beneficial effect of thymectomy combined with azathioprine for two of the three outcomes investigated, but found no beneficial effects of thymectomy alone. Neither study reported on adverse events.²²³

Other

A variety of other interventions have been investigated for their effects on disease progression. Five studies were included in this category, four RCTs (Ib) and one CCT (IIa), all included a placebo or no treatment arm. Interventions which were shown to have no effect on disease progression included tolbutamide,²²⁴ atromid,²²⁵ and 8-methoxypsoralen.²²⁶ An average

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quality RCT of Padma 28,²²⁷ a herbal mixture, reported a positive effect of treatment on disease progression. A poor quality CCT²²⁸ of Chinese medicine reported a positive effect on the incidence of relapses. Neither study provided any details on adverse events.

▷ Economic evidence

An HTA systematic review of immunomodulatory drugs for the treatment of people with MS was carried out in 1999.¹⁵² This review found no cost-effectiveness studies of azathioprine, cladribine, cyclophosphamide, intravenous immunoglobulin, methotrexate or mitoxantrone. The costs of these drugs vary enormously from around £60 per year to treat one person with methotrexate or cyclophosphamide, to around £9,000 per year for cladribine or intravenous immunoglobulin. There will be considerable extra costs associated with the administration and monitoring of these drugs. Of course, cost savings may also accrue to health and social services due to reduced hospital admissions, reduced disability and maintenance of employment for the person with MS and/or their carer. A full economic evaluation would need to assess the costs along with the benefits, side effects and acceptability of these treatments to people with MS.

▷ From evidence to recommendations

The recommendations made here had to consider not only the evidence reviewed above but also:

- existing NICE recommendations concerning disease-modifying drugs (this evidence was not reviewed for this guideline)
- the Department of Health's risk sharing scheme
- the need to advise against any treatments known to be ineffective or harmful
- the need to encourage caution where there is some evidence that is equivocal, but where the drug may carry significant risks
- the considerable uncertainty surrounding many drugs
- the large number of drugs that have been researched and that some people may still consider or ask about.

The recommendations try to cover all likely drugs in a logical order, starting with the drugs with the strongest recommendations in their favour and finishing with the drugs with the strongest recommendations against them.

Many drugs have been tried for reducing disease progression. The recommendations given have been influenced by several factors:

- in the development of this guideline we referred to the NICE technology appraisal relating to interferon beta or glatiramer acetate
- the Department of Health risk sharing scheme was also outside of our scope
- aminopiridines, which were reviewed in this section, are not intended to effect disease progression, have risks and are not available on the NHS.

Consequently we have not been able to draw comparisons between the various disease-modifying drugs in terms of cost-effectiveness. The recommendations primarily summarise existing guidance with some recommendations concerning other drugs.

RECOMMENDATIONS

R52	People with relapsing-remitting MS, and those with secondary progressive MS in which relapses are the dominant clinical feature, who meet the criteria developed by the Association of British Neurologists are eligible for treatment under the risk sharing scheme. See Health Services Circular 2002/004 (www.doh.gov.uk/pricare/drugsmultiplesclerosis.htm) and Table 5.	HSC

Table 5 Summary of the criteria suggested by the Association of British Neurologists, and agreed by the Department of Health, to determine eligibility for treatment using interferon beta and glatiramer acetate for people with MS within the 'risk sharing scheme'

- A People with **relapsing-remitting** MS should be offered **interferon beta** (any type) provided that the following four conditions are met:
- can walk 100 metres or more without assistance
 - have had at least two clinically significant relapses in the past two years
 - are aged 18 years or older
 - do not have contraindications (see specific summary of product characteristics (SPC) for details).
- B People with **relapsing-remitting** MS should be offered **glatiramer acetate** provided that the following four conditions are met:
- can walk 100 metres or more without assistance
 - have had at least two clinically significant relapses in the past two years
 - are aged 18 years or older
 - do not have contraindications (see specific SPC for details).
- C People with **secondary progressive** MS should be offered **interferon beta** (any type licensed for this use) provided the following five conditions are met:
- can walk 10 metres or more with or without assistance
 - have had at least two disabling relapses in the past two years
 - have had minimal increase in disability due to gradual progression over the past two years
 - are aged over 18 years
 - do not have contraindications (see specific SPC for details).
- D People with MS offered treatment with **interferon beta** should have the following **stopping criteria** discussed and agreed before starting treatment:
- intolerable side effects
 - becoming or trying to become pregnant
 - occurrence of two disabling relapses within a 12-month period
 - secondary progression with an observable increase in disability over a six-month period
 - loss of ability to walk, with or without assistance, that has persisted for longer than six months.
- E People with relapsing-remitting MS offered treatment with **glatiramer acetate** should have the following **stopping criteria** discussed and agreed before starting treatment:
- intolerable side effects
 - being pregnant or planning pregnancy
 - occurrence of two disabling relapses within a 12-month period
 - development of secondary progressive MS
 - loss of ability to walk, with or without assistance, that has persisted for longer than six months.

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- R53 People with MS should be advised that linoleic acid 17–23g/day may reduce progression of disability. Rich sources of linoleic acid include sunflower, corn, soya and safflower oils. A
- R54 The following treatments should not be used except in these specific circumstances: D
- after full discussion and consideration of all the risks
 - with formal evaluation, preferably in a randomised or other prospective study
 - by an expert in the use of these medicines in MS with close monitoring for adverse events.
- The treatments are:
- azathioprine A
 - mitoxantrone A
 - intravenous immunoglobulin A
 - plasma exchange, and A
 - intermittent (four-monthly) short (1–9 days) courses of high-dose methylprednisolone. A
- R55 The following treatments should not be used (because there is no research evidence for beneficial effects on the course of the condition):
- cyclophosphamide A
 - antiviral agents (for example, aciclovir, tuberculin) A
 - cladribine A
 - long-term treatment with corticosteroids A
 - hyperbaric oxygen A
 - linomide A
 - whole-body irradiation A
 - myelin basic protein (any type). A

LOCAL IMPLEMENTATION POINTS

These should cover:

- which neurological services have responsibility for initiating and monitoring treatment with interferon beta and glatiramer acetate, and funding arrangements for the risk-sharing scheme
- which neurological services are going to be responsible for initiating and monitoring treatment with other specialist treatments
- how patients may be recruited into ongoing trials of disease-modifying agents
- how people with MS, if they so wish, obtain advice on dietary changes needed to achieve the linoleic acid intake recommended.

4.7 Other issues around altering the risk of relapses

There are many beliefs held by those with MS, professionals, relatives and others about factors that might precipitate a relapse. This section covers some of the common areas of concern including:

- infections and immunisations

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- pregnancy
- stress (emotional and physical).

4.7.1 Infections and immunisations

People with MS who develop infections often experience worsening of impairments and disabilities. The main reason is probably the rise in temperature, which is known to exaggerate neurogenic impairments in MS. However it has also been suggested that infections may trigger actual relapses of MS, leading some people to try to avoid infection by immunisation. On the other hand, immunisations to reduce the risk of infections have sometimes been avoided in case they also trigger a relapse.

▷ Evidence statements

There are two cohort studies^{229,230} and one case-control study^{193,231} on infections and MS (II). The relevant evidence suggests:

- that relapses are more frequent during the five week period following common infections (particularly upper respiratory tract infections)
- bacterial infections are of less importance in causing relapses.

There are two RCTs (I), two cohort studies and two case control studies (II) looking at the effect of vaccinations and MS.^{191,193,232–235} The evidence suggests that:

- 33% of MS patients experience an acute exacerbation following influenza
- vaccination does not cause relapses.

▷ From evidence to recommendations

Many people with MS and their doctors are concerned about infection and vaccination, and although the evidence does not show unequivocal benefit, it certainly shows lack of harm. The GDG agreed that the recommendations could be derived safely from the evidence.

RECOMMENDATIONS

R56	People with MS should be offered immunisation against influenza.	C
R57	People with MS should have any other immunisation they need, with advice that there is no known risk of causing a relapse of their MS.	C

LOCAL IMPLEMENTATION POINT

The local guidelines should cover how routine influenza immunisation will be offered and mechanisms to ensure that every person with MS is contacted.

▷ Resource implications

The resources currently devoted to immunisation are unknown, but probably small. Setting up and running a prophylactic service would best be achieved by using the existing service for the elderly. General practitioners are given financial incentives to immunise patients at risk (the

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elderly) and if patients with MS were added to the group at risk then there would be a small increase in expenditure (1–2 patients/GP). The potential benefits are significant in terms of reduced relapses and so reduced admissions and use of steroids. Furthermore people with MS would generally avoid hospital admission with influenza.

4.7.2 Pregnancy

The possible effect of pregnancy on the course of MS is often a dilemma for those with MS and doctors alike. First, it is perceived that it might alter the immediate or long-term natural history of the disease. Second, any disability might affect both obstetric care and, later, child care.

▷ Evidence statements

The evidence comes from seven cohort studies^{236,237–242} (IIa) and it suggests that:

- the relapse rate is stable or declines during pregnancy particularly in the third trimester
- the relapse rate increases during the first three months post-partum
- the relapse rate returns to pre-pregnancy rate six months post-partum
- there is no association between pregnancy and worsening of long-term disability
- there is no association between oral contraceptive use, breast-feeding, epidural analgesia or the number of pregnancies with MS relapses.

▷ From evidence to recommendations

Only observational evidence was available, but the GDG agreed that the recommendations could be derived safely from the evidence

RECOMMENDATIONS

R58	Women with MS who wish to become pregnant should be advised that the risk of relapse decreases during pregnancy, and increases transiently post-partum.	C
R59	When giving birth, women with MS should have the analgesia that seems most appropriate and acceptable to them, without fear of its affecting their MS.	C

LOCAL IMPLEMENTATION POINTS

Local services should identify:

- an obstetrician and members of the obstetric department with a knowledge of supporting women with disabilities in the decision to try and become pregnant, during pregnancy and at birth
- local services and support groups for new mothers with disabilities.

▷ Resource implications

Currently people with MS already see obstetricians and others, but sometimes are given inappropriate advice. There are few direct resource implications, though some special training might be needed if no one locally has an interest. The benefits would largely accrue to the person with MS and child.

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4.7.3 Stress (various types)

There is a widespread belief among people with MS, relatives and some professionals that stress of almost any type may precipitate a relapse and worsen the manifestations of MS. Some patients are advised to avoid certain (but varied) stressors. Putative stresses include emotional stress, trauma, and other medical interventions. This section reviews the topic to draw appropriate recommendations where possible. It covers emotional stress, trauma, and surgical treatments.

▷ Evidence statements

Anaesthesia – There are three cohort studies^{241,243,244} of the effects of anaesthesia/surgery, and the evidence (II) suggests that there is no association between type of anaesthetic and deterioration of MS.

Stress – There are two cohort studies and two case-control studies of emotional stressors^{245–248} and the evidence (II) suggests that:

- there is conflicting evidence regarding an association between stress and MS relapses
- several studies have shown no significant association between stressful life events and psychological stress with MS relapses
- increased conflict and disruption in routine, daily hassles have been reported to increase relapse rate
- there is significantly increased risk of reported stressful events when rate of MS progression higher
- there is significantly increased risk of MS progression when rate of reported stressful events higher.

Trauma – There is one cohort study²⁴⁹ and two case control studies^{247,248} of trauma, and the evidence (II) suggests that:

- there is insufficient evidence to support any significant association between trauma and MS relapses
- head injury and lumbar disk surgery are not associated with the onset of MS
- peripheral fractures are not associated with increased disease exacerbation.

RECOMMENDATION

In the absence of conclusive evidence, it has only been possible to make a recommendation on stress relative to surgery.

R60	People with MS should be encouraged to have any surgery they need, using whichever anaesthetic technique is appropriate. They should be informed that there is no known increase in the risk of relapse.	B

LOCAL IMPLEMENTATION POINT

The local service should identify anaesthetists with a particular interest in undertaking anaesthesia in people with MS or other neurological conditions.

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▷ Resource implications

There are few resources currently devoted to this specific topic, and there are no great implications because the guidelines relate primarily to advice and information. The benefits are that patients and others will be less concerned and anxious about the consequences of trauma and stress.

5 Rehabilitation and maintenance: functional activities and social participation

5.1 General introduction

The guidelines to this point have primarily concentrated upon issues that concern the early phases of MS. At that time most people with MS are leading normal unrestricted lives, but rehabilitation should be considered from the time of diagnosis, especially for anyone who has any symptoms or limitations on activities that concern them. Progression is not inevitable but in those who do worsen, it is likely that roles such as work and active leisure pursuits will be affected first. The smaller number of people who go on to develop more severe limitations on their activities will usually only do so later in their life. Furthermore, even those people who do develop more severe impairments usually still wish to maximise their level of independent activities and social participation.

This rehabilitation section therefore starts by considering those recommendations that specifically concern social participation, activities and contextual factors because a) they are likely to be of greatest concern to most people with MS, b) they will arise before or at the same time as concerns about more basic activities and c) even the recommendations concerning impairments covered in Section 6 will all be set in the context of maximising participation and activities.

One key feature of rehabilitation is that it involves a structured, organised approach to complex problems (ie problems that many factors influence and that require multifocal interventions and/or interventions spread over a long time). Consequently many of the recommendations made in Section 3 concern rehabilitation.

The reader is strongly advised to read Section 3 in conjunction with this section.

It is also worth stressing that many of the interventions that may help people with MS require close collaboration with other statutory and non-statutory services. The most obvious is social services who have, for example, shared responsibility for much equipment supplied and for providing personal care in the home. However, other services such as employment and housing will often be involved. Given the closer collaboration being fostered nationally and the blurred and indistinct boundaries that vary around the country, these guidelines have made some recommendations that will apply to the NHS more in some parts of the country than in others, but that certainly are of importance to the person with MS.

It is therefore important at all times to recall recommendation R18.

While many of the recommendations in this section are generally applicable to the process of rehabilitation, it is important to stress some special features particular to the person with MS. As in any patient, rehabilitation for people with MS should first be directed towards the restoration of activities and functions that have become limited.

In people with MS, rehabilitation must also take account of the fact that the disease process may cause progressive impairment and consequent loss of abilities, so that maintenance of activities

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in the face of physical deterioration is a common goal of rehabilitation. Another common goal is to minimise the secondary effects of the disease process such as the development of contractures or pressure ulcers, the stress on relatives, and the emotional consequences for the person with MS. This proactive and preventative approach should if possible be adopted at a very early stage in the condition and is likely to be centred in the individual's home and/or workplace rather than in a rehabilitation unit.

The evidence base specifically concerning rehabilitation for people with MS is relatively limited. Interventions in these areas do not easily lend themselves to the traditional randomised control trial approach because rehabilitation interventions are individually tailored, and outcomes expressed in specific rather than general terms. Research is further complicated by the difficulty in describing accurately but succinctly the nature of the tailored intervention. Comparison groups often tend to be those given traditional or no treatments or those treated after a delay. Few studies specifically investigate rehabilitation in specific domains of disablement.

However the general principles of rehabilitation are similar whatever the disease or domain, and so the recommendations are similar for each part and draw on general evidence from other diseases. Therefore this section has the following structure:

- general rehabilitation recommendations
- recommendations relating to vocational and leisure activities
- recommendations concerning mobility
- recommendations specific to other domains including equipment and environmental alterations.

The whole section depends upon initial recognition that the person with MS has a difficulty in some area of their life that might benefit from further assessment and treatment. R7 to R11 in Section 3 covers this.

5.2 General rehabilitation

Rehabilitation is a process that focuses on increasing performance of activities and aims to optimise social participation and to minimise stress and distress for both the person with MS and any carers involved. The rehabilitation process is mainly a problem-solving approach that will involve multifocal interventions at differing levels (eg impairment, environment) from a specialist team over time. Consequently the process of rehabilitation will only begin when a problem has been recognised, and it starts with a detailed assessment of the individual's problem(s). This part focuses on two aspects of rehabilitation:

- ensuring that the persons' situation is considered as a whole, and not piecemeal, and
- making recommendations about specific ways of treating activities that are limited.

The processes involved in rehabilitation are often described as being a 'black box', although in fact they are better considered as a 'Russian doll'. This is because they can be described at many levels, from the global (assess, plan, intervene, review) to the very specific (for example, 'This person will benefit most from 20mg baclofen at night, botulinum toxin injection into the right gastrocnemius muscle, a resting splint at night and a daily stand in a standing frame ...'). Given the large number of impairments that may arise secondary to multiple sclerosis, the large variety of contexts that will apply to people with MS, and therefore the almost infinite number of particular situations, each being unique, it is not practical for these guidelines to give specific

5 Rehabilitation and maintenance: functional activities and social participation

detailed recommendations to cover each potential limitation of activities. Therefore the recommendations made in this section are necessarily only at a relatively high level, covering only more general principles.

There are only a few studies on the general effectiveness of rehabilitation in MS^{49,250,251} but the effectiveness of rehabilitation from a specialist multidisciplinary team has been demonstrated beyond all reasonable doubt in other situations, notably stroke.¹⁵ The effectiveness of multidisciplinary rehabilitation has also been shown in other disabling conditions such as head injury^{43,44} and back pain.²⁵² In these studies the patients have had complex problems with many interrelated factors and the rehabilitation process of multifocal interventions by a team has been the intervention investigated and found to be effective. People with MS also have similar features, and it is reasonable to generalise from this evidence. The evidence suggests that in this circumstance an expert (specialist) multidisciplinary team that involves the patient and family actively will achieve a better patient outcome, often at no extra cost.

► Evidence statements

Three RCTs, two CCTs and two uncontrolled studies assessed the effectiveness of multidisciplinary rehabilitation programs. The first RCT examined an inpatient rehabilitation program, comprising medical, nursing, occupational therapy and physiotherapy input. The results indicated beneficial effects on the functional independence measure (FIM), London Handicap Scale score, improvements in functional abilities and levels of handicap. The second RCT focused upon physical rehabilitation. Results showed significant positive changes on two of the five outcomes assessed, FIM and self-care abilities.²⁵¹ The third RCT examined the effectiveness of an outpatient rehabilitation treatment programme. This study reported significant beneficial effects on various outcome measures including the SF-36 (all subscales, fatigue, social experience and depression). No significant effect was found on the EDSS score²⁵³ (Ib). One CCT assessed the efficacy of an occupational and physiotherapy program for MS patients who suffered from moderate to severe ataxia of the upper limbs and trunk. The results indicated significant improvement on half of the outcome measures assessed, which included ADL indices.²⁵⁴ The second CCT assessed the effectiveness of an outpatients rehabilitation programme. This reported beneficial effects on two of the three outcomes assessed⁴⁹ (IIa). Both uncontrolled studies assessed multidisciplinary inpatient rehabilitation programmes. The results of the first study showed beneficial effects on four out of seven subscales of the Nottingham Health Profile Part 1 (NHP-1) assessed, including pain, physical mobility and emotional reactions.²⁵⁵ The results of the second study indicated beneficial changes on five out of the six RIC-FAS subscales assessed, including transfers, toileting, grooming and dressing²⁵⁶ (IIb).

► Economic evidence

There is very little economic evidence relating to rehabilitation in MS. The establishment of a multidisciplinary rehabilitation programme can result in significant benefits to people with MS and their families and carers. An effective programme may also result in future savings to the NHS and social services by reducing subsequent dependency, and in particular by reducing the need for hospitalisation at certain stages during disease progression.

The establishment of a multidisciplinary community MS team in Newcastle increased contacts with many health professionals following team referral, among the 38 people with MS whose

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data was analysed. However, these additional referrals were offset by a decrease in GP contacts, hospital consultant contacts and occupied bed days. Over the six-month period of the evaluation total costs for these people were lower than in the six months prior to the establishment of the team. No firm conclusions could be drawn about the effectiveness of the team but survey evidence showed a high degree of patient satisfaction with the team.²⁵⁷

An older study from the US considered the costs and benefits of a multidisciplinary, inpatient rehabilitation program designed along the same lines as similar programs that had been shown to be effective in stroke patients.²⁵⁸ Only 20 people were assessed in this study, but it did suggest that active, intensive multidisciplinary rehabilitation can improve functional outcomes and may result in cost savings in the long term.

▷ From evidence to recommendations

The GDG considered the evidence available here in the light of other evidence concerning MS reviewed elsewhere in this document and also in the light of strong evidence supporting specialist rehabilitation in other fields. It also noted that people with MS might present with new onset activity limitations needing medical diagnosis of the cause. Next, it noted that some readers might need explicit guidance on the components of the rehabilitation process. Finally, it was aware of emerging evidence in stroke that task-centered therapy may be more effective. The GDG agreed the recommendations made by unanimous consensus where direct evidence was lacking.

RECOMMENDATIONS

R61	If a person with MS starts to experience a new limitation on his or her activities, the cause should be identified medically, and the following considered:	D
	● is it due to an unrelated disease? ● is it due to an incidental infection? ● is it due to a relapse of the MS? ● is it part of a gradual progression?	
R62	If the limitation persists, despite treatment of any identified cause, the person with MS should be seen and assessed by a multidisciplinary service, specialised in neurologically based disability. This service should implement a rehabilitation programme.	D A
R63	The components of the rehabilitation programme should include the following:	D
	● establishing the wishes and expectations of the person with MS ● assessing and, if necessary, measuring relevant factors, in order to identify and agree goals with the person; these might include one or more of the following: – identifying and treating any treatable underlying impairments – giving task-related practice of a specific activity or activities – providing suitable equipment (with training in its use) – altering the environment as needed – teaching others how to assist with (or take over) tasks ● monitoring progress against set goals; the goals should be reviewed and reset, until no further goals exist and no further interventions are needed.	

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- R64 Where possible, both assessment and task-related practice should take place in the environment most appropriate to the task (for example, home, work or leisure). D

LOCAL IMPLEMENTATION POINTS

Local services will need to:

- identify how people with MS access neurological rehabilitation services at any stage in the course of their disease
- ensure that people working within neurological rehabilitation services work with appropriate statutory and voluntary organisations, both health and non-health.

5.3 Vocational activities: employment and education

Many people who develop or have MS will be finishing education or training, or will be in employment. In some people the MS will have little impact, but for most people MS will have some impact. It is important to minimise the impact if possible because being in employment has many health benefits and among other things enables an individual to retain self-esteem, social contacts, financial independence and a valued place in society. The importance of vocational rehabilitation services for people with MS at all stages but especially in the early stages was emphasised many years ago,¹⁷ and has been reiterated recently.²⁵⁹

The Department of Employment has some schemes available for people with disability, but generally specialised vocational rehabilitation services are not available. MS is relatively rare and usually poses very specific problems. For example cognitive losses and fatigue are probably the major impairments affecting employment, yet both are outside the normal scope of employment services. Therefore health service personnel have a vital role to play in providing people with MS and their employers with accurate, impartial information and advice, recognising both the abilities and limitations of the person with MS. Sometimes they may need to offer advice about alternative appropriate work.

▷ Evidence statement

Two studies were identified that examined interventions for limitations in undertaking employment in persons with MS. One RCT examined the effectiveness of a job retention programme combined with standard medical care compared to standard medical care alone.²⁶⁰ The results indicated no beneficial effect of the programme (Ib). One CCT²⁶¹ assessed the utility of an accommodation team planning approach compared to traditional job seeking skills for people who were unemployed.²⁶¹ Again the results indicated no benefit for the programme (IIb).

▷ From evidence to recommendations

The very little evidence on vocational rehabilitation available does not allow any conclusion to be drawn. However the Department for Work and Pensions, the British Society of Rehabilitation Medicine, and the Department of Health all recognise the potentially important role of the NHS in vocational rehabilitation. The GDG therefore thought it important to make recommendations to support this approach, and a consensus was easily reached.

RECOMMENDATIONS

R65	Any person with MS who is in work or education should be asked specifically whether they have any problems, for example motor, fatigue or cognitive difficulties.	D
R66	Any individual who has problems that affect their work or education should be seen for further assessment of their difficulties, preferably by a specialist vocational rehabilitation service, or specialist neurorehabilitation service.	D
R67	The results of the assessment should be used: ● to advise the person with MS on strategies, equipment, adaptations and services available to assist with vocational difficulties; and/or ● to advise the employer or others, with permission from the person with MS, on strategies, equipment and adaptations to assist; and/or ● to give information to the disability employment advisor, if involved (see R68).	D D
R68	The person should always be informed about available vocational support services (currently including Disability Employment Advisers and the Access to Work Scheme), and that there may be adjustments at work to which they are entitled under the Disability Discrimination Act.	D
R69	Any individual who cannot stay in or find alternative employment should be advised about other options such as voluntary work and where to find information about these options.	D

LOCAL IMPLEMENTATION POINTS

Local health, social and employment services will need to:

- agree an integrated approach to vocational rehabilitation, including defined referral criteria for relevant services, and methods for exchanging relevant information
- disseminate information on the location of and means of referral to the Disability Employment Officer at the local job centre and other employment services (including those in the voluntary sector)
- collect, collate and disseminate information about educational and retraining opportunities, and work within the voluntary sector.

5.4 Leisure and social interaction

All people, those in and out of employment, will have a range of key leisure activities. Leisure gives balance to life, as well as giving opportunities for social interaction. The impairments and disabilities that may affect work will usually also affect leisure, but the person with MS can have more control over their leisure pursuits. Loss of independent social activity is very common in people with MS; one survey in the USA found that 62% of people with MS were either socially inactive or depended upon the initiative of others.²⁶² The importance of leisure as a valid focus for specialist rehabilitation services is being increasingly recognised, but specific services are rare and are often run by social services or voluntary agencies. While the NHS does not have a responsibility to provide specific ongoing opportunities to undertake leisure (eg day centres), the NHS does have a clear responsibility to all patients, including people with MS, to assess their needs in relation to leisure activities and then to give, where possible, the skills and techniques

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needed to pursue chosen leisure pursuits and then to identify local resources and put the person with MS in touch with them.

▷ Evidence statements

No studies were identified that met the inclusion criteria.

▷ From evidence to recommendations

Although no research on leisure rehabilitation specific to MS has been undertaken, there is evidence that quality of life (in patients with stroke) is related to leisure activities and the GDG agreed that recommendations were needed and agreed those made by consensus.

RECOMMENDATION

- R70** Any person with MS whose participation in or enjoyment of a leisure or social activity becomes limited should be referred to a specialist neurological rehabilitation service which should: **D**
- identify whether previous activities are still achievable and, if not, help the person consider new activities
 - assess for, and then teach, the skills and techniques that could help achieve these activities
 - if necessary refer the person to local services that might help them establish and continue leisure and social activities.

LOCAL IMPLEMENTATION POINTS

The local services should:

- maintain an up-to-date list of local organisations that can provide information on social activities for people with disabilities
- maintain an up-to-date list of local community transport providers
- have procedures to enable easy cross-agency working to optimise leisure activities for people with MS.

5.5 Mobility

The ability to negotiate the environment independently is fundamental to all aspects of daily life and almost all aspects of social participation are dependent upon adequate mobility. Limitation in mobility is one of the prime determinants of the amount (time and number of people) of 'care needs', whether given by family or paid carers. Limitation in mobility is common in people with MS. For example in one study 58% of people could not climb stairs unaided and 42% needed mobility aids including wheelchairs.²⁶²

The construct of mobility is or can be much broader than simply walking. It includes moving in bed, getting out of bed, moving into and out of chairs, going up and down stairs and slopes, getting to and from shops, using special mobility equipment such as walking aids and wheelchairs, and using public transport. It may also include endurance.

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Reduced mobility is a common disability in many neurological and non-neurological conditions, and many studies have investigated treatments focused on improving mobility, usually walking. Furthermore, improvements in (or reduction in loss of) mobility are a common outcome measure in many other studies, including almost all interferon beta trials (the EDSS is primarily a measure of mobility).

▷ Evidence statements

Two RCTs and one randomised crossover trial assessed different interventions for mobility problems (**Ib**). The first RCT examined the use of fully trained service dogs for wheelchair mobile people with MS.²⁶³ The results showed significant beneficial effects on all of the eight outcome measures assessed including psychological, social, employment and care needs indices. The second RCT assessed the intervention of awareness through movement classes compared to just educational sessions. The results showed no difference in the number of falls or functional balance performance or self-efficacy between the groups.²⁶⁴ The randomised crossover trial compared hospital outpatient physiotherapy to home-based physiotherapy and no treatment. The results showed beneficial effects for the majority of outcomes assessed for physiotherapy interventions. There were no overall differences observed between the different physiotherapy interventions.²⁶⁵

▷ Economic evidence

There are no formal economic evaluations of any interventions for mobility problems in MS. However the randomised crossover trial of physiotherapy described above²⁶⁵ did consider the costs of providing home- and hospital-based therapy alongside the outcomes. No significant difference was found between the outcomes of home-based against hospital-based physiotherapy. Home therapy was more expensive than hospital outpatient sessions, even when patient travel costs to hospital (including time) were taken into account. Patient travel costs were approximately 40% of total hospital session costs.

▷ From evidence to recommendation

The evidence reviewed only considered one intervention (physiotherapy) and only in one group of patients (those able to walk, or likely to). The section refers to all aspects of mobility. Furthermore, many of the topics considered elsewhere in this guideline might improve mobility. The recommendations therefore approach all aspects of mobility, taking into account not only the specific evidence reviewed above but a) other evidence within this document, b) general principles of rehabilitation, and c) evidence in other conditions such as stroke.

RECOMMENDATIONS

- R71** Any person with MS who experiences reduced mobility (and it affects or threatens his or her activities) should be seen and assessed by a specialist neurorehabilitation service. The assessment should determine which of the following interventions are needed: **D**
- identification and treatment of any underlying impairment, especially weakness, fatigue, spasticity, ataxia, sensory loss and loss of confidence

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- task-related practice of a specific mobility activity or activities (for example, walking, transferring, using a wheelchair, climbing stairs)
- provision of suitable equipment, including wheelchairs, driving equipment and adaptive technology (with training in its use)
- alteration of the environment to increase independent mobility
- teaching of others how to safely assist with (or take over) tasks such as walking, climbing stairs, moving in bed or transferring.

- R72 Physiotherapy treatments aimed at improving walking should be: A
- offered to a person with MS who is, or could be, walking
 - given at home or on an outpatient basis, depending on the preference of the person with MS and local resources.

LOCAL IMPLEMENTATION POINTS

Local services will need to:

- identify how people with MS whose activities are affected or threatened by reduced mobility can easily access neurological rehabilitation services
- agree common measures of mobility to be used locally.

5.6 Activities of daily living

A significant proportion of people with MS may eventually experience limitations on their ability to undertake a variety of activities needed to live independently such as shopping, housework and undertaking personal care. Collectively these activities are referred to as activities of daily living (ADL), in contrast to vocational and leisure activities. Occupational therapists are usually the professional group with most expertise in, and who lead on the rehabilitation of, activities of daily living. The limitation may arise from many of the common impairments including cognitive losses. The amount of direct support from other people needed by a person is determined primarily by their need for support with personal activities and/or with their mobility. Various terms are used in this part.

‘Community activities’ are those that involve the person leaving their home and undertaking activities in public areas and buildings, such as shopping, using public transport, negotiating the environment safely (primarily avoiding traffic), and accessing other public amenities (eg leisure facilities). Parents may also need to accompany children to school. Community activities depend greatly upon adequate independent mobility and upon adequate cognitive skills.

‘Domestic activities of daily living’ are those activities needed around the house to maintain life and safety, and a reasonable standard of cleanliness. They include cooking, washing up, all aspects of managing clothing (eg washing, ironing) and keeping the house clean. They may also include in some people other activities such as caring for children, and responding to financial and other demands such as paying bills. In contrast to personal activities, domestic activities often make more demands on cognitive skills, and consequently may be influenced more by cognitive deficits.

‘Personal activities of daily living’ refers to basic daily activities such as dressing, washing and bathing, grooming, using the toilet, controlling continence and getting around the house.

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▷ Evidence statements

No studies were identified that met the inclusion criteria.

▷ From evidence to recommendations

No studies explicitly studied rehabilitation of these activities, but measures of these activities, especially personal activities of daily living, were the primary outcome measure in the RCTs of specialist neurological rehabilitation already reviewed (see 5.2.1). The GDG agreed unanimously that the recommendations below were reasonably derived from evidence reviewed elsewhere in this document, and from the evidence in other neurological conditions such as stroke.

RECOMMENDATIONS

Activities of daily living are usually divided into personal, domestic and community activities.

R73	Any person with MS who experiences a limitation in personal, domestic or community activities should receive a comprehensive multidisciplinary assessment. This should be carried out by a team experienced in the treatment and management of MS, and should cover the person's previous and current functioning in the following areas:	D
	● personal activities such as dressing, eating, using the toilet and washing ● domestic activities such as cooking, washing and ironing clothes, keeping the house clean and dealing with household bills ● community activities such as shopping, using public transport, negotiating the environment safely (for example, avoiding traffic) and accessing other public amenities ● any caring or support activities within the home, including caring for children.	
R74	A comprehensive assessment of this type should:	D
	● actively involve the person with MS, encouraging them to think about and define what they need to continue to achieve their goals and aspirations ● take place on more than one occasion and in different environments ● take into account the individual's priorities, interests, goals and potential ● consider environmental factors, and the support available from family and carers ● take into account both current and future needs.	
R75	After the assessment, a programme of interventions should be developed for the person with MS, with the aim of increasing and maintaining independence wherever possible. The programme of interventions should be agreed by the individual. The interventions specified should be goal-directed, and designed to meet the individual's priorities, interests and potential.	D
R76	If the individual agrees, the programme of interventions should be shared with social services, and this must occur if social services are to be responsible for maintenance interventions.	D
R77	There should be regular monitoring to check how effective the interventions are, with a view to changing them if necessary.	D

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- R78 At the end of the planned programme, the person should know how to obtain a re-assessment if their situation changes. D

5.7 Equipment, adaptations and personal support

The consequences of any disease are influenced greatly by the person's environment. This includes both peri-personal (within immediate reach, eg clothes, wheelchairs) and local (outside immediate reach, eg ramps, rails) environmental factors and extends to the general community. The importance of providing equipment has been stressed by the Audit Commission,¹²² who also illustrated the enormous variability in current provision. The effectiveness of providing equipment has also been demonstrated in an RCT in the USA.²⁶⁷ These guidelines do not consider the need to ensure that the public environment is made more appropriate for individuals with a variety of impairments, but this is important to people with MS.

The physical environment, as the term is used here, also includes the availability of other people in a supporting role (ie as assistants, not specifically as social contact). In most instances family members will undertake this role but it must be recognised that friends and neighbours also provide additional support, and that for a substantial number of people paid carers provide support. It should also be recognised that the support offered by the carer may extend (legitimately) well beyond hands-on support to include monitoring safety, providing prompts, and even providing the reassurance needed to allow the person to perform the activity independently.

Increasingly, services are being encouraged to have a joint approach to funding and providing equipment. However at present some equipment and adaptations may be provided by social services and they may seek advice from health professionals about the current health of the individual with MS and about the likely course of the illness. It may be important to stress that the course of MS is unpredictable in any individual and that appropriate equipment should be made available both for the current needs of the individual and for their needs at any predictable or likely worse state, such as when suffering an incidental infection.

Equipment and adaptations can be costly but they can also make an enormous difference to the quality of life of people with MS and their families and carers. The Audit Commission report argued that resources could be saved by better targeting of equipment to people's needs and better coordination of services to improve the efficiency of provision.¹²² In addition if equipment and adaptive technology enable people to remain independent in the community, this is preferable to admitting them for treatment in other parts of the health care system. There is a clear need for research on the costs and benefits of equipment and adaptive technology for people with MS.

► Evidence statement

One two-phase study encompassing both an RCT and an uncontrolled pre-post phase examined the effects of tilting the wheelchair seating position for patients with MS.²⁶⁸ The results of the uncontrolled phase showed beneficial effects on four of the five outcome measures assessed, namely measures of respiration and voice volume, with a tilt of the seating angle of 25 degrees. The results of the RCT phase indicated that there were no differences between the groups when the seating angle was tilted by either 25 or 45 degrees. This phase did not include a 'no tilt' control group (Ib).

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▷ From evidence to recommendations

There are few randomised studies of the value of equipment, and the best (Mann *et al*, 1999) was the basis of the Audit Commission report.¹²² Much equipment is so self-evidently effective (eg a wheelchair for someone whose legs are paralysed) that trials are probably unethical. The GDG drew on the Mann *et al* study and Audit Commission report, and easily reached consensus on the recommendations made.

RECOMMENDATIONS

- R79 Every person with MS whose activities are persistently affected should be assessed by a specialist neurological rehabilitation service to determine how their environment might be improved, enabling for example: D

- an increase in the person's independence
- the impact on their activities to be minimised
- a reduction in risk to the person or their carers.

The environmental changes considered should include the following: D

- provision of (or changes in) equipment
- alterations in the structure of the building
- provision of (or change in) the personal support provided.

Equipment and adaptations

- R80 If a person with MS depends on someone else for an activity (especially in mobility), an expert should assess whether an aid or adaptation, including an environmental control system, could be of benefit. For example, it may increase the independence of the person with MS, and/or minimise the stress on, or risk for, the person who assists them. The person with MS or, if necessary, their family and/or carers, should be taught how to use the equipment. Ability and safety in using the equipment should be checked at least once, after a suitable interval. D

- R81 The service providing or recommending the equipment should ensure the equipment's continuing appropriateness and safety, at appropriate intervals. D

Personal support

- R82 If a person with MS receives support or supervision from someone, for any particular activity, an assessment should be made to determine whether a greater level of independence could be achieved. D

- R83 If personal support is provided by family, friends or paid carers, an expert should offer knowledge and skills to help the carer(s) provide assistance in ways that maintain the dignity and utmost independence of the person with MS, while also not threatening the health or well-being of the carers. D

- R84 If support is given on a daily basis for more than one hour, then the level and appropriateness of the support offered should be monitored, at a minimum, on a yearly basis. It should also be reviewed after any significant event (for example, infection, relapse, complication, departure of family member). Any person involved in hands-on D

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activities, especially physical moving and handling, should be taught appropriate, safe techniques for the individual situation, and should be able to seek further tuition or advice when they need it.

LOCAL IMPLEMENTATION POINTS

Local health and social services must have systems in place to provide an integrated approach to assessment and provision of a) non-specialist equipment, b) specialist equipment and c) personal support services. To this end they need to:

- identify who assesses people with MS for specialist and non-specialist equipment and home adaptations they may need
- identify funding mechanisms in collaboration with social care providers
- set up local audit mechanisms showing average delays and the proportion of equipment which is actually used
- specify how pieces of equipment are monitored and maintained, and changed as necessary in line with changing needs
- agree how carers, including family members, are taught necessary skills and are assessed for competence in all aspects of caring undertaken
- specify how family members and other carers can contact appropriate experts for further advice and tuition.

6 Diagnosis and treatment of specific impairments

Lesions within the CNS in MS may or may not cause the nervous system to function abnormally. There is evidence that most episodes of demyelination do not cause any specific symptoms or signs at the time.¹¹⁰ Moreover, factors other than episodes of demyelination may cause change in or occurrence of symptoms and signs. Nonetheless most people with MS will experience some specific impairments from time to time, if not constantly.

This section covers the assessment and management of many of the specific impairments that people with MS may experience. It considers each impairment individually, although in reality they will rarely occur in isolation. It does not cover the more general aspects of management nor does it cover the disabilities or other consequences of impairment. The primary outcome in the studies that support this section will generally be a change in the level of the impairment rather than the level of activities.

Effective management of any impairment depends upon its initial identification and so the first recommendation in most sections covers the detection of the impairment. While it is not necessary to ask every person with MS about every possible impairment, it is important to remember that any person with MS might have any of these impairments. Therefore the professional person in contact with the person with MS will need at least a mental checklist similar to that set out in Table 3. They should always ask specific questions in an appropriate and sensitive manner.

When considering how to act in any particular situation it is vital to take into account not only the recommendation(s) appropriate to the specific impairment but also all other aspects of the person's situation such as other impairments that they may have. **Thus for each impairment there is an unwritten first recommendation – do not start or modify treatment until all aspects of the person's clinical situation have been established and understood, and the wishes and expectations of the person with MS have been established.**

6.1 Fatigue

Fatigue is probably one of the commonest, most disabling and frustrating symptoms experienced by people with MS, although they may not explicitly complain about it. It varies widely both between people with MS and within a person from time to time. In a tertiary centre in the USA, fatigue limited activity in 78% of 224 people with MS, compared with 17% of 93 controls²⁶⁹ and in an epidemiologically sound sample of 124 people with MS in Norway, 39% reported frequent problems with fatigue limiting activity.²⁷⁰ A study in South Wales found that 48% of people with MS had fatigue at any one time.²⁷¹ In the audit of Oxfordshire people with MS, nearly half had fatigue on entry although only 3% (7/226) complained of new fatigue over a ten month period.⁶

Fatigue is associated with both disability and depression, and management of fatigue should consider all aspects of a patient's situation, not simply the fatigue. Furthermore, it is in practice often difficult to distinguish complaints of fatigue from complaints about weakness, both in research studies and in clinical practice.

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Clinically, recommendations are needed to ensure that fatigue:

- is recognised as being present
- is analysed to determine whether it is primary or symptomatic
- is managed as far as possible, to try and ameliorate its effects.

▷ Evidence statements

Interventions for fatigue were investigated in one systematic review (Ia), one RCT, two randomised crossover trials (Ib) and one CCT (IIa).

Amantadine – The review included four RCTs which compared the effects of amantadine to placebo, and in addition one randomised crossover trial and one CCT also met the inclusion criteria. The review reported that all four RCTs showed a pattern in favour of amantadine but as the effect size was small there is considerable uncertainty about the validity and clinical significance of the findings.²⁷² The CCT also reported positive findings on the two outcomes assessed, namely overall improvement and patient's selection of drug for continuing therapy. The incidence and type of side effects reported were similar between the intervention and the control group.²⁷³ The randomised crossover trial²⁷⁴ examined the effects of amantadine on cognitive functioning in patients with fatigue. There were no differences reported on two of the three outcome measures assessed, with the only positive measure being attained on a test of stimulus selection with event-related potentials (ERP) as the outcome measure.

Pemoline – Pemoline was investigated in two RCTs included in the review and also one RCT and one randomised crossover trial not included in the review. The review showed that there was no beneficial effect of pemoline over placebo and an excess number of reports of adverse effects were recorded in the intervention groups.²⁷² The RCT not included in the review supports these findings, with no difference between the groups being evident on four of the five outcomes measures assessed.²⁷⁵ The final randomised crossover trial²⁷⁶ reported beneficial effects on the two patient report outcomes assessed. Drop outs were similar between the two intervention periods.*

▷ Economic evidence

The HTA systematic review found no formal economic evaluations of amantadine or pemoline. The review then attempted to identify indirect data on potential costs and benefits 'that might allow tentative modelling of cost-effectiveness'. Unfortunately, no information about the reduction in quality of life in MS due to fatigue, or the costs of managing fatigue, was identified. The HTA report concludes that:

if the interventions were of similar cost to amantadine [Amantadine costs £15.35 for 56 × 100mg tablets (BNF, 43) – therefore, a dose of 100mg twice a day costs approximately £200 per year] ... and costs of administration were minimal, it seems likely that such interventions would be cost-neutral. Although the NHS bears only a small proportion of the total burden of cost for MS, such is the size of this burden, that any savings in hospital and other treatment services may well outweigh the extra drug costs. Undoubtedly however, the bulk of the benefit arising from an effective treatment for

* NB Pemoline is no longer available in the UK

6 Diagnosis and treatment of specific impairments

fatigue in MS would be to the individual themselves, who might be able to remain in full-time paid employment for longer.²⁷²

▷ From evidence to recommendations

The clinical significance of the benefits shown in the studies reviewed was judged to be too low to allow any firm recommendations in favour of amantadine. The GDG was also aware that modafinil is being used on the basis of one published study,²⁷⁷ but felt that until RCT evidence was available no recommendation should be made for this. The GDG therefore has recommended a simple approach, including traditionally used, though not researched approaches; this was agreed by consensus.

RECOMMENDATIONS

R85	Each professional in contact with a person with MS should consider whether fatigue is a significant problem or a contributing factor to their current clinical state.	D
	<i>If fatigue is disrupting the individual's life, then the following recommendations apply.</i>	
R86	The presence of significant depression should be considered; if significant depression is present, it should be treated.	D
R87	Other factors causing fatigue, such as disturbed sleep, chronic pain and poor nutrition, should be identified and treated if possible.	D
R88	Some medicines may exaggerate fatigue, thus any medication being taken should be reviewed.	D
R89	General advice and training on how to manage fatigue should be given, including encouragement to undertake aerobic exercise and to use energy conservation techniques.	D
R90	At present, no medicines targeted at fatigue should be used routinely, although people with fatigue should be informed that a small clinical benefit might be gained from taking amantadine 200mg daily.	D A

LOCAL IMPLEMENTATION POINTS

The local services should:

- identify which health workers have expertise in fatigue management for people with MS and how they are accessed
- decide whether a specific measurement tool is to be used, and if so which one.

6.2 Bladder problems

Urinary tract symptoms are common in people with MS. In a population-based sample in the USA, 25% of people with MS had intermittent or constant catheterisation for bladder dysfunction²⁶² and in a second American survey 59% had some bladder disturbance.²⁷⁸ A study in South Wales suggested that 14% of all people with MS had an indwelling urethral catheter and 44% of the remainder had bladder dysfunction.²⁷⁹ In the Southampton survey of

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people with MS, 33% suffered urinary incontinence.²⁸⁰ In the Oxfordshire audit⁶ bladder problems were the most common presenting problem affecting 39/226 patients on 78 occasions over ten months, and they were the fifth most common problem in terms of prevalence.

Bladder dysfunction can be very disabling and may have many adverse consequences, including great emotional distress, curtailed social activities, and disturbed sleep. Incontinence also increases the risk of pressure ulcers. Its effects may be compounded by reduced mobility. Unfortunately matters are worsened by the reluctance of people with MS, their families and professional staff to discuss the problems.

While it is likely that disturbed bladder control is the commonest general cause of bladder symptoms, some bladder symptoms may be indicative of infection, and infection not only causes pyrexia (high temperature) and malaise but can also cause general exacerbation of all impairments, especially spasticity. Urinary tract infection (UTI) may also, rarely, cause pyelonephritis and septicaemia. The frequency of actual UTI is unknown and so, although the potential importance of urinary tract infection is great, its actual medical importance is unknown.

This section will first cover the assessment and management of disturbed bladder control leading to urinary frequency, nocturia, urgency of micturition, and incontinence. Then the specific issues of UTI will be covered. Many of the issues are not specific to people with MS, being similar to those faced by other people with neurogenic bladder disturbance and so some recommendations are based on generic evidence. The main issues to be covered are:

- detection and diagnosis of disturbed bladder physiology
- management of disruptive bladder function
- diagnosis and treatment of UTIs
- management of intractable incontinence.

6.2.1 *Bladder dysfunction*

This part considers disturbances in the control of bladder emptying. The use of catheters is mentioned, but 6.2 should also be consulted for further recommendations concerning the use and management of long-term catheters.

▷ Evidence statements

Ten systematic reviews were identified that assessed the efficacy of a number of different interventions for urinary incontinence, though some of these contained data from the same trials (IIa). Four reviews examined the effectiveness of different behavioural bladder training programmes for urge, mixed and stress incontinence. The first review compared bladder training to no intervention, drug therapy (oxybutynin and flavoxate hydrochloride plus imipramine), pelvic floor muscle training and electrical stimulation. The results showed that there was weak evidence to suggest that bladder training is more effective than no treatment, and that bladder training is better than drug therapy. There was insufficient evidence that electrical stimulation is more effective than sham electrical stimulation.²⁸¹ The second review assessed the efficacy of prompted voiding either alone or in combination with oxybutynin. The results indicated that prompted voiding was beneficial compared to no intervention, and that prompted voiding combined with oxybutynin was superior to prompted voiding alone.²⁸² The

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third review compared the effectiveness of pelvic floor muscle training against placebo, electrical stimulation, vaginal cones and bladder training either alone or in combination. The results indicated that pelvic floor muscle training was superior to either no treatment or placebo, and that 'intensive' appeared to be better than 'standard' training. The effect of adding adjunctive treatments to pelvic floor training was unclear due to the limited amount of evidence.²⁸³ The last review compared bladder training to flavoxate hydrochloride and imipramine, electric prompting devices and combinations of training plus terodoline or oxybutynin. The results from the review tended to favour bladder training but data was only available for a limited number of prespecified outcomes.²⁸⁴

Four reviews were included that examined the use of different devices or surgical interventions as management options for incontinence. The first review compared suburethral slings to abdominal retropubic suspension and needle suspension. The results showed no differences between suburethral slings and abdominal retropubic suspension or needle suspension. However sling operations had a significantly higher complication rate.²⁸⁵ The second review compared the effect of weighted vaginal cones to control, electro stimulation, pelvic floor muscle training and these interventions in combination. The results showed that cones were better than no active treatment, but that there were no differences between cones and pelvic floor muscle training or electrostimulation. There was not enough evidence to show that cones plus pelvic floor muscle training was different to either cones alone or pelvic floor muscle training alone.²⁸⁶ The third review compared anterior vaginal repair to pelvic floor muscle training, open abdominal retropubic suspension and bladder neck needle suspension. The results indicated that anterior vaginal repair was less effective than open abdominal retropubic suspension both in the short and long term. There were no differences between anterior vaginal repair and bladder neck needle suspension.²⁸⁷ The last review assessed the efficacy of a number of different surgical procedures for stress incontinence. Overall, the results indicated that colposuspension may be more effective and the effect more long-lasting than that for anterior colporrhaphy and needle suspension. It was also found that second and subsequent operations to correct stress incontinence are less successful than first procedures.²⁸⁸

One small review compared the effectiveness of tolterodine to oxybutynin. The results showed that both drugs had similar effects on the number of micturitions in a 24-hour period, but that oxybutynin was marginally superior in decreasing incontinence and increasing the mean voided volume per micturation.²⁸⁹

The last review assessed the effects of different types of absorbent product for the containment of urinary and/or faecal incontinence. The results indicated favourable outcomes in terms of skin problems, the number of changes, ease of disposal and cost for disposable *vs* non-disposable body worns.²⁹⁰

Five RCTs and nine randomised crossover trials examined different interventions for bladder impairment (Ib).

Six placebo-controlled randomised crossover trials assessed the effect of desmopressin on voiding frequency and incontinence. Three of the trials specifically examined nocturia, whilst the other three assessed daytime voiding frequency. The three trials that reviewed nocturia all reported beneficial effects on the frequency of voiding, night-time urine volumes and sleep duration.^{291–293} No significant differences were reported in the number of episodes of incontinence. All three trials report a number of side effects of a minor nature. The trials that

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examined daytime voiding frequency reported significant effects upon both frequency and volume up to six hours after drug intake.^{294–296} However, no benefit was observed on the frequency of night-time voiding; the 24-hour urine volume was unaffected. None of the trials reported side effects of a significant nature.

Four placebo-controlled trials assessed the efficacy of different drug interventions. One RCT examined the effect of synthetic capsaicin solution in patients with hyperreflexic bladder.²⁹⁷ The results showed an overall significant benefit in terms of voiding patterns, leakage, bladder pressure and the need to use pads. There were no differences in the incidence of side effects between the groups. The second RCT reviewed the use of indoramin in male patients with symptoms of urinary tract dysfunction.²⁹⁸ The study reported significant effects upon two of the five outcome measures assessed (flow rates) but not upon the overall symptoms score. Two randomised crossover trials assessed the efficacy of different drugs in patients with detrusor hyperreflexia. The first trial examining the use of atropine reported significant differences in bladder capacity.²⁹⁹ The second trial assessed the intervention of flurbiprofen.³⁰⁰ The study reported beneficial effects on five of the seven outcomes assessed. However, side effects were more common during the intervention phases although all of these were minor.

Two further placebo-controlled RCTs addressed the effectiveness of biofeedback and electrical stimulation of the pelvic floor muscles. The first RCT addressed biofeedback in combination with behaviour modification, pharmacological adjustment and pelvic floor training.³⁰¹ The results showed no significant differences between the groups on any of the outcome measures assessed. The other RCT examined the use of electrical stimulation of the pelvic floor muscles followed by pelvic floor exercises.³⁰² Significant beneficial effects were observed on all but one of the outcomes measures assessed.

Two studies, one RCT and one randomised crossover trial, compared different interventions against active comparators. One RCT compared oxybutynin to propantheline and reported no significant differences between the groups either in terms of benefits or the side effects observed.³⁰³ The randomised crossover trial examined the three interventions; methantheline bromide, meladrazine tartrate and flavoxate chloride in patients with detrusor hyperreflexia.³⁰⁴ The results showed that methantheline bromide was superior to the other two interventions on the outcomes measures of patient preference, entire cystometric pattern and micturition reduction. No significant differences were observed on measures of incontinence or residual urine volumes between the interventions. Meladrazine tartrate caused side effects so severe that the drug was discontinued. No serious adverse events were reported for the other two interventions.

At the time of writing there is insufficient evidence to comment on the use of cannabinoids in MS. However, we are aware that further evidence is likely to be published and that NICE intend to conduct a technology appraisal on cannabinoids in MS with a projected publication date of April 2004.

▷ Economic evidence

There are no formal economic evaluations of interventions for bladder impairment in MS. A study of the use of sacral rhizotomies and electrical bladder stimulation in people with spinal cord injury, showed this to be a cost-effective strategy in comparison to standard care, with

► From evidence to recommendations

RECOMMENDATIONS

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- R95 Any person with MS who, despite treatment, has incontinence more than once a week should:
- be referred to a specialist continence service for further assessment and advice D
 - be considered for a course of pelvic floor exercises, A
 - preceded by a course of electrical stimulation of the pelvic floor muscles (if such a B
 - course is available).
- R96 Any person with MS who experiences persistent incontinence should be offered a D
convene drain (for men) or pads (for women).
- R97 Any person who has continued bladder symptoms despite pharmacological and other D
treatments should be considered:
- for intermittent self-catheterisation taught by a suitably trained specialist, or
 - for longer-term urethral catheterisation as a means of control, with suprapubic catheterisation being considered especially when active sexual function is still wanted. See R99 to R102.
- R98 Intravesical botulinum toxin should only be used by suitably trained doctors in the D
context of clinical research.

LOCAL IMPLEMENTATION POINTS

The local health system should identify:

- which community health workers have a particular expertise in managing incontinence and how they are accessed
- who can measure post-micturition bladder volume locally and how they are contacted
- the local urology service responsible for all managing aspects of neurologically-based bladder problems and incontinence and how it is contacted.

6.2.2 Urinary tract infections

This part discusses the prevention, identification and management of urinary tract infections (UTIs). It also specifically covers all aspects of long-term catheter use and management, drawing upon guidelines for preventing health care associated infections during long-term urinary catheterisation in primary and community care.³⁰⁷

▷ Evidence statements

All evidence statements for UTIs are level Ia.

Prevention of UTI – Five SRs were identified which assessed interventions for the prevention of UTI.^{308–311} A review of five studies looking at the effects of cranberry extract in elderly patients, patients needing intermittent catheterisation, and women with recurrent UTI, found no reliable evidence of the effectiveness of cranberry juice and other cranberry products.³⁰⁹ A review of eight RCTs comparing the effectiveness of indwelling silver coated urinary catheters and uncoated indwelling urinary catheters found that silver alloy catheters were significantly more effective in preventing UTIs as measured by the presence of bacteriuria than uncoated catheters but these studies were confined to relatively short-term use of catheters (2–10 days).³¹¹ The results from three of the eight trials indicated that women benefited from the silver-coated

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urinary catheters more than men. The third review looked at risk factors for UTI and the effects of antibiotic prophylaxis in patients with neurogenic bladder due to spinal cord dysfunction.³¹⁰ This review found that indwelling catheterisation was associated with more frequent infections than intermittent catheterisation, which in turn is associated with more frequent infection than methods not involving a catheter. The literature did not support firm conclusions regarding most other risk factors. It also reported that antibiotic prophylaxis significantly reduces bacteriuria among acute spinal cord injury patients. However, antibiotic prophylaxis was not associated with a reduced number of symptomatic infections in the populations studied. Antibiotic prophylaxis resulted in a twofold increase in the occurrence of antibiotic-resistant bacteria. A second review assessing the effectiveness of antibiotic prophylaxis reported similar findings. However, this review only found reduced bacteriuria among patients with acute spinal cord injury, not in those with non-acute spinal cord injury.³⁰⁸ A final review of 11 studies assessed the efficacy of methenamine hippurate in patients at risk of developing a UTI. Four of the trials studied symptomatic bacteriuria and six studied bacteriuria as an outcome measure. The direction of six of the seven pooled trials was towards a favourable treatment effect for methenamine hippurate. However, due to heterogeneity interpretation of the pooled estimates could not be undertaken.³¹²

Health economic analysis of interventions to reduce the risk of UTIs – Only one economic study was identified with any relevance to the population of people with MS.³¹³ This was a decision analytic model to compare the cost-effectiveness of silver alloy-coated urinary catheters with standard (uncoated) catheters. Coated catheters are more expensive (per unit) than uncoated catheters but are more effective; hence the relevant decision is whether the improved efficacy is worth the additional per unit cost?

The base case simulation showed silver-coated catheters to be a *dominant strategy*, ie more effective and less costly, due to savings in costs of treating symptomatic UTIs and bacteraemia. One-way sensitivity analysis revealed that the strategy remained dominant throughout the ranges evaluated. In the multivariate sensitivity analysis the strategy provided clinical benefits over standard catheters in all cases and cost savings in 84% of cases.

Interventions to treat UTI – Two reviews which assessed the effectiveness of interventions for the treatment of UTI met inclusion criteria. The first review assessed the effectiveness of cranberry juice or cranberry products for the treatment of UTI, but did not find any RCTs which met inclusion criteria and so was unable to draw any conclusions.³¹⁴ The second review compared the effectiveness of single dose and multi-dose antibiotic treatment in female adult patients with UTI.³¹⁵ This review found no significant differences between women treated with single dose and multi-dose antibiotic therapy (1a). One further RCT comparing cranberry concentrate supplements to placebo found no significant difference between the groups in terms of the number of patients developing a UTI³¹⁶ (1b).

Areas where evidence was not found – No evidence was found to allow recommendations on several important clinical issues including altering fluid intake, the frequency of changing long-term catheters, the use of bladder wash-outs, the appropriate use of suprapubic catheters, and the best policy concerning routine monitoring of renal tract structure and function.

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▷ From evidence to recommendations

The recommendations made draw largely on the published NICE document,³⁰⁷ which itself is largely based on consensus. However, where adequate evidence exists, grade A recommendations have been made

RECOMMENDATIONS

R99	Any person with MS at risk of urinary tract infections should not be recommended prophylactic use of antibiotics or cranberry juice.	A
R100	If a person with MS experiences new urinary tract symptoms, or develops general malaise and/or worsening of existing symptoms with a raised temperature, they should: ● be given a urine dipstick test for infection, and culture, if necessary ● be offered treatment with an appropriate antibiotic.	D A
R101	Any person with MS with more than three confirmed episodes of urinary tract infection in a period of one year should be assessed by a continence specialist for residual urine and other evidence of risk factors, and offered appropriate treatment and guidance.	D
R102	The general principles of care for people with long-term urinary catheters, as described in the NICE guideline on prevention of health care associated infection in primary and community care (see Table 6) should be followed. Of particular note in treating a person with MS are that long-term indwelling catheters should: ● be used only after all reasonable non-invasive methods have been tried ● be reviewed regularly, to check whether less invasive methods can be used and that drainage systems from the catheter should: ● be emptied regularly, before the bag is overfull ● bladder installations and wash outs should not be routinely used.	D A

LOCAL IMPLEMENTATION POINTS

The local health system should identify:

- specific guidance on choice of antibiotics for suspected or confirmed urinary tract infection
- the local urology service responsible for all aspects of managing neurologically-based bladder problems and incontinence.

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Table 6 The general principles of bladder management

Long-term indwelling bladder catheters should:

- only be used after all reasonable non-invasive methods have been tried **(D)**
- be inserted by fully trained and competent personnel using aseptic procedures with cleaning of the meatus and the use of an appropriate lubricant **(D)**
- be reviewed regularly, to check whether alternative less invasive methods can be used **(D)**
- be clearly documented, including insertion, changes and routine care **(D)**
- only be changed when clinically necessary or according to the manufacturer's recommendations **(D)**.

Drainage systems from the catheter should:

- be attached to a catheter valve outlet when the patient wishes and the system can be used **(D)**
- be kept sterile and continuously closed through ensuring clean handling whenever changes are required **(D)**
- be kept below the bladder but off the floor at all times to prevent stagnation or reflux of urine **(D)**
- emptied regularly, before the bag is over-full **(D)**
- have any samples taken using an aseptic technique through a sampling port **(D)**.

Bladder instillations and wash-outs should not routinely be used **(A)**.

From NICE's *Infection control: prevention of health care associated infection in primary and secondary care*.³⁰⁷

6.3 Bowel problems

People with MS may suffer bowel problems in two ways: reduced gut mobility may follow from immobility and the drugs used to treat various impairments; and neurological control of defecation may be directly impaired. One survey of 280 people found 43% to be suffering constipation.³¹⁷ More importantly the same survey found that 25% had been incontinent of faeces once a week or more frequently and 51% had been incontinent in a three month period. The total prevalence of bowel problems was 68%. In the South Wales survey, 29% of those with MS suffered faecal incontinence, and 54% suffered constipation.²⁷⁹ In another American study 39% had bowel problems.²⁷⁸ In the Oxfordshire audit, 19% of patients were experiencing problems with their bowels at any one time, and 26/226 presented with gastrointestinal problems over a ten month period, with 16 of these being specific problems with bowel control.⁶

Although constipation is probably clinically recognised in most instances, it is likely that health care professional staff are woefully unaware of how much faecal incontinence affects their patients with MS. The consequences of faecal incontinence are great: social embarrassment, risk of pressure ulcer, curtailment of activities etc.

Recommendations are needed to ensure that disturbed bowel control, both constipation and incontinence, is detected early, is evaluated to determine its aetiology, and is managed actively.

► Evidence statements

One systematic review of seven RCTs that assessed the effects of different management strategies for faecal incontinence and constipation in people with neurological diseases was identified. The results showed that psyllium was superior to placebo in terms of bowel movements and stool weight. A comparison of different suppositories indicated that

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polyethylene glycol-based bisacodyl suppositories initiated defecation faster than hydrogenated vegetable oil-based bisacodyl suppositories. A comparison of bowel programmes indicated participants assigned to morning schedules were more likely to established successful bowel regimes than those assigned to evening schedules. No differences between the use of mandatory or optional suppositories was noted³¹⁸ (Ia).

▷ Economic evidence

No relevant economic evidence relating to bowel impairment was identified.

▷ From evidence to recommendations

The guideline developers noted the general lack of evidence concerning this important question and although a systematic review was found, the studies were small and of low quality and it was difficult to draw any firm conclusions. The recommendations made are largely on the basis of consensus, considering the experience of geriatric services that are faced with similar problems.

RECOMMENDATIONS

R103	Each professional in contact with a person with MS should consider whether the person has any problems controlling bowel function. Potential problems include urgency, difficulty, pain, constipation or incontinence.	D
R104	Any person with MS who has apparent constipation (pain on or difficulty with defecation, bowels open less than twice a week) should be offered advice on fluid intake and dietary changes that might help, and then be considered for oral laxatives.	D
R105	Any person with faecal incontinence should be assessed for constipation with overflow, possibly exacerbated by laxative use.	D
R106	If a person with MS has apparent constipation (pain on or difficulty with defecation, bowels open less than twice a week) despite treatment with oral laxatives he or she should be considered for the routine use of suppositories or enemas.	D

LOCAL IMPLEMENTATION POINT

Local guidelines need to consider which local specialist (medical or surgical) services should be approached for advice in cases of difficulty.

6.4 Weakness and cardiorespiratory fitness

Many people with MS will experience 'weakness'. In a survey of 656 people with MS in the USA, 63% had 'weakness or paralysis' which affected 45% of those with limitations on personal ADL.²⁷⁸ In the same survey, 77% had fatigue and 74% had 'balance problems'. In South Wales weakness was the commonest single symptom experienced (89% at any time, 80% at any one time).²⁷¹ However, the term weakness may include many different phenomena and have many different contributing factors. This part specifically considers both actual or perceived weakness of voluntary muscle contraction and also more general lack of cardiorespiratory fitness.

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Reduced strength of voluntary muscle contraction (weakness) is a common consequence of damage to 'upper motor neurone' tracts within the CNS, but it may be associated with several other impairments of motor function including clumsiness, spasms and spasticity. In people with MS muscle weakness may occasionally be a side effect of medication such as steroids or anti-spastic agents. Complaints of weakness may also be referring to or caused by: fatigue, the development of weakness only after some muscular exercise, reduced cardiorespiratory endurance, and depression. Consequently it is vital to establish exactly what the person with MS means when complaining of weakness.

In this guideline weakness and alterations in tone are considered separately as they may occur separately. Balance problems are not considered separately because they are also difficult to define, and will usually be associated with, if not caused, by weakness, spasticity, sensory loss or ataxia and all these are discussed. This section of the guideline needs to cover:

- detection and diagnosis of weakness and its associated phenomena
- management of and advice about weakness, especially relating to exercise
- management of secondary consequences.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions to treat weakness. Four RCTs assessed interventions for cardiovascular dysfunction. Two trials examined the efficacy of expiratory muscle training *vs* sham training in patients who were bedridden or wheelchair bound (EDSS score 6.5–9.5). The first trial reported no overall significant improvement in the intervention group, whilst the second trial showed mixed results. Significant beneficial effects were reported for expiratory muscle strength, but not for inspiratory strength.^{319,320} The third study examined the effectiveness of an aerobic exercise training program. The results indicated positive effects on four out of eleven of the outcome measures assessed, namely aerobic capacity, physical work capacity, isometric strength and skinfold thickness. No effect however was seen on any of the general health indices measured.³²¹ The last trial assessed the use of music therapy with relaxation and diaphragmatic breathing in patients who were wheelchair bound. The results showed no significant effect³²² (Ib).

▷ Economic evidence

No relevant economic evidence relating to weakness in MS was identified.

▷ From evidence to recommendations

In the absence of any specific MS-related evidence the guideline developers drew on general principles often derived from research in patients with other neurological conditions such as stroke.

RECOMMENDATIONS

R107	Each professional in contact with a person with MS should consider whether muscular weakness is a significant problem, or contributing factor, to the person's current clinical state. If so, the person should be assessed to determine the nature and cause of the weakness.	D

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- R108** People with a limitation of their activities should be assessed for weakness of voluntary motor control using a valid technique. **D**
- R109** People with motor weakness should be shown and advised to undertake exercises and techniques to maximise strength and endurance appropriate to their circumstances (**D**), including aerobic training (**B**). Usually, specific exercises should be selected and explained by a neuro-physiotherapist, or other members of the neurological rehabilitation team (**D**).
- R110** People with motor weakness should be taught techniques and given equipment, such as orthoses, needed to optimise performance of activities appropriate to their circumstances. **D**
- R111** People with weakness sufficient to cause postural abnormalities should be assessed for specialist supportive equipment, including but not limited to seating. **D**

LOCAL IMPLEMENTATION POINTS

These should include:

- advice on measures and assessment techniques to be used locally
- list of gyms, health centres and other places where people with health conditions and/or disability can take exercise, with systems for collaboration and discussion between the NHS (likely to be physiotherapists) and gym instructors being developed. The Department of Health exercise referral national quality assessment framework provides more detail (www.doh.gov.uk/exercisereferrals/).

6.5 Spasticity, spasms and contractures at joints**6.5.1 Spasticity and spasms**

Many patients with upper motor neurone weakness from any cause have altered tone in their limbs, and when increased this may be referred to as hypertonia or, most commonly, spasticity. There are continuing debates as to the meaning of the terms. However in practice it is characterised by increased stiffness and slowness in limb movement, the development of certain postures, an association with weakness of voluntary muscle power, and with involuntary and sometimes painful spasms of limbs. Spasticity and spasms are common in people with MS, and may be the dominant disabling impairment in some people. Spasms were present in 21% of the people surveyed in Oxfordshire, and new problems with spasms were the commonest single specific complaint relating to reduced mobility.⁶ Painful leg spasms were reported in 21% of 159 community patients with MS in Ontario, Canada³²³ and spasticity was reported in 49% of 656 people surveyed in the USA.²⁷⁸ The underlying neurophysiology in MS is likely to be similar to that seen in most other diseases associated with spasms and spasticity such as stroke, head injury and spinal cord injury. Consequently evidence from and recommendations for spasms and spasticity in these conditions will be applicable to people with MS.

It must be emphasised that treatment for spasticity and spasms may be necessary or justified simply to reduce the spasticity and/or spasms without expecting any other functional benefit for the patient. These impairments can cause pain and distress by their very presence. Furthermore it must be emphasised that amelioration of spasticity and spasms may be an integral part of a wider plan of management, for example through reducing the burden of care,

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through enabling appropriate seating to be provided and used, or through reducing the risk of pressure ulcer. Lastly and of great importance, control of spasticity is vital in the prevention and management of joint contractures (fixed limitations on the range of movement available at a joint). Given the close connection between spasticity and contractures, contractures are also covered in this section (6.5.2).

The guideline recommendations need to ensure:

- identification of spasticity and spasms
- diagnosis and management of any treatable causes
- a stepped approach to management, tailoring interventions to each person's needs and wishes
- a cautious but appropriate use of more risky or expensive interventions
- prevention of complications of spasticity.

▷ Evidence statements

Two systematic reviews that examined interventions for spasticity were identified. In addition 46 studies that looked at a number of different interventions for spasticity and spasms in patients with MS met the inclusion criteria. These consisted of 16 RCTs, 27 randomised crossover trials, (Ib) two CCTs and three non randomised crossover trials (IIa).

Baclofen – One RCT and six randomised crossover trials compared baclofen to placebo (Ib). Overall three of the trials^{324–326} showed significant beneficial effects on the outcome measures assessed. All these measures were directly related to the number and intensity of spasms. Two further randomised crossover trials reported mixed results with significant differences being reported on direct measures of spasticity, but no benefit being evident on outcomes measures of ambulation or transfer activity.^{327,328} The last two small crossover trials reported no overall significant differences between the intervention groups.^{329,330} Six out of the seven trials that reported adverse events, stated that minor side effects were more common in the intervention phase than in the placebo phase. None of the trials reported serious adverse events.

Four RCTs, two randomised crossover trials and one CCT also examined the effect of baclofen against an active comparator. Three RCTs and one randomised crossover trial compared the efficacy of baclofen to tizanidine^{331–334} (Ib). All four of these trials reported no significant differences between the groups on any of the outcomes measured or in terms of side effects reported. A further RCT that compared baclofen to tetrazepam and tizanidine also reported no significant differences between any of the group.³³⁵ One randomised crossover trial examined the effects of baclofen alone against baclofen combined with stretching exercises, stretching exercises alone and placebo alone.³³⁶ The results showed significant differences upon a measure of spasticity for baclofen alone and baclofen combined with stretching exercises, but no differences were observed between the groups on the Ashworth scale score or a measure of functional abilities. A last CCT assessed baclofen against clonazepam and placebo³³⁷ (Ia). No differences were reported between the groups upon either the measure of spasticity or the number of side effects reported.

Baclofen pump – One systematic review of 27 studies conducted in patients with MS and other neurological conditions and one randomised crossover trial reviewed the efficacy of intrathecal baclofen via pump delivery. The review reported a beneficial effect with both the Ashworth scale score and Penn spasm score significantly reduced³³⁸ (Ia). The results of the crossover trial also indicated significant beneficial effects on all the outcome measures assessed.³³⁹

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Tizanidine – Three RCTs and two randomised crossover trials compared the effect of tizanidine to placebo. One of the RCTs reported beneficial effects on four of eight of the outcomes measures assessed, including a reduction in muscle-tone score.³⁴⁰ One of the randomised crossover trials also reported beneficial effects on the number of patients in whom spasticity improved.³³⁴

However, none of the other three trials reported any overall effect on any of the outcome measures assessed.^{341–343} One further RCT compared tizanidine to the active comparator diazepam. The results indicated no difference in the clinical symptoms between the groups, and that diazepam was better tolerated.³³⁴

Dantrolene sodium – One non-randomised and two randomised crossover trials compared dantrolene sodium against placebo^{344–346} (Ib). Two of the trials reported no differences between the groups, whilst data from the third trial was not reported adequately. No serious adverse events were reported in any of the trials. One further randomised crossover trial compared dantrolene sodium to diazepam and placebo.³⁴⁷ The results showed that both dantrolene sodium and diazepam were superior to placebo on measures on spasticity, reflexes and clonus. However, dantrolene sodium was reported to have a negative effect relative to diazepam and placebo on both hip flexor strength and deltoid strength.

Gabapentin – Two placebo-controlled randomised crossover trials investigated the efficacy of gabapentin. The first trial reported significant differences between the groups on all of the eight outcomes measures assessed, with no minor or severe adverse effects being reported from the trial.³⁴⁸ The second trial reported significant effects on three of the seven outcomes measures, including the Ashworth scale score and the EDSS. Again no major side effects were reported in the trial.³⁴⁹

Progabide – One randomised and one non-randomised crossover trial compared progabide to placebo.^{350,351} Both of the trials reported no overall significant effects on either measures of spasticity or functional tests. The non-randomised trial reported eight cases of serious adverse events (IIa).

Progabide is not available in the UK.

Diazepam – Two randomised crossover trials compared diazepam to different active comparators. The first compared diazepam to ketazolam and placebo, with no significant differences between the groups being reported.³⁵² The second trial compared diazepam to dimethothiazine. However, the significances of the results for the trial was not reported³⁵³ (IIb).

Other pharmacological interventions – One systematic review and a further nine studies examined the efficacy of a variety of pharmacological interventions for spasticity. The systematic review of three RCTs, and one additional RCT assessed the efficacy of botulinum toxin. The review compared botulinum toxin to placebo and plaster casts for the treatment of lower limb spasticity in children with cerebral palsy. The results reported no significant differences between those treated with botulinum toxin and those treated with either placebo or plaster casts³⁵⁴ (Ia). The RCT compared three different doses of botulinum toxin to placebo.³⁵⁵ No overall significant differences were reported between the groups with a number of side effects reported for all three of the intervention groups, with these being proportional to the intervention dosage.

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Two randomised crossover trials that assessed L-threonine and threonine respectively compared to placebo both reported no significant effects.^{356,357} Neither of the trials reported any major adverse events (Ib). Likewise a further non-randomised crossover trial examining brolitene and placebo reported no effect³⁵⁸ (IIa). One placebo-controlled randomised crossover trial that assessed 3,4 diaminopyridine reported significant differences on five of the six outcomes measures examined, including the ambulation index (AI). However side effects were reported by a high proportion of patients in the intervention group.³⁵⁹

Four placebo-controlled crossover trials examined the efficacy of different cannabis derivatives for spasticity. The first randomised crossover trial compared Delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and a combination of THC and CBD to placebo. The results indicated that THC and the combination of THC and CBD showed beneficial effects on four of the seven outcome measures assessed, whilst CBD alone showed positive effects on three when compared to placebo.³⁶⁰ The second trial assessing Delta-9-THC reported no overall significant effects at lower doses, with a significant reduction in symptoms being noted only at high doses of the drug which was intolerable due to the number of side effects reported.³⁶¹ The third trial assessed the effect of active smoked marijuana on postural stability and reported negative effects on both outcome measures recorded.³⁶² The last randomised crossover trial compared THC and cannabis sativa plant extract to placebo. The results showed no overall beneficial effects for either of the interventions compared to placebo.³⁶³

Although four studies on the use of cannabinoids are reviewed, the totality of evidence is small with few patients included, so it was felt inappropriate to make any recommendations.

However, we are aware that further evidence is likely to be published and that NICE intend to conduct a technology appraisal on cannabinoids in MS with a projected publication date of April 2004.

Other non-pharmacological interventions – Seven RCTs investigated the efficacy of a number of different non-pharmacological interventions for spasticity (Ib). The first RCT assessed the utility of the interadductor *vs* the traditional approach to obturator nerve blockade for bilateral adductor muscle spasms. The results reported positive effects on four of the six outcomes examined, including discomfort, spasms and hygiene scores. No complications were reported with either approach.³⁶⁴ Two RCTs assessed different physiotherapy approaches. The first examined whether an inpatient physiotherapy rehabilitation program would lead to functional gains in mobility in the home.³⁶⁵ The trial reported no overall significant differences between the intervention group and the waiting list control group. The second RCT examined the utility of impairment-based physiotherapy approaches compared to disability-orientated approaches.³⁶⁶ Again no significant effects were observed on any outcome measures between the groups. Four further RCTs examined different interventions. The first assessed the use of muscle passive shortening with traction stress for patients with hip abductor hyposthenia.³⁶⁷ The results showed a positive benefit on the range of motion against gravity for the intervention, but other outcome measures assessed were not interpretable. The second RCT examined electrical neuromuscular stimulation (ENS) against sham stimulation.³⁶⁸ No significant benefits were seen for the intervention. The third examined the effects of magnetic stimulation. This RCT reported beneficial short-term effects on the stretch reflex but these did persist at longer term follow-up, it also found no significant effect on ADL.³⁶⁹ The last RCT assessed the use of weighted leg extension exercises for strengthening the quadriceps against a standard prescribed exercise program.³⁷⁰ Again, no significant benefits were observed for the intervention.

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▷ Economic evidence

The forthcoming HTA review of treatment for pain and spasticity in MS could identify no formal review of current clinical practice regarding the treatment of spasticity. Anecdotal evidence suggests that it may be variable, with an MS society survey reporting that 32% of people did not see a hospital specialist for treatment.³⁷¹ In the systematic review of economic evidence the forthcoming HTA report identified no formal economic evaluations. The only existing economic analysis considers the effect of continuous intrathecal baclofen infusion (CIBI) on hospitalisation rates. At present CIBI is not commonly used in Britain; in 1998 only around 200 people were implanted with a pump for intrathecal baclofen of which only around 60 had MS.^{371a}

None of the identified studies are based in the UK, they only include small numbers of patients, and they include people with spinal cord injury as well as MS. The studies all show significant savings in terms of hospitalisation, implying significant potential cost offsets and patient benefits.

A working group on acute purchasing report in 2000 attempted to model the costs and benefits of intrathecal baclofen in the management of people with severe spasticity (not only from MS).³⁷² The estimated cost per quality-adjusted life year (QALY) was around £20,000, which is relatively high but is within the acceptable range identified in historical NICE appraisal decisions. However, the report commented on the poor clinical evidence for CIBI, hence there is a large amount of uncertainty surrounding the cost per QALY estimate.

In general, though, the initial high cost of CIBI implantation could be offset by reductions in pressure ulcer and other admissions related to spasticity, orthopaedic procedures and reductions in requirements for aids. On the basis of the advice provided in this report, the Trent Development and Evaluation Committee recommended that CIBI be made available to those patient groups for which there is evidence of greatest benefit; that is 'patients who are bedbound due to severe spasticity, patients who cannot be seated in a wheelchair due to severe extensor spasms, and other wheelchair-bound patients in whom spasm-related pain or skin breakdown is a severe problem'.

▷ From evidence to recommendations

In formulating its recommendations, the guideline developers noted the relatively low level of evidence available for most of the commonly used drugs, that comparative studies were very rare, the absence of evidence for most of the commonly used physical therapies, and the difficulty in defining and measuring the benefits of treating spasticity in formal trials. Further, we recognise that cannabis derivative and extracts are currently being researched with several large studies to be published and that NICE is undertaking a review of cannabis drugs. It also recognized that the management of spasticity was an important topic, and hence derived a series of recommendations that drew on clinical consensus as well as the limited evidence.

RECOMMENDATIONS

R112	Each professional in contact with a person with MS who has any muscle weakness should consider whether spasticity or spasms are a significant problem, or a contributing factor, to the person's current clinical state.	D

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R113	If spasticity or spasms are present, then simple causative or aggravating factors such as pain and infection should be sought and treated.	D
R114	Every person with MS who has persistent spasticity and/or spasms should be seen by a neurophysiotherapist to assess and advise on physical techniques, such as passive stretching and other physical techniques, to reduce spasticity and especially to avoid the development of contractures. Families and carers should be taught how to prevent problems worsening, and a monitoring system should be put in place.	D
R115	More active specific measures should be considered only if the spasms or spasticity are causing pain or distress, or are limiting (further) the individual's dependence and activities. In this case, both benefits and risks should be considered carefully. A specific goal (or goals) should be set, but will rarely include improved performance in activities.	D
R116	Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with: baclofen or gabapentin. The following should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable:	A
	● tizanidine ● diazepam ● clonazepam or ● dantrolene.	A D D D
	Combinations of medicines, and other medicines such as anticonvulsants, should only be used after seeking further specialist advice.	D
R117	People with MS who have troublesome spasticity and spasms unresponsive to simpler treatments should be seen by a team specialising in the assessment and management of spasticity. The team should consider using one or more of the following:	D
	● standing and weight-bearing through legs ● splints ● serial casting ● special or customised seating, such as tilt-in-space chairs ● intrathecal baclofen ● phenol injections to motor points or intrathecally.	D D C D A D
R118	Intramuscular botulinum toxin should not be used routinely, but can be considered for relatively localised hypertonia or spasticity that is not responding to other treatments. It should be used when specific goals can be identified, and:	B
	● in the context of a specialist service that can consider all aspects of rehabilitation (for example, seating) ● by someone with appropriate experience and expertise ● followed by active input from a neurophysiotherapist.	

LOCAL IMPLEMENTATION POINTS

These will need to:

- identify who within local neurological rehabilitations services will deal with difficult problems of spasticity and how they are accessed
- identify who may assess and give botulinum toxin injections and how they are accessed
- identify how preventative stretching and handling are delivered to people with MS in the community
- identify what assessment protocols and measures for spasticity should be used locally
- ensure collaborative working with those providing services such as specialized seating to give a comprehensive service to people with MS affected by spasticity
- agree funding arrangements (and prioritising mechanisms if any) for botulinum toxin, baclofen pumps and other specific treatments.

6.5.2 *Contractures at joints*

A contracture is a shortening in the soft tissues (ie tendons, muscles or ligaments) around a joint that limits the passive (and active) range of movement at that joint. Contractures generally arise when a joint is not moved through a full range of movement on a regular basis, for whatever reason. In people with MS the common reasons are spasticity and weakness. The prevalence of contractures in people with MS is not known, nor is it known how frequently they start to develop, but they are seen commonly in daily clinical practice, and much effort is devoted to their prevention and treatment. Contractures may cause pain, and may sometimes be the primary impairment limiting activities such as walking, feeding or dressing. Contractures frequently make caring for, and positioning, seating, walking, dressing and feeding people with MS extremely difficult, requiring expensive care packages to be set up and specialist seats to be made. Prevention and treatment of contractures always involves attempts to ameliorate underlying impairments or other causes.

The main aim of management is to prevent contractures, but some are inevitable and then specific treatments may be needed.

▷ Evidence statements

All evidence statements for contractures at joints are level **Ib**.

No SRs or primary studies in patients with MS were identified which assessed interventions to prevent contractures at joints. An ongoing study was identified on the national research register, which aims to investigate whether a daily muscle stretch regime prevents the development of contractures and muscle stiffness in stroke patients. However, this study is not due to be completed until December 2003.³⁷³

Five RCTs were identified which looked at interventions for the treatment of contractures (**Ib**). Three RCTs looked at various stretching programmes,^{374–376} one looked at a topical cream³⁷⁷ and the last looked at a bed positioning programme.³⁷⁶ Two of the studies, which assessed the effectiveness of a stretching programme, found a beneficial effect of treatment compared to the control group. The first of these studies evaluated the effectiveness of a low-load prolonged stretch in geriatric patients with bilateral knee flexion contractures and found a significant improvement in the passive range of motion in legs treated with the low-load prolonged stretch compared to those receiving a traditional high-load brief stretching programme. The other, a

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crossover RCT, evaluated a below-the-knee cast and stretch in patients with traumatic head injury who had ankle contractures. This study reported a significant improvement in passive ankle dorsiflexion motion during the intervention period compared to the control period.³⁷⁶ The third study evaluated the 'Dynasplint', which applies a prolonged stretch unilaterally, in geriatric patients, and found no beneficial effect of treatment.³⁷⁴ An RCT, in people with joint disease, of a cream containing chlorprothazine, a muscle relaxant (not available in the UK), found significant improvements in a range of outcomes including pain intensity, tender point palpitation, patients evaluation of treatment, and contracture severity in patients receiving the active cream compared to those receiving a placebo cream. No effects were found for one of the outcomes investigated (limitation of movement).³⁷⁷ No beneficial effect was found for a bed-positioning treatment programme in older patients.³⁷⁸

▷ Health economics

No relevant economic evidence relating to contractures was identified.

▷ From evidence to recommendations

In the absence of much specific evidence the guideline developers drew upon consensus when developing recommendations in this area.

RECOMMENDATIONS

R119	Any person with MS who has weakness and/or spasticity sufficient to limit the regular daily range of movement around a joint should be considered at risk of developing a contracture at that joint, and should be considered for preventative measures.	D
R120	Any person with MS at risk of developing contractures should have the underlying impairments assessed and ameliorated if possible (see sections on weakness (6.4) and spasticity (6.5)).	D
R121	Any person with MS at risk of developing contractures should be informed; the individual, and/or carer(s) should be taught how to undertake preventative measures, such as regular passive stretching of the joint(s) at risk and appropriate positioning of limbs at rest. In more severe instances, specialist advice should be obtained on seating and positioning, including positioning in bed.	D
R122	Any person with MS who develops a contracture should be assessed by a suitable specialist for specific treatment; the assessment should take into account the problems caused by the contracture, the discomfort and risk of any treatment and the wishes of the person. At the same time, renewed efforts should be made to reduce the underlying causes and to prevent further contracture.	D
R123	Specific treatment modalities to be considered should include prolonged stretching using: ● serial plaster casts ● other similar methods, such as standing in a standing frame and removable splints. These are usually combined with: ● local botulinum toxin injection, and ● surgery when necessary.	A D D D

6.6 Ataxia and tremor

Ataxia refers to uncoordinated voluntary movement usually attributed to disturbed function of the cerebellum or associated pathways and not attributable to direct motor weakness or sensory loss. When present it may be extremely disabling. Ataxia may also arise from loss of adequate sensory feedback. Tremor is a broader term referring to any regular or rhythmic alternating movement affecting a joint or group of joints, and in practice it is difficult to distinguish the precise nature or cause of uncoordinated tremulous movements. The presence of ataxia often indicates lesions in areas that also control bulbar functions (articulation and swallowing) and eye movement control.

Although some people feel that ataxia and tremor are quite distinct,³⁷⁹ in practice there are great difficulties in describing and classifying tremor and ataxia in people with MS.³⁸⁰ Both will be considered at once because it is unlikely that most studies have made unequivocal distinctions. Generally the word 'tremor' will be used to include ataxia, but ataxia will be used primarily to refer to uncoordinated intentional movement thought to arise from cerebellar disturbance.

Tremor of some sort was a newly presenting symptom in 6 of 226 patients followed up over nine months in Oxfordshire.⁶ In a randomly selected group of 100 people with MS in London, tremor was reported by 37 but detected in 58: 15 had 'severe tremor' and 27 had disability attributable to the tremor.³⁸⁰ In another sample, 27% had shaking (tremor).²⁷⁸ In a South Wales survey, ataxia was experienced by 82% of people with MS, and had a point prevalence of 82%.²⁷¹

Although there are no proven treatments, the clinician will need guidance that describes possible managements, and also that alert them to possible complications that arise in people with tremor.

► Evidence statements

One RCT compared the use of Johnstone pressure splints as an addition to standard PNF physiotherapy approaches for ataxia. The results showed that the use of Johnstone pressure splints plus exercise using the proprioceptive neuromuscular facilitation technique was only beneficial on two of the eight outcome measures assessed, single limb stance time (right and left), compared to exercise alone³⁸¹ (**Ib**).

One RCT, two randomised crossover trials and one CCT assessed different interventions for tremor. The RCT examining thalamotomy compared to thalamic stimulation (implanting of electrodes) reported that thalamic stimulations was more beneficial. A large number of relatively serious adverse events were also reported in both groups in the six month period post surgery.³⁸² The first randomised crossover trial compared a single intravenous infusion of ondansetron to placebo, with positive results being reported on all three outcome measures at 60 minutes follow-up. The incidence of side effects was low and these were of a minor nature.³⁸³ The second crossover trial examined the efficacy of isoniazid with no effect being reported on either of the two outcome measures³⁸⁴ (**Ib**). The CCT which assessed the utility of unilateral stereotactic surgery also reported no overall effect, although beneficial results were reported for two out of the five outcomes examined.³⁸⁵ The trial also reported a number of adverse events both at the time of surgery and post-operatively (**Ila**).

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▷ Economic evidence

No relevant economic evidence relating to ataxia or tremor was identified.

▷ From evidence to recommendations

The guideline development group recognises that many drugs are tried for this distressing and disabling impairment, although there is no evidence. It also noted that the only 'positive' drug trial was insufficient to make any recommendation, and that the evidence supporting neurosurgery was limited for such a risky and expensive procedure. The recommendations made reflect the lack of strong evidence or even consensus on specific interventions.

RECOMMENDATION

R124 Any person with MS who experiences a limitation of activities due to tremor should be assessed: **D**

- by a specialist rehabilitation team for medicines, treatment techniques and equipment (using the general principles of goal setting and evaluation recommended)

and, if problems remain severe and intractable, the person should be assessed:

- by a neurosurgical team from a specialist centre, for suitability for an operation to reduce ataxia (after being given a full explanation of its major risks and possible benefits).

LOCAL IMPLEMENTATION POINTS

These should identify:

- the local specialist rehabilitation service able to assess and advise on treatment and compensatory techniques and equipment
- the neurosurgical centre able to assess for and undertake neurosurgical interventions
- the preferred local measures and assessment techniques, if any.

6.7 Sensory losses

Altered sensation in the form of tingling, numbness, 'odd' feelings etc are common in people with MS. In one sample of 656 people, 63% with MS had 'numbness, tingling or other sensory disturbance'.²⁷⁸ In one survey²⁷¹ sensory disturbance was the commonest first symptom (34%) and was the second most common symptom experienced (87%) and still existing at prevalence point (73%). Sensory losses may be associated with painful hypersensitivity and spontaneous neuralgic pain. The treatment of neurogenic pain is covered separately. Sensory disturbance can directly limit activities; for example numbness in a hand can make fine dextrous activities impossible and people may drop items or injure themselves. Abnormal sensation was present in 49/150 people surveyed at one point, and was a new problem in 6/226 people followed up over nine months in Oxfordshire.⁶

Although there are no proven treatments, the clinician will need guidance about possible managements, and also to alert them to possible complications that arise in people with sensory loss.

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▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of sensory losses.

▷ Economic evidence

No relevant economic evidence relating to sensory losses was identified.

▷ From evidence to recommendations

In the absence of any evidence even from other conditions or situations, the GDG has limited itself to simple advice, emphasising the risk that may follow on from loss of sensation.

RECOMMENDATIONS

R125 Any person with MS who experiences a limitation of activities not otherwise explained should be assessed for sensory losses. **D**

R126 Any person with sensory disturbance sufficient to limit activities should be seen and assessed by a specialist rehabilitation team; the individual should be given advice on techniques and equipment to ameliorate their limitations, and advice on personal safety. **D**

6.8 Visual problems

Demyelination within the optic nerve is a common if not universal occurrence in MS. Surprisingly, most people with MS do not have significant symptoms from this demyelination, though on formal testing visual acuity and colour vision are often impaired. Some people do suffer direct visual loss from optic nerve damage but more people suffer significant, sometimes severe visual problems from disturbed oculo-motor control (ie abnormalities in the control of eye movements) that may lead to double vision and movement of images. Reading is difficult for many people with MS. There are few studies on the frequency of significant limitations of visual function in people with MS but one survey did note that 30% had significant disturbance of visual function.²⁷⁸ In Southampton 10% had seriously impaired vision,²⁸⁰ and in South Wales 51% had experienced double vision and the prevalence of visual disturbance was 33%.²⁷¹ In Oxfordshire, 18 of 150 people mentioned problems with their eyes and eyesight at one point, and 3 of 266 developed new problems with their eyes and/or eyesight over nine months, with one having an episode of optic neuritis.⁶

This part aims to ensure that difficulties in this under-recognised area are identified and diagnosed accurately, and that people reach the services most equipped to help, and that the few specific treatments available are tried.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of visual problems.

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▷ Economic evidence

No relevant economic evidence relating to visual problems in MS was identified.

▷ From evidence to recommendations

Although there was no MS-specific evidence, the GDG has made several recommendations for two reasons. First, there was a strong view that visual impairments are often overlooked and that people with MS and visual impairment did not benefit from any specialist advice, which often may improve their abilities. Second, there is reasonable (RCT) evidence supporting the use of gabapentin for nystagmus, and it is widely used.^{386,387}

RECOMMENDATIONS

R127	Each professional in contact with a person with MS should consider whether the individual's vision is disturbed, by considering, for example, the individual's ability to read the text of a newspaper, book or other written material and to see the television.	D
R128	Any person with MS who is unable to read normal print or to see the television should be assessed for glasses by an optometrist.	D
R129	Any individual who experiences reduced visual acuity, despite using suitable glasses, should be assessed in a specialist ophthalmology clinic.	D
R130	Any person with MS who has nystagmus that causes reduced visual acuity or other visual symptoms, should be offered a time-limited trial of treatment with oral gabapentin. This should be initiated and monitored by a suitable specialist.	D
R131	Any person with MS who is unable to read (due to low visual acuity) or to see television, despite all available treatment, should be: ● assessed for low-vision equipment and adaptive technology ● referred to the appropriate specialist social services team ● registered as partially sighted.	D

LOCAL IMPLEMENTATION POINTS

These should identify:

- which local ophthalmologist has an interest in neuro-ophthalmology
- the nearest specialist low-vision service
- the social service team responsible for people with visual impairment.

6.9 Pain

People with MS may suffer pain in at least three ways: specific 'neuropathic' pain arising from areas of demyelination (trigeminal neuralgia is the most well known but not the most common); musculoskeletal pain secondary to postural and other consequences of the disease; and pain from an incidental medical problem unrelated to their MS. Unfortunately, anecdotal experience suggests that much pain is incorrectly diagnosed and poorly managed. A survey of 159 people with MS in Ontario found that 88 had had either an acute or chronic pain syndrome, and that

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78 were experiencing chronic pain of one or more types: 46 had neuropathic pain, 22 had back pain, 21 had painful leg spasms.³²³ Pain was present in 42 of 150 people with MS surveyed in Oxfordshire, and 24 of 226 people with MS followed up for nine months developed new pain requiring diagnosis and management.⁶ Fifteen had neurogenic and eight had musculoskeletal pain (six more presented specifically with secondary musculoskeletal pain) and one had headaches (no specific cause). In another survey, pain was the second most frequent 'worst symptom' at 12% (fatigue achieved 17%).²⁶⁹ In a third survey, 36% of 656 people with MS had pain.²⁷⁸ One may conclude that pain is common, and anecdotal experience suggests that pain is often misdiagnosed and mistreated such that patients may suffer unnecessarily.

This section covers all aspects of pain management in people with MS. However the evidence relating to the management of non-neuropathic pain has not been reviewed, and only the evidence that concerns pain that is specific to neurological disease is included. The recommendations are intended to ensure that pain is adequately detected and correctly diagnosed so that the most specific and appropriate treatments available are used.

▷ Evidence statements*

A relatively large number of reviews were identified which assessed the effectiveness of a wide variety of interventions for the treatment of secondary pain. In total, 17 reviews met inclusion criteria. These can be grouped into three main categories: behavioural interventions ($n = 4$ SRs), pharmacological interventions ($n = 7$ SRs) and other therapies ($n = 6$ SRs).

Behavioural interventions showed mixed results in terms of effectiveness. A fairly poor review of cognitive coping strategies found that cognitive strategies were generally effective in enhancing pain tolerance, and that imagery methods were the most effective.³⁸⁸ A review of cognitive behavioural therapy also reported a beneficial effect of treatment on chronic pain.³⁸⁹ A review of multidisciplinary rehabilitation in patients with musculoskeletal pain reported no overall beneficial effects of treatment,³⁹⁰ and a review of non-pharmacological intervention for the treatment of chronic pain reported that studies were too heterogeneous to detect an effect of treatment.³⁹¹

The reviews of pharmacological interventions also reported mixed effects of the interventions evaluated. Two reviews assessed the effectiveness of antidepressants for the treatment of neuropathic pain,^{392,393} one of these also included patients with chronic pain.³⁹³ Both reviews found that antidepressants were more effective than placebo in the treatment of neuropathic pain.^{392,393} One of the reviews reported no difference between the different tricyclic antidepressants in terms of efficacy but that these were more effective than the benzodiazepines.³⁹² Three reviews looked at the effectiveness of anticonvulsant drugs in the treatment of chronic pain. Two looked at these drugs in general^{394,395} and one only looked at gabapentin.³⁹⁶ These reviews reported conflicting results. The first found that generally anticonvulsants were effective for trigeminal neuralgia, diabetic neuropathy, and migraine prophylaxis, but that minor adverse events occurred as often as benefit.³⁹⁵ The second reported that few trials

* Beard S, Hunn A, Wight J. Treatment for spasticity and pain in multiple sclerosis: a systematic review. *Health Technology Assessment* 2003;7:40, was published in December 2003, after the cut-off date for evidence in this guideline. It can be obtained at www.nchta.org/fullmono/mon740.pdf

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showed analgesic effectiveness and concluded that these drugs should be withheld until other interventions have been tried for patients with chronic pain, with the exception of trigeminal neuralgia.³⁹⁴ The review which only considered gabapentin reported positive effects in diabetic neuropathy and post herpetic neuralgia compared to placebo, and found it similar in effectiveness to amitriptyline. However, intolerable side effects occurred in up to 10% of recipients.³⁹⁶ A poor quality systematic review found that chemical sympathectomy was effective in relieving pain in around half those receiving treatment.³⁹⁷ However, these results came mainly from uncontrolled studies, and the results of controlled studies were not reported separately. It is therefore difficult to draw conclusions from these results.

The remaining reviews looked at transcutaneous electrical nerve stimulation (TENS), phytodolor (a herbal preparation), acupuncture, ultrasound and low-level laser therapy (LLLT). TENS was reported to be better than inactive control but high frequency TENS (HFTENS) and low frequency TENS (LFTENS) were found to be similar.³⁹⁸ The effectiveness of phytodolor in treating osteoarthritis, chronic epicondylitis and rheumatic diseases was found to be superior to placebo and similar to synthetic drugs.³⁹⁹ There was limited evidence that acupuncture was more effective than no treatment in treating chronic pain, but the evidence was inconclusive as to whether it was more effective than placebo, sham acupuncture or standard care.⁴⁰⁰ Two reviews of ultrasound therapy and a review of LLLT for musculoskeletal pain reported no beneficial effects of treatment.^{401–403}

A review of cannabinoids for the treatment of cancer pain, post-operative pain and non-malignant pain found that cannabinoids were more effective than placebo in relieving pain but similar to codeine.⁴⁰⁴

At the time of writing there is insufficient evidence to comment on the use of cannabinoids in MS. Further evidence on the use of cannabinoids in MS is likely to be published and NICE intend to conduct a technology appraisal on cannabinoids in MS with a projected publication date of April 2004.

▷ Health economics

The forthcoming HTA review of treatment for pain and spasticity in MS found no studies that looked explicitly at the impact of pain on the quality of life of people with MS and no studies that considered the health economics of treatment for pain in MS. In addition, no formal review of current clinical practice was identified. However, there is some evidence that despite the high prevalence of pain as a symptom in MS, few patients are referred to pain specialists – fewer than 2% in an MS Society survey.³⁷¹

▷ From evidence to recommendations

When drawing up recommendations, the guideline developers was aware that although there were few MS-specific studies on pain and its treatment, much of the more generic evidence should be applicable. Consensus was achieved easily on the recommendations made.

RECOMMENDATIONS

R132	Each professional in contact with a person with MS should ask whether pain is a significant problem for the person, or a contributing factor to their current clinical state.	D
R133	All pain, including hypersensitivity and spontaneous sharp pain, suffered by a person with MS should be subject to full clinical diagnosis, including a referral to an appropriate specialist service if needed.	D
	<i>Musculoskeletal pain</i>	
R134	Every person with MS who has musculoskeletal pain secondary to reduced or abnormal movement should be assessed by specialist therapists to see whether exercise, passive movement, better seating or other procedures might be of benefit.	D
R135	If non-pharmacological means are proving unsuccessful in managing the musculoskeletal pain (arising from reduced movement and/or abnormal posture), the individual should be offered appropriate analgesic medicines.	D
R136	Any person with MS who has continuing unresolved secondary musculoskeletal pain, should be considered for transcutaneous nerve stimulation or antidepressant medication.	A
R137	Treatments that should not be used routinely for musculoskeletal pain include ultrasound, low-grade laser treatment, and anticonvulsant medicines.	A
R138	Cognitive behavioural and imagery treatment methods should be considered in a person with MS who has musculoskeletal pain only if the person has sufficiently well-preserved cognition to participate actively.	A
	<i>Neuropathic pain</i>	
R139	Neuropathic pain, characterised by its sharp and often shooting nature, and any painful hypersensitivity, should be treated using anticonvulsants such as carbamazepine or gabapentin, or using antidepressants such as amitriptyline.	A
R140	If the neuropathic pain remains uncontrolled after initial treatments have been tried, the individual should be referred to a specialist pain service.	D

LOCAL IMPLEMENTATION POINTS

These need to specify which specialist services can assess and advise on pain associated with MS, especially:

- musculoskeletal pain and the use of equipment and exercises
- neuropathic pain (neurology, neurorehabilitation or pain service).

6.10 Cognitive losses

About half of all people with MS experience cognitive losses. Indeed, MS is probably the commonest single cause of acquired severe cognitive loss in adults aged under 65 years. For example in the Oxfordshire audit, 12 of 150 individuals felt they had problems with concentration and 10 of 150 with thinking, and only 2 of 226 people present new cognitive problems over a nine month period of follow-up.⁶ In another community-based survey, 43 of

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100 individuals had measurable cognitive losses⁴⁰⁵ and in a third community study of 200 people, 46% had measurable cognitive deficits with 34% having impaired memory and 33% impaired planning and other 'frontal lobe functions'.⁴⁰⁶ Other studies have shown similar findings.²⁷⁸

The main implication is that all people, professional and otherwise, who interact with the person with MS should be aware at all times that cognitive loss may be present. It is also important for the person with MS to be aware and to know how to minimise any problems. In practical terms cognitive losses will influence almost all aspects of life, but may be most important in their effects on more complex activities such as community and domestic ADL, making judgements and taking part in legally important decisions, work, and in communication. Other impairments such as disinhibition may also affect control of behaviour and social interaction.

Cognitive impairments in people with MS may have several causes and associated factors. They may be exacerbated by or associated with depression, drugs taken for other impairments, and fatigue. Relapses may cause cognitive impairment, in which case it may well improve. Cognitive loss may occasionally be the presenting or main feature of the disease. Its presence should always be considered but never assumed; formal assessment is usually necessary to clarify the situation. Although the severity of cognitive losses is generally associated with the severity of dependence, this is often not the case and the possible presence of cognitive impairment should always be considered.

The recommendations below should ensure that:

- cognitive impairments are always considered
- any factors that worsen cognitive impairment are identified and treated
- the effects of cognitive impairment are minimised
- any risks associated with cognitive impairment are identified and prevented if possible.

▷ Evidence statements

Four RCTs examined the efficacy of cognitive remediation programs for cognitive dysfunction. The first trial assessed the effectiveness of cognitive training and neuropsychotherapy in comparison to non-specific mental stimulation. The results showed no overall beneficial effect for the intervention at six month follow-up.⁴⁰⁷ The second trial examined the use of cognitive assessment plus remediation, compared to assessment alone, or no treatment. The results indicated no significant differences between the groups on any of the outcomes measures.⁴⁰⁸ The third study assessed the use of cognitive remediation strategies in patients who were resident in long-term nursing facilities. The results showed no beneficial effect for the intervention as compared to the no treatment control group.⁴⁰⁹ The last study compared the use of the story memory technique to no intervention. The results showed positive effects on three out of five of the outcomes assessed, including patients self report of memory functioning⁴¹⁰ (Ib).

▷ Economic evidence

No relevant economic evidence on treatment for cognitive losses was identified.

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▷ From evidence to recommendations

The GDG noted that cognitive impairments affected at least half of all people with MS, and that cognitive impairments were often not recognised even though they have pervasive effects. The evidence does not currently support any specific intervention, but nonetheless it was felt important to ensure that cognitive impairments were identified, and that simple advice and actions were undertaken. The recommendations made were agreed by consensus.

RECOMMENDATIONS

R141	Health care staff should always consider whether the person with MS has any impairment of attention, memory and executive functions sufficient to be a problem, or to be a contributing factor to their current clinical status.	D
R142	When a person with MS is being involved in making a complex medical decision, or is starting a course of complex treatment that requires their active participation, they should have their cognition sensitively assessed to ascertain their ability to understand and participate adequately, and to determine what support they may need.	D
R143	Any person with MS experiencing problems due to cognitive impairment should: • have their medication reviewed, to minimise iatrogenic cognitive losses • be assessed for depression, and treated if appropriate.	D D
R144	Any person with MS complaining of cognitive problems, and any person where this is suspected clinically, should be: • offered a formal cognitive assessment, coupled with specialist advice on the implications of the results • advised, if necessary, about any vulnerability to financial or other abuse that may arise, and how to reduce the risk • asked whether the results can be communicated to other people.	D
R145	Any person with MS whose level of dependence or whose social behaviour cannot be easily understood in terms of other known impairments or factors should be offered a formal neuropsychological assessment by a specialist clinical psychologist (and speech and language therapist if appropriate); it should be investigated whether cognitive or communicative losses are a contributing factor and, if so, appropriate management should be recommended.	D

LOCAL IMPLEMENTATION POINTS

These need to:

- agree simple assessments of cognition for use by staff interacting with people with MS
- identify which specialist psychology service (usually that within the neurological rehabilitation service) should be approached for assessment and treatment, and how they are accessed.

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6.11 Emotionalism

People with MS can suffer several disturbances in their emotions and emotional control. Emotionalism refers to a tendency to cry, or more rarely laugh, when this is not the felt emotion and often without any ability to control the behaviour. It is associated with depression, in stroke patients. It has also been referred to as pathological crying and laughing, pathological emotionalism, and one aspect of pseudobulbar palsy. There are no clear-cut, agreed definitions. It can be extremely distressing to the person with MS but fortunately rarely causes severe or prolonged problems.

The frequency of emotionalism is not known. One study suggests that 10% of people with MS experience 'pathological laughing and crying',⁴¹¹ and another that 32% found that they laughed or cried easily.²⁷⁸

▷ Evidence statements

One randomised crossover trial compared the effect of amitriptyline to placebo. The results showed a beneficial effect on both clinical improvement and the number of episodes of lability. No adverse events were reported⁴¹² (Ib).

▷ Economic evidence

No relevant economic evidence on treatment for emotionalism was identified.

▷ From evidence to recommendations

Although there is little MS-specific evidence; there is some evidence from other neurological conditions. Because emotionalism can be so distressing, the GDG drew on all this evidence to reach the consensus recommendations made.

RECOMMENDATIONS

R146	A person with MS may comment (or it may be noticed) that they may cry or laugh with minimal provocation and with little control; the individual should be offered a full assessment of their emotional state by someone with suitable expertise.	D
R147	If the emotionalism is sufficient to cause concern or distress to the person with MS, or their family, then treatment with an antidepressant should be offered:	
	● usually a tricyclic antidepressant, or ● a selective serotonin re-uptake inhibitor.	B D
R148	If the person with MS still has uncontrolled emotionalism, is unwilling or unable to take antidepressants, or is not responsive to antidepressants, then advice on behavioural management strategies should be offered by a suitable expert.	D

LOCAL IMPLEMENTATION POINTS

These need to specify:

- which local specialist(s) (neuropsychologist, psychiatrist or clinical psychologist) has/have appropriate expertise to assess and manage emotional impairments
- whether one particular antidepressant is preferred.

6.12 Depression

Depression is a common emotional consequence in MS. For example, it was found in 36% of one sample.²⁷⁸ Depression may arise as a specific impairment secondary to neurological lesions and it may be secondary to disability, altered life circumstances, pain, or loss of employment.⁴¹³ It is also likely that depression in turn may cause or worsen some impairments and disabilities. There is some evidence that people with MS have a higher rate of suicide than people with most other chronic disabling conditions, and this risk may be highest within the first five years of diagnosis. In the Oxfordshire audit, 13 of 150 individuals complained of disturbed emotions or emotional control at one time, and 11 of 226 presented with depression or low mood over a nine month period.⁶ In the Southampton survey every person with MS was assessed formally using the Hospital Anxiety and Depression (HAD) scale and 7% were rated depressed and 9% borderline depressed.²⁸⁰

Consequently guidance needs to ensure that all professionals involved are aware of depression, and that it is identified and treated appropriately, not only by drugs but also through ameliorating some of the other causative factors. However it is also important that the important associations between depression, fatigue, social circumstances and other factors are always considered.

In the absence of strong evidence that depression in MS is different from depression in other people, the forthcoming NICE guideline on depression should be used once available.

▷ Evidence statements

Three RCTs examined the effect of cognitive behavioural therapy (CBT) compared to placebo or other active treatments. The first study compared weekly CBT, supportive expressive group (SEG) therapy and sertraline. The results showed that on all three of the outcome measures CBT was significantly superior to SEG; and that there were no differences in the results between CBT and sertraline. No adverse events were reported in the trial.⁴¹⁴ The other two trials both compared CBT to a waiting list control. The first trial reported positive effects on four of six outcome measures assessed, whilst the second that examined the use of individual telephone therapy also reported significant beneficial effects. Neither of the trials reported any adverse effects^{415,416} (Ib).

▷ Economic evidence

No relevant economic evidence on treatment for depression in MS was identified.

▷ From evidence to recommendations

The GDG felt that this was an important topic and in the absence of much evidence used consensus to develop the recommendations made.

RECOMMENDATIONS

R149	If depression is suspected, the person with MS should be assessed:	
	by asking 'Do you feel depressed?', or using a similar screening method	DS
	clinically if necessary	D
	by a liaison psychiatrist if severe depression is present.	D
R150	In any person with MS who is depressed, a list of possible contributing factors (such as chronic pain and social isolation) should be drawn up.	D
R151	Assessment and interventions should be undertaken to ameliorate those contributing factors, where possible.	D
R152	Specific antidepressant medication,	D
	or psychological treatments such as cognitive behavioural therapy	A
	should be considered but only as part of an overall programme of depression management.	D
R153	Other concurrent psychological diagnoses, especially anxiety, should be considered.	D

LOCAL IMPLEMENTATION POINTS

These should consider:

- which screening question or questionnaire is recommended locally
- which formal depression questionnaire is recommended locally
- which psychiatrist and/or clinical psychologist should be approached when more specialist advice or treatment is required
- what antidepressants are preferred locally.

6.13 Anxiety

Although poorly studied, this is probably the commonest emotional impairment associated with MS. In one study the rate of anxiety at 25% (of 252 consecutive patients with MS) was three times the rate for depression in the same group.⁴¹⁷ In the Southampton survey using the HAD scale, 16% were anxious and 20% borderline anxious, over twice the rate of depression.²⁸⁰ The precise aetiology is not known, although it is probably not due to any specific lesions.⁴¹³ Nevertheless it can significantly increase dependence and distress. In the Oxfordshire audit only one patient (from 226) presented with anxiety over nine months.⁶

► Evidence statement

No RCTs or CCTs in patients with MS which assessed intervention for the treatment of anxiety were identified.

Three systematic reviews assessed different interventions for anxiety in patient populations other than MS (Ia). The first review examined the utility of self-help treatments for patients with anxiety presenting in primary care settings. The results showed advantages associated with self-help on at least one measure, although most studies reported multiple comparisons. There were no data available concerning the long term clinical benefits.⁴¹⁸ The second review of seven

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trials compared the efficacy of kava extract (a herbal treatment) to placebo. All the trials showed superiority of kava extract, with any adverse effects being mild and transient.⁴¹⁹ However, it should be noted that kava extract has been voluntarily withdrawn from the market because of fears of liver toxicity. A more permanent ban of kava extract is currently being considered by the MCA. The last review compared the effectiveness of group therapy, individual therapy, couple therapy and relaxation therapy in patients with a diagnosis of cancer who were at risk of developing anxiety. The results indicated that all the four treatments were superior to placebo, with psycho-education and group therapy being the most effective.*⁴²⁰

Readers should note that there is a NICE guideline on anxiety in development.

▷ Economic evidence

No relevant economic evidence on treatment for anxiety in MS was identified.

▷ From evidence to recommendations

The recommendations made by the guideline developers depend largely on consensus because the limited evidence available was difficult to translate into useful guidance.

RECOMMENDATIONS

R154	Any person with MS whose function or happiness is being adversely affected by anxiety should be offered specialist assessment and management.	D
R155	In people with MS with marked anxiety, psychologically-based treatment should be offered.	A
R156	Pharmacological treatment of anxiety should be through using antidepressants or benzodiazepines. The Committee on Safety of Medicines (CSM) guidelines on the use of benzodiazepines (reproduced in the British National Formulary) should be used.	D

LOCAL IMPLEMENTATION POINTS

These need to specify:

- how to access specialist psychological advice
- how to access specialist psychiatric advice.

6.14 Swallowing difficulties

Dysphagia is a difficulty with swallowing which may cause choking and aspiration of food or liquid into the lungs. There have been few studies on its actual prevalence, let alone its importance and treatment. One study found 49 of 143 consecutively identified people to have dysphagia, and that it was more common in more dependent people and in those with evidence of brainstem dysfunction such as dysarthria – compensatory treatment strategies were successful in 46.⁴²¹ In a second study, 43% of 79 people with MS had dysphagia and about half of these did

* Kapezinski F, Lima MS, Souza JS, Schmitt R. Antidepressants for generalized anxiety disorder. *Cochrane Database Syst Rev* 2003;(2):CD003592, has been withdrawn for updating and was therefore unavailable for inclusion.

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not complain of swallowing difficulties.⁴²² Similar associations were found, and any complaint of difficulty swallowing, or coughing on swallowing, was a specific but insensitive marker. In the Oxfordshire audit 18 of 150 people had swallowing difficulties at one point in time, 5 of 226 people developed problems with swallowing over nine months.⁶

Dysphagia (choking, difficulty in swallowing, aspiration of food or fluid into the lungs) is not only distressing but it also may cause chest infections and death. Furthermore, inappropriate management may lead to malnutrition if the person fails to take an adequate diet. It is an important area of concern and the problem is quite common and probably underdiagnosed.

Fortunately, many patients will only have short-term difficulties with swallowing, usually associated with an acute relapse or an infection. Early detection is particularly important in these circumstances, but management is often only needed for a few days or weeks.

Guidance needs to consider various issues:

- early detection, before complications arise
- management that is appropriate to the nature and severity of the problem
- pro-active management to reduce complications
- clinical consideration of the ethical and resource implications of percutaneous endoscopic gastrostomy (PEG) feeding.

▷ Evidence statement

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of swallowing difficulties.

Two systematic reviews, both of good quality, investigated interventions for the treatment of dysphagia in patients with acute stroke or neurological disease^{423,424} (Ia). Both reviews compared PEG to nasogastric (NGT) feeding; there was some overlap in the studies included in these reviews. Both reported that PEG was superior to NGT for the various outcomes assessed, including a reduction in mortality.^{423,424} One of these reviews also investigated a variety of other interventions for the treatment of dysphagia. This review found that swallowing therapy, treatment with nifedipine, nutritional supplementation and fluid supplementation were not more effective than control in the treatment of dysphagia.⁴²⁴

▷ Economic evidence

No relevant economic evidence on treatment for swallowing difficulties was identified.

▷ From evidence to recommendations

The guideline developers recognized that the published evidence only covered a few of the important issues concerned with feeding, swallowing and nutrition and so used consensus to guide most of the recommendations in this important area.

RECOMMENDATIONS

R157	Any person with MS who is unable to transfer from bed to chair independently, or who has any symptoms or signs of bulbar dysfunction such as any abnormality of eye movements, slurring of speech or ataxia, should be asked whether they have difficulties with chewing, or swallowing food or fluids (for example, coughing), and also whether they have altered their diet because of previous problems.	D
R158	Any person with MS with any bulbar symptoms or signs, and any person with MS who has a chest infection, should have their swallowing assessed by a competent person (using a standardised swallowing test).	DS
R159	People with MS who, on formal assessment, have an abnormality of swallowing should be further assessed by a specialist speech and language therapist. Advice should be given on specific swallowing techniques, and on adapting food consistencies and dietary intake. Further diagnostic assessment (for example, by videofluoroscopy) should be undertaken if: ● first-line therapy and advice are ineffective ● a specific objective of the investigation can be identified.	D
R160	Any person with MS who has difficulty swallowing for more than a few days should be assessed by a neurological rehabilitation team, to review the need for: ● adjustments to or provision of seating that will increase ease and safety of swallowing and feeding ● chest physiotherapy ● short-term use of nasogastric tube, especially if recovery is anticipated.	D
R161	Any person with MS who has swallowing difficulties for more than one month should have his or her weight or nutritional status checked on a monthly basis (using a validated nutritional measure if needed). Dietary intake should be reviewed if there is continuing weight loss or evidence of malnutrition.	D
R162	If PEG feeding is anticipated as being a likely future option, discussions with the person with MS should be commenced at an early stage and their wishes documented.	D
R163	If swallowing difficulties persist, a PEG tube should be considered if any of the following occur: ● recurrent chest infections ● inadequate food and/or fluid intake ● prolonged or distressing feeding ● nasogastric tube <i>in situ</i> for over one month.	D
R164	If PEG placement is indicated and agreed, the PEG tube should be inserted by a suitable specialist. Before the person with MS is discharged from hospital, full training should be given to any family members and carers who are going to be involved in feeding.	A

LOCAL IMPLEMENTATION POINTS

These need to:

- produce brief guidance for health workers in contact with people with MS on warning signs of bulbar dysfunction and screening questions for swallowing problems
- agree which formal swallowing test should be used locally

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- specify who may request and undertake additional investigative assessments
- specify how PEG tubes are requested, serviced and replaced
- agree who may train carers about PEG feeding
- specify funding arrangements for all equipment and feeds associated with PEG feeding.

6.15 Speech difficulties

Slurred speech (dysarthria) is another problem in people with MS where the prevalence and importance is little researched. In Oxfordshire the prevalence of speech difficulties was 11 of 150, but only one person of 226 developed a new speech difficulty over nine months.⁶ A survey in Sweden found that 44% of people with MS experienced speech or voice difficulties,⁴²⁵ and another study in Sweden found a prevalence of dysarthria of 51% in 77 people, and that a clinical dysarthria test was sensitive.⁴²⁶ The survey in the USA found that 23% had speech or communication difficulties.²⁷⁸ Undoubtedly a significant number of people have mild problems, and some people have problems so severe that communication is limited or prevented. This will usually be in people with severe disability, but sometimes it will be specifically associated with cerebellar disturbance and ataxia.

Other impairments may affect communication. Language disturbance (aphasia) is rare, although it can occur with a relapse leaving mild long-term word-finding difficulties. Cognitive losses can markedly affect communication. The voice can also be affected, causing changes in volume or pitch. Sometimes several impairments will combine to affect communication.

Guidance is needed to encourage recognition of the difficulty and its implications with appropriate management being followed.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of speech difficulties.

Four systematic reviews assessed the effectiveness of various interventions for speech difficulties in patients with Parkinson's disease and/or stroke^{427–430} (Ia). Three reviews investigated the effects of different forms of speech and language therapy. The first concluded that it was impossible for the review to determine whether formal speech and language therapy is more effective than informal support.⁴²⁷ The second, which included only patients with Parkinson's disease, found that all trials reported a significant positive effect of speech and language therapy on dysarthria on a variety of outcome measures. However, this review concluded that it is unsafe to draw firm conclusions regarding the efficacy of speech and language therapy considering the small number of patients examined and the methodological flaws in the included studies.⁴²⁹ The third review also found that the limitations of the studies in terms of methodological inadequacies and small numbers of participants meant that it was not possible to draw conclusions regarding the efficacy of one form of speech and language therapy over another.⁴³⁰ The fourth review investigated the effectiveness of various forms of pharmacological therapy in the treatment of patients with aphasia due to stroke.⁴²⁸ This review found that there was some evidence that piracetam was more effective than placebo in the treatment of aphasia. For other interventions investigated (bifemelar, pirbedil, bromocriptine and idenone) the data was not in an appropriate format for analysis. No significant beneficial effects of treatment with dextran 40 were found.

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▷ Economic evidence

No relevant economic evidence on treatment for speech difficulties was identified.

▷ From evidence to recommendations

Although four systematic reviews met inclusion criteria these did not provide conclusive evidence on any of the interventions investigated; consensus was therefore used to agree the recommendations.

RECOMMENDATIONS

R165	Any person with MS who has dysarthria sufficient to affect communication with people outside the home or over the phone, and any person who is concerned about their speech sound or clarity, should be assessed and given advice by a specialist speech and language therapist.	B
R166	Any person with MS whose ability to communicate is affected significantly by dysarthria should be taught techniques to improve and maintain speech production and clarity; tuition should be provided by a specialist speech and language therapist, working with any other members of the neurological rehabilitation service who are involved.	D
R167	Any person who continues to have difficulties in communication should be considered for, and if appropriate taught the use of, alternative non-verbal means of assisting with or replacing speech.	D
R168	Any person with MS who cannot communicate effectively should be assessed by a specialist speech and language therapist for an augmentative aid to communication, which should then be provided as soon as possible. The family members, carers and other frequent communicators with any person with MS who has significant communication difficulties should have discussions with the speech and language therapist on how best to help the person communicate.	D

LOCAL IMPLEMENTATION POINTS

These need to specify:

- which speech and language therapist should see people with dysarthria
- who may assess for and recommend augmentative equipment and adaptive technology to communication
- funding arrangements for augmentative aids to communication (AACs).

6.16 Sexual dysfunction

MS almost always affects the spinal cord, and disturbance of sexual functions is a common concomitant of any spinal cord damage. The precise frequency of direct sexual dysfunction is unknown. In the Southampton study, 55% of people with MS reported a change for the worse in their sexual relationships, although only 77 (44%) reported a change in their emotional relationship with a partner and 19 of these changes were reported as improvements.³²³ Another

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study suggested that about 70% of people with MS had sexual dysfunction compared with 40% in non-neurological disabling conditions and 12% in the general population.⁴³¹ This study suggested that neurological damage was the single most common primary cause of sexual dysfunction. Nonetheless it must also be recognised that sexual behaviour will also be affected by many other impairments such as pain, sensory dysfunction, motor impairments, bladder dysfunction, bowel dysfunction, mood disturbance etc. Furthermore, physiological sexual dysfunction must always be considered in the much wider context of sexual behaviour and relationships. This section not only covers erectile dysfunction and disorders of sexual arousal mechanisms, but also covers wider aspects of sexual behaviour and social relationships that are probably of much greater importance.

Guidance needs to reflect the complexity of the problem, ensuring that problems are detected and then analysed fully so that targeted effective intervention is given where appropriate, while also ensuring that specific treatments are not given inappropriately.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of sexual dysfunction.

Four systematic reviews which included men with erectile dysfunction were identified.^{432–435} All were of good quality (Ia). Two reviews examined the effects of sildenafil (Viagra), one looked at yohimbine (a herbal preparation) and the fourth looked at a variety of interventions including both yohimbine and sildenafil. There was overlap in the trials included in these reviews. All three reviews which looked at the effectiveness of sildenafil reported that it was significantly better than placebo in the treatment of sexual dysfunction in men.^{432,433,435} One review also reported that sildenafil was effective in all subgroups investigated.⁴³³ Both the review which looked exclusively at yohimbine⁴³⁴ and the review which also looked at a variety of other treatments⁴³² found that yohimbine was significantly better than placebo in the treatment of erectile dysfunction. The side effect profile of both drugs was reported to be good. The review which looked at a large variety of interventions for the treatment of erectile dysfunction found that inconsistent or lack of clinically relevant reported outcomes together with a lack of long-term follow-up or comparisons with active treatments and selection bias of enrolled patients limited study results.⁴³²

▷ Economic evidence

No relevant economic evidence on treatment for sexual dysfunction was identified.

▷ From evidence to recommendations

The only evidence available related to pharmacological treatments, but the GDG recognised that sexual activity and function depended upon far more than the neurophysiology of sexual structures.

The recommendations, agreed by consensus, therefore cover a much wider range of important issues.

RECOMMENDATIONS

- R169** Men with MS:
- should be asked whether they experience erectile dysfunction (relative or absolute) and, if so, whether it is of concern **D**
 - who have persisting erectile dysfunction and who do not have contraindications should be offered sildenafil 25–100mg **A**
 - who do not respond to sildenafil should be assessed for the general and specific factors that might cause or worsen erectile dysfunction and that are amenable to treatment (such as depression, anxiety, vascular disease, diabetes and taking medicines that may cause erectile dysfunction). Other specific treatments such as alprostadil or intracavernosal papaverine should then be considered. **D**
- R170** Women with MS should be asked whether they experience sexual dysfunction (such as failure of arousal or lubrication or anorgasmia) and, if so, whether it is of concern. **D**
- R171** Women with sexual dysfunction should be assessed for the general and specific factors that might cause or worsen sexual dysfunction and that are amenable to treatment (such as depression, anxiety, vascular disease, diabetes and taking medicines that may cause sexual dysfunction). **D**
- R172** Every person (or couple) with MS should be asked sensitively about, or given the opportunity to remark upon, any difficulties they may be having in establishing and/or maintaining wanted sexual and personal relationships; they should be offered information about locally available counselling and supportive services. **D**
- R173** Every person (or couple) with persisting sexual dysfunction should be offered the opportunity to see a specialist (with particular expertise in sexual problems associated with neurological disease) and offered, as appropriate, advice on lubricants and the use of sexual aids, and other advice to ameliorate their sexual dysfunction. **D**

LOCAL IMPLEMENTATION POINTS

These need to specify:

- urologist or other doctor with expertise in male sexual dysfunction
- gynaecologist or other doctor with expertise in female sexual dysfunction
- all local services available to individuals and couples with difficulties in establishing and maintaining personal and sexual relationships for whatever reason, and especially any that have experience of neurological diseases.

6.17 Pressure ulcers

A pressure ulcer (pressure sore or decubitus ulcer) is an area of broken skin that is secondary to unrelieved pressure on the skin, often exacerbated by slight trauma, for example when being moved. A pressure ulcer may range from a minor break to very large deep areas of dead tissue extending over many square centimetres and down to bone. Once present they can be difficult to heal, and can cause general malaise and worsening of most impairments, and they carry a risk of generalised or localised infections. Many people with MS are at high risk of developing a pressure ulcer because they may have, for example, limited mobility, impairment of sensory

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functioning, and reduced cognitive function or undernutrition. In an audit of 226 people followed over 10 months, 10 people experienced 14 pressure ulcers, three acquiring them during hospital admission.⁶ Surveys and formal reports have repeatedly emphasised the costs of pressure ulcers both to the health service and to the patient with the ulcer.⁴³⁶ Prevention must be a high priority yet they continue to occur with monotonous regularity. This section covers both prevention and treatment.

Readers should be aware that a NICE guideline on pressure ulcer management is currently in development.

► Evidence statement

All evidence statements for pressure ulcers are level Ia.

Monitoring for the development of pressure ulcers – Two reviews were identified which looked at the assessment of pressure ulcers.^{437,438} The first review found great variation in the estimates of predictive validity both across scales and between assessment of the same scale, and that ultimately none of the scales appears to be unambiguously superior.⁴³⁷ The second reported similar findings, concluding that no scale appears to be more accurate in identifying those patients at most risk from developing pressure sores although the Braden scale has been the most extensively tested.⁴³⁸ This review also reported that there was no evidence that risk assessment scales are effective in reducing the incidence of pressure sores or that they improve preventive care.

Intervention to reduce the risk of pressure ulcers – Two reviews assessed the effectiveness of interventions to reduce the risk of pressure ulcers. Both reviews assessed the effectiveness of pressure-relieving interventions. Both reviews found that higher specification foam mattresses were more effective than ordinary foam mattresses in reducing pressure ulcer incidence in patients at risk of pressure ulcer.^{437,439} The first review reported that the relative merits of higher-tech constant pressure and alternating pressure beds and mattresses were unclear.⁴³⁹ However, the second found that these were more effective than standard hospital mattresses in preventing pressure ulcer. This review also reported that some types of large-cell alternating pressure devices (cell diameter 10cm or greater) may be more effective than simple, low-pressure mattresses, that low-air-loss beds are effective in preventing and treating pressure ulcer compared with foam mattresses and that there was no evidence to indicate the degree to which manual repositioning is effective, or what the optimum turning regime would be.⁴³⁷

Intervention for the treatment of pressure ulcers – Five reviews assessing the effectiveness of treatments for pressure ulcer met inclusion criteria.^{437,439–442} Two reviews, both of which also looked at the prevention of pressure ulcers, looked at the effectiveness of pressure supports. The first review found that standard hospital mattresses are outperformed by a range of foam-based, low-pressure mattresses and overlays, and also by ‘higher-tech’ pressure-relieving beds and mattresses, in the treatment of pressure ulcer. It also found that some types of large-cell alternating pressure devices may be more effective than simple, low-pressure mattresses, that low-air-loss beds are more effective in treating pressure ulcer than foam mattresses, and that there is no evidence to indicate the degree to which manual repositioning is effective, or what the optimum turning regime would be.⁴³⁷ The second review reported that air-fluidised supports and low-air-loss beds may improve pressure sore healing rates and that seat cushions have not been adequately evaluated.⁴³⁹

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Two reviews looked at the effectiveness of topical agents for the treatment of pressure ulcers, one of these also looked at the effectiveness of various different dressings and compared dressings to topical agents. The first review found that there was not sufficient evidence to draw conclusions regarding the effectiveness of any topical agent. The second review reported that there was no significant difference in healing rates between topical agents and placebo. However, it found that topical hydrogel promoted healing more than hydrocolloid dressing, and that topical polysaccharide beads were less effective than calcium alginate dressings. It found good evidence (five RCTs) to suggest that hydrocolloid dressings were preferential to traditional therapies (saline gauze and antiseptics) for the treatment of pressure ulcer. Comparisons between dressings were unable to show any statistically significant difference in healing rates.

The fifth review looked at the effectiveness of therapeutic ultrasound, electrotherapy and electromagnetic therapy for the treatment of pressure ulcer.⁴⁴¹ This review found no evidence to support the use of ultrasound or electromagnetic therapy. It reported some evidence in favour of electrotherapy in the treatment of pressure ulcer, but highlighted that this evidence came from three small studies and so should be interpreted with caution.

One RCT assessed the effectiveness of providing personalized information and advice to patients with the aim of reducing the incidence of pressure ulcer and falls. This study found a negative effect of the intervention with an increase in the reports of pressure ulcer and falls in the group receiving information.⁴⁴³

► Health economic evidence on interventions to treat skins breaks and pressure ulcers

No formal economic evaluations of any interventions involving people with MS were identified. A systematic review in 1995 concluded that there was little evidence on the cost-effectiveness of methods of prevention or treatment (not MS specific).⁴³⁷ The pre-NICE guideline on the risk assessment and prevention of pressure ulcers does not consider the cost-effectiveness of interventions.⁴⁴⁴ A report by Touche Ross in 1993 estimated the costs of preventing and treating pressure ulcers in a 600-bed general hospital at between £600,000 and £3 million per year.⁴³⁶ A recent pilot study has attempted to estimate the cost-effectiveness of a potential prevention programme *vs* standard care of geriatric inpatients with pressure ulcers. This study concluded that the prevention programme was the dominant strategy reducing both the incidence of pressure ulcers and the costs of care. This study was of poor quality and is of limited relevance to the population of people with MS so it is *not* included in the evidence tables.⁴³⁶

RECOMMENDATIONS

R174	Every person with MS who uses a wheelchair should be assessed for their risk of developing a pressure ulcer. The individual should be informed of the risk, and offered appropriate advice.	D
R175	Every person with MS who uses a wheelchair daily should be assessed by a suitably trained person, whenever they are admitted to hospital (for whatever reason), for their need for pressure-relieving devices and procedures. The assessment should be clinical,	

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specifically taking into account the risk features associated with MS, and not simply the recording of a pressure ulcer risk score; it should lead to the development and documentation of an action plan to minimise risk, including:

- optimisation of nutritional status D
 - provision of suitable equipment B
 - documentation of agreed manual handling techniques. D
- R176 Every person with MS who is provided with a wheelchair by a statutory organisation (NHS or social services), or whose wheelchair seating is being reassessed, should specifically be considered for pressure-relieving procedures and devices – not only in the wheelchair, but in all other activities, especially transfers and sleeping. D
- R177 For every person with MS considered to be at risk on their bed (in hospital or in the community):
- an appropriate specialist mattress should be provided wherever they are lying down A
 - regular turning should not be depended upon as a policy for preventing pressure ulcers A
 - the skin areas at risk should be inspected to ensure adequate protection is being provided. D
- R178 If a pressure ulcer occurs, it should be considered an adverse event worthy of investigation, and advice should be sought from a specialist service. D
- R179 Any person with MS who develops a pressure ulcer should be nursed on a low-loss mattress (while in bed). A
The ulcer should be dressed according to appropriate local guidelines. D
(See also the NICE Clinical Guideline on prevention of pressure ulcers.^{444,445})

LOCAL IMPLEMENTATION POINTS

The local services will need to consider:

- procedures and funding mechanisms to ensure that specialist pressure-relieving devices are made available promptly to people needing them wherever they are
- who has appropriate training to assess for risk of pressure ulcer
- which dressings are to be used locally
- which team specialises in prevention and management of pressure ulcer
- mechanisms for reporting the development of pressure sores and investigating why they occurred.

6.18 Other treatments including complementary therapies

Most people with MS take an active interest in managing their illness. This includes the use of unlicensed interventions that are not generally recognised by health professionals as influencing the disease process or ameliorating specific symptoms. A survey of 117 people in Cardiff showed that people with MS are high users of non-prescription medicines, and that these were usually purchased from sources where no health professional was available to give advice.⁴⁴⁶ These interventions are often referred to as alternative or complementary therapies. The stated

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or expected effect of these treatments may not be clear. Where a rationale does exist it should be recognised that there may be an overlap between alternative therapies taken in the belief that they affect the disease process, and those taken in the belief that they ameliorate the effects of the disease in some way. Some benefit may arise through placebo mechanisms but for the individual this may be an important effect.

Some of these treatments may cost the person with MS substantial sums of money, or expose them to risk. Further information on complementary and alternative medicines and other lifestyle recommendations are available from various MS support organisations. It should also be recognised that the boundaries between complementary/alternative and orthodox treatments varies between countries, cultures, over time and even between members of the health care professions. This section covers a variety of interventions that are used in non-specific ways, usually to ameliorate several symptoms. It includes both standard interventions and those that may be considered alternative.

The aims of the recommendations are similar to those concerning all treatments, namely to ensure that people with MS:

- are facilitated in pursuing any treatments that they wish to
- are given or directed to any information that may be available concerning any proposed treatment
- are specifically recommended to consider risks, cost and benefits for any treatment
- keep the health care professionals aware of all treatments being pursued.

▷ Evidence statement

One systematic review of 12 RCTs assessed the efficacy of a variety of complementary and alternative therapies used by people with MS⁴⁴⁷ (Ib). The specific therapies addressed in the review were nutritional therapy ($n = 4$), Feldenkrais bodywork ($n = 1$), reflexology ($n = 1$), magnetic field therapy ($n = 2$), neural therapy ($n = 1$) and psychological counselling ($n = 2$). It reported some evidence to suggest some benefit of nutrition therapy, linoleic acid ($n = 3$) and fish oils ($n = 1$) for the physical symptoms of MS. Likewise, magnetic field therapy and neural therapy also appeared to have a short-term beneficial effect on physical symptoms. The results also showed that massage/bodywork and psychological counselling appear to improve depression, anxiety and self-esteem. However, the strength of evidence for any of the therapies was limited as many of the trials suffered from significant methodological flaws. One further CCT that also examined reflexology reported no effect on a range of symptoms, and although symptoms scores improved slightly during treatment this was not maintained at follow-up⁴⁴⁸ (IIa).

Two small randomised crossover trials examined the effectiveness of body cooling for heat sensitive patients^{449,450} (Ib). The first placebo-controlled trial reported beneficial effects on three out of four of the indices tested, namely visual acuity, timed walk test and muscle strength, but no effect on coordination.⁴⁵⁰ However, the length of follow-up was not reported and so it is impossible to determine whether these effects were transitory. The second trial reported no significant effects on either tympanic temperature decreases or on any of twelve performance tests.⁴⁴⁹

Three RCTs assessed the effectiveness of different exercise programmes for increasing the fitness and well-being of individuals with MS^{451,452,453} (Ib). The first that examined the effectiveness of a water exercise training program found positive effects upon pain, energy, social and sexual

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function as assessed by the MSQOL-54, and tension, fatigue and vigour, assessed by the POMS-SF.⁴⁵² However, the second RCT that examined an exercise programme using a leg cycle ergometer found no improvement in either the physical fitness indices assessed or grades of fatigue, as assessed by the Fatigue Severity Scale.⁴⁵³ The last RCT examined the utility of lectures on exercise philosophy combined with nutrition, stress management and an individualised exercise programmes.⁴⁵¹ The results showed no effect on either graded exercise time or on EDSS scores.

Two RCTs (Ib) and one CCT (IIa) investigated the effects of antidepressants.^{454,456} The antidepressants assessed included imipramine, lofepramine combined with phenylalanine, and tranylcypromine. None of these trials reported an overall beneficial effect of the intervention, although one of the RCTs reported some beneficial effect. This good quality RCT found a greater improvement on the Chalder fatigue scale score in those receiving lofepramine combined with phenylalanine compared to those receiving placebo, however, it found no effect of treatment for any of the other five outcomes investigated.⁴⁵⁴ Side effects were relatively minor but occurred more frequently in the intervention group.

Two further RCTs (Ib) and two CCTs (IIa) examined the interventions of t'ai chi, Chinese medicine, relaxation training and a multimodal intervention program. The results of the CCT assessing t'ai chi reported significant changes in patients' assessment of their symptoms at three month follow-up.⁴⁵⁷ One CCT of a multimodal intervention program reported significant effects on five of the eight areas assessed. These included two measures of list learning and memory, improved BDI scores, one measure of grip strength and one of tactile sensitivity⁴⁵⁸ (Iib). One of the RCTs looked at relaxation training and biologically orientated imagery treatment.⁴⁵⁹ The results showed a significant improvement on state anxiety, but not on trait anxiety or the other three tests examining mood or health states. The last RCT compared the efficacy of traditional Chinese medicine combined with Western medicine to treatment with Western medicine alone. The results indicated beneficial effects upon remittance of symptoms.⁴⁶⁰

▷ Economic evidence

There are no economic studies of complimentary therapies in MS.

▷ From evidence to recommendations

This section, and the evidence in it, covers a wide range of potential treatments that are considered or used by a large number of people. The evidence does not support any particular treatment, though conversely it does not show that any are specifically harmful. The GDG felt it was important to steer readers towards any available information, while also making it clear that it was insufficient to recommend use or non-use. The GDG was also especially concerned that people with MS were encouraged to inform professionals about any treatments being used so that potentially harmful interactions or effects could be avoided.

RECOMMENDATIONS

R180	People with MS should be informed that there is some evidence to suggest that the following items might be of benefit, although there is insufficient evidence to give more firm recommendations:	A
	● reflexology and massage ● fish oils ● magnetic field therapy ● neural therapy ● massage plus body work ● t'ai chi ● multi-modal therapy.	A A A A A A A
R181	A person with MS who wishes to consider or try an alternative therapy should be recommended to evaluate any alternative therapy themselves, including the risks and the costs (financial and inconvenience).	D
R182	A person with MS should be encouraged to discuss any alternative treatments they are considering, and to inform their doctors and other professionals if they decide to use any.	D

LOCAL IMPLEMENTATION POINTS

These should cover:

- how and where people may find more information about, and access/purchase, most common alternative therapies
- which alternative therapies are going to be supported by health funds, if any.

7 Monitoring quality: audit and governance

Table 7 Suggested measures for auditing MS services in the NHS

Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)
1. Specialist neurological and neurological rehabilitation services should be available to every person with MS, when they need them. This is usually when they develop any new symptom, sign, limitation on activities or other problem, or when their circumstances change.	The presence (or not) of a specific contract between the health commissioning organisation (primary care trust or local health board) and: • specialist neurological services • specialist neurological rehabilitation services and the quantity of service delivery with a currency to be agreed but probably for a defined population on a yearly basis: • number of new cases of MS seen by neurology service • number of confirmed cases seen by neurology (for disease diagnosis and treatment, including interferon beta) • number of people seen by neurology for methylprednisolone treatment • number of new cases seen by neuror rehabilitation service • number of cases seen (excluding new) • equipment provided or maintained.	There are no exceptions. These data are not currently collected, and there are no data to predict a likely caseload and so initial data will be to establish a baseline that could be compared with known epidemiological figures on incidence and prevalence. The neurology rate of seeing confirmed cases is likely to be higher where neuror rehabilitation services are limited. The effects on other services of the regular monitoring of patients in the risk-sharing scheme are unpredictable.	The neurology contract may be split to cover the specific work associated with the risk-sharing scheme, and the remaining work.
			<i>continued</i>

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Table 7 Suggested measures for auditing MS services in the NHS – continued				
Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)	
2. An individual who is suspected of having multiple sclerosis should be referred to a specialist neurology service and be seen rapidly within an audited time. The individual should be seen again after all investigations necessary to confirm or refute the diagnosis have been completed (also rapidly* within an audited time).	The time in weeks - from referral with diagnosis of 'possible MS' to being seen in a specialist neurology clinic and, in those requiring further investigation, the time in weeks - from being seen in the neurology clinic to being seen again after any investigations organised.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline that could be compared to other timescales suggested in other conditions. Any standard set should recognise that: - some people with MS will need urgent investigation because serious alternative disease (for example, spinal cord compression in case of transverse myelitis) is possible, whereas - other people with MS may have had symptoms for years and may not be overly concerned, but - in general, uncertainty is itself stressful.	Some people will be diagnosed as definitely having MS, a small number will be diagnosed as definitely having some other condition (eg stroke), a large number will not achieve a diagnosis of any alternative condition and the majority of these will be experiencing somatisation (symptoms associated with no known disease, possibly related to emotional dysfunction).	
3. Every health commissioning organisation should ensure that all organisations in a local health area agree and publish protocols for sharing and transferring responsibility for and information about people with MS, so as to make the service seamless from the individual's perspective.	The presence (or not) of agreed protocols for identifying and sharing responsibility - between different parts of health organisation, and - between health and social services. The time in weeks between initial contact about a problem with any service, including community NHS and social services, and contact with the 'final' service that can and does take responsibility for resolving the problem. The number of onward referrals made by services after initial contact before making contact with the final effective service.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline. Any standards set should: - focus on areas of concern locally (to people with MS and/or service providers and/or commissioners) initially - recognise that generic protocols (for example, for urinary incontinence) may be totally appropriate, and that not all protocols need to be MS-specific.	The presence or absence of protocols should be easily established, but it will be difficult to agree what protocols should exist as it would be unrealistic for every eventuality to have a protocol. Protocols could be given to every person with MS on making contact with the service to help them help themselves. It will be difficult to agree when the person has reached the final service. However, a method of people with MS collecting these data has been used and found to be effective, and so this is an achievable process.	

7 Monitoring quality: audit and governance

Table 7 Suggested measures for auditing MS services in the NHS – <i>continued</i>				
Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)	
4. All services and service personnel within the health care sector should recognise and respond to the varying and unique needs and expectations of each person with MS. The person with MS should be involved actively in all decisions and actions.	The number of complaints made to each service organisation that might reflect a failure to be responsive and to involve the person with MS actively.	There are no exceptions. These data are not currently collected, either specifically in relation to people with MS or specifically in relation to a service being responsive and patient-centred. It may not be appropriate to set a standard, and current NHS policies on complaints and the improvement of services should use the data.	As this standard should apply to all people making contact with NHS services (and other statutory services), it may not be necessary to separate out people with MS. A patient-centred audit of services would be able to monitor this without involving formal complaints.	
5. Health service professionals in regular contact with people with MS should consider in a systematic way whether the person with MS has a 'hidden' problem contributing to their clinical situation, such as fatigue, depression, cognitive impairment, impaired sexual function or reduced bladder control.	No data can realistically be collected on a routine basis. However, many specialist services may wish to develop and use a formal structured assessment protocol (centres participating in the risk-sharing scheme will do so) and for these services the data to collect would be: the number of people with MS who had a formal, documented (that is, able to be found in the notes) assessment on first contact in any episode.	These data are not currently collected by any service, and so initial data will be needed to establish a baseline for any service doing this. The data should only refer to an agreed initial 'screening' assessment aimed to detect major problems needing further attention An episode is a series of ongoing attendances, all of which concern a specified programme of care, and does not include monitoring visits.	Any specialist service that decides to use a formal structured approach to assessment should monitor its use.	
				<i>continued</i>

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Table 7 Suggested measures for auditing MS services in the NHS – continued				
Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)	
6. Every person with MS who has been seen by a specialist neurological or neurological rehabilitation service should be informed how to make contact with the service when no longer under regular treatment or review. The individual should be given guidance on when such contact is appropriate.	The presence (or not) of a formal procedure for responding to self-referral by someone with MS in the: - neurology service - neurorehabilitation service. The time taken between initial contact by person with MS, and initial clinical contact by the service.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline. It is important to recognise that 'initial clinical contact by the service' is: - more than a simple routine letter acknowledging the contact, but - not necessarily seeing the person in a clinic or their own home, and - implies a reasoned, personal response with action as necessary.	Often the response needed may be no more than reassurance or the provision of information. Some – perhaps many – centres already offer this level of service but probably in an intermittent and variable way.	
7. The commissioning health organisation should require all health care services including community services:	Presence (or not) in all health service organisations of a procedure to identify and report every new (and existing) pressure ulcer. Presentation of reports on each pressure ulcer identified in a person with MS. Count of a) new and b) prevalent pressure ulcers in people with MS. Presentation of an action plan derived from the report.	There are no exceptions. Data on pressure ulcers are not currently collected in relation to people with MS, and so initial data will be needed to establish a baseline. Ideally none should occur, but in reality some will occur. Not every pressure ulcer represents a direct failure of the health care system. Some will reflect failures in other organisations (for example, social services), others will reflect the choices of the person with MS and a few may be 'inevitable'.	Properly executed, this audit could save huge resources but it requires continued vigilance by all staff to detect and report pressure ulcers, which will be inhibited by any suggestion that the inquiry will attribute blame to any individual or organisation. Pressure ulcers may be first recorded or detected in one organisation that was not responsible for the person at the time of occurrence, but once detected a full investigation should still be initiated.	
*The Guideline Development Group debated the meaning of the word 'rapidly'. In this context, it is taken to mean that the exact time will vary according to clinical need but should, in the opinion of the development group, be no more than six weeks from referral to being seen by a neurologist, and a further six weeks until any necessary investigations are completed.				

8 Research questions

As the tables of evidence and the list of references show, there is a large volume of research relevant to the guidelines available. Despite this, the great majority of recommendations are graded D – dependent on consensus – although this is partly a consequence of the system of grading evidence (which emphasises only one research method – RCTs) and translating this to the strength of the recommendation. Although a few might become more highly graded if evidence from other neurological conditions, notably stroke, were to be included, it is nonetheless obvious that there is a great lack of evidence relevant to day-to-day clinical practice, particularly relating to the long-term effects of treatments. This section of the document puts forward some research priorities that arise from the work undertaken to develop the national clinical guidelines on MS.

Choosing research priorities is not easy. Most people, when asked, will focus on relatively specific questions that are undoubtedly important for particular patients, but do not necessarily address questions that have a large general impact. This problem has been discussed in relation to rehabilitation research priorities.⁶ Within the field of MS there are hundreds of potential specific research questions such as what dose of intramuscular botulinum toxin is effective in the biceps to control the development of contractures, do silver-coated catheters reduce morbidity if used long term, and is exercise specifically effective at reducing fatigue?

Those here have been chosen using the following criteria:

- the answer may benefit a large number of people with MS
- the process consumes significant resources.

The research priorities are given in no particular order.

8.1 Epidemiology of relapses, impairments and activity limitations

The epidemiology of multiple sclerosis has been well studied in relation to the aetiology of the disease. There are many studies on the incidence and prevalence of MS in different populations, in different parts of the world, in those who migrate, and in genetically related people. These studies have given some clues as to the cause of MS – as was the intention.

There have been some studies on the prevalence of the consequences of the disease, but these are relatively rare. They have used crude measures of impairment or disability, and they are often not fully representative. There have been no significant studies on the incidence of specific consequences of the disease, such as how many people in a given population will have a relapse each year. Indeed there is no agreed definition of a relapse, let alone studies on the reliability of its diagnosis. There are few studies investigating the mechanisms linking progressive impairments to limitations in activities and participation.

The lack of any firm data on the incidence, prevalence or severity of almost all impairments and activity limitations is one major problem in planning services, and in recommending service organisation. How many people have a relapse each year? How many people need a new wheelchair each year? How many people temporarily need a wheelchair? How many people have continuing faecal incontinence? How many people require more than four hours personal care each day?

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Furthermore there is relatively little good information on the economic consequences of the disease. How many people have to stop work? How many family members have to stop work on account of the disease? How much money does the NHS spend on managing the consequences of MS?

The current cost-sharing scheme has highlighted the extreme poverty of useful information available to model the possible cost-effectiveness of expensive disease-modifying drugs. The scheme will not generate any information because it is not based on an epidemiologically sound sample.

This research recommendation does not relate specifically to any recommendation within the guidelines but without the information this recommendation should deliver, health commissioners will be unable to make estimates about the resources needed to enable any of the recommendations.

RECOMMENDATION

- R183** There should be a prospective study on an epidemiologically sound defined population to establish reasonable estimates of:
- the frequency of relapses sufficient to cause increased limitation on activities
 - the prevalence and yearly incidence of the most common impairments described in this guideline document
 - the prevalence and yearly incidence of the most common limitations on activity including work described in this document
 - the direct and indirect costs of the condition and how they relate to levels of limitation on activity, including not only NHS direct costs but all direct costs.

8.2 Diagnosing multiple sclerosis

There is much evidence that the MRI brain scan is abnormal in most people with MS. Further, it can indicate continuing disease activity in the absence of new impairments and this disease activity is dramatically reduced by disease-modifying drugs. There is also reasonable evidence that an MRI scan can predict reasonably the likelihood of MS developing in someone with an isolated first attack of optic neuritis.

However, the utility of MRI scans in clinical practice (as opposed to as part of research) is still not supported by much evidence, although major resources are involved in their use. Should MRI scans be offered to everyone, even if the diagnosis is clinically confirmed? Should second or subsequent MRI scans ever be undertaken?

Moreover the utility of other ancillary investigations is also unknown (given the predominance of MRI scanning). Is CSF examination ever helpful in confirming the diagnosis? When are visual evoked potentials useful?

This research recommendation relates primarily to recommendation R29 and may influence key recommendation 7 (Section 7).

RECOMMENDATION

- R184** There should be a prospective study on an epidemiologically sound population to investigate the most cost-effective protocols for investigating people presenting with (potential) MS to establish:
- the sensitivity and specificity of MRI scanning in people with different levels of clinical diagnostic certainty
 - the role of other investigations in confirming or positively excluding the diagnosis of MS
 - the prognostic value of MRI scan information over five years.

8.3 Rehabilitation assessment protocols

In sections 5 and 6 there is great emphasis upon initial identification of specific impairments or activity limitations. This is emphasised because specific treatments can only be given if a specific difficulty is recognised. In addition, it is important to have as good an understanding of a situation as possible before initiating interventions, if only to avoid doing harm (and usually to guide one on the best course of action). Yet, as has also been emphasised, people with MS can have one or more of a large range of problems, and both the person with MS and the clinician will rapidly become fatigued and fed up by long, detailed assessments of each potential problem.

Consequently, research is needed on the best way to approach the identification (detection) of impairments and activity limitations. This research area is *not* concerned with developing measures; it concerns the development of short, simple protocols or 'data collection tools' for identifying possible areas of need, screening for referral on to other specialist/non-specialist staff. These protocols would be designed for use by any person making contact with the person with MS, with the priority being members of the neurology and neurological rehabilitation services. The protocols should also extend possibly to monitoring people in a non-threatening and efficient way when no longer in routine contact with any service.

RECOMMENDATION

- R185** There should be a programme of research to develop and evaluate protocols, procedures or data collection tools that can be used by any profession to:
- identify the probable presence of most common impairments
 - approximately quantify activity performance in personal and household activities of daily living
 - identify areas of activity limitation that are present in people with MS.

8.4 Specialist neurological rehabilitation services

The guidelines recommend repeatedly that people with MS with any impairments or limitations on activities or social participation should be seen by a specialist neurological rehabilitation service. The recommendation is based upon some MS-specific evidence, but primarily draws upon evidence from stroke and other conditions. There are currently few specific neurological rehabilitation services in England and Wales, and certainly a completely inadequate level of services to meet even a small percentage of the needs of people with MS (let alone other neurological conditions).

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Consequently this recommendation will have a major impact upon the allocation of health resources, partially through reorganisation of current resources but mainly through provision of new services. The evidence suggests that this may well be an effective and efficient use of resources – the evidence from stroke suggests that better outcomes may be achieved with similar or possibly less resources. Ultimately the cost of these services may well still be less than the cost of interferon beta. However it is notable that even strong evidence in favour of stroke units has not affected health commissioners much, and health commissioners may require more direct evidence.

Given the differing circumstances around England and Wales, with some areas being urban, others rural, and with some areas preferring outpatient and others inpatient services, it is probably best not only to investigate whether specialist services are effective but also whether one pattern of delivery is better than another. This research should certainly also investigate the health economic aspects of any service, and it would be important to consider whether there are any disbenefits for people with MS.

RECOMMENDATION

- R186** A programme of research into the relative costs (direct and indirect) and benefits (direct and indirect) should be undertaken comparing:
- current rehabilitation practice with rehabilitation given by a specialist neurological rehabilitation service
 - primarily inpatient with primarily outpatient or home-based neurological rehabilitation.

8.5 Acute relapse management: methylprednisolone and rehabilitation

Although some people with MS never have a relapse, having a progressive form from the onset (or a very benign form), it is likely that most people will have several relapses if not more. At present, treatment often involves hospital attendance if not admission, and the resources devoted simply to giving medical treatment are considerable. In addition many relapses are associated with a significant increase in activity limitation, often sufficient to require hospital admission.

Although there are many trials of many treatments for acute relapse it is still extremely difficult to give strong recommendations based on the evidence. Many questions remain unanswered, such as what dose of steroids, how long for, is oral as good as intravenous, are different types of steroids equivalent, how frequently can short courses be given, and what are the significant risks and side effects?

This lack of useful evidence needs to be set in a larger context. There is minimal evidence available on the diagnosis of a relapse and its distinction from minor progression, worsening associated with an intercurrent illness or simple normal fluctuations in a person's clinical status. In addition, the only way to access rehabilitation is often through hospital admission, and rarely can care needs be met quickly at home also often requiring hospital admission.

RECOMMENDATION

- R187 A programme of research should investigate the management of acute relapse including comparing the costs and benefits associated with policies of:
- oral methylprednisilone against intravenous methylprednisolone
 - hospital admission with early discharge once rehabilitation has started and support has been arranged against home care with rapid response care and rehabilitation input (with steroids if indicated).

8.6 Disease-modifying therapies

A recent publication has questioned the cost-effectiveness of interferon beta and glatiramer acetate and the current risk-sharing scheme.⁴⁶¹ The amount of money spent by the NHS on disease-modifying therapies (DMTs), including not only the drugs themselves but all the extra resources needed to run the scheme and to monitor the people on the scheme, is large. And this scheme only affects less than 15% of people with MS and many of those eligible withdraw due to side effects.

The guideline developers therefore agreed (by a large majority) that further well-designed research into DMT was a high priority, including impartial evaluation of their effectiveness in terms of reducing limitations on activities, the costs associated with any benefits at the level of activities, the type of side effects seen in both the short and long term, and the duration of any benefit.

RECOMMENDATION

- R188 A programme of research into disease-modifying treatments sponsored and run by an organisation independent of either health purchasers or pharmaceutical companies should be set up to investigate interferon beta, glatiramer acetate, linoleic acid and azathiaprine (and any other newly licensed medicines) in terms of:
- benefits, specifically in terms of activity performance
 - costs, including the medicines and all associated monitoring, etc
 - disbenefits, both immediate side effects and longer-term rates of withdrawal and side effects
 - effects of stopping treatment after two and four years.

8.7 Relationship between impairments and limitations in activities

The links between individual impairments and combinations of impairments and the resultant limitations on activities, and how these links may be affected by treatments including changing the environment, are unknown. If more were known, more effective interventions could be researched and undertaken. Investigations will require a prolonged programme of research based on epidemiologically sound populations of people, not only with MS but also with other neurological conditions.

RECOMMENDATIONS

- R189 A programme of research extending over many years should be instigated to investigate the nature and extent of relationships between impairments and activities and how they change over time.

APPENDICES

Appendix A: Expanded model of illness (WHO ICF plus)^{467,468}

A way of describing someone's situation

People with long-term conditions such as MS may face a large range of changes in, or effects on, their life. When considering their situation and how it might be analysed and improved, it is helpful to have a consistent framework or way of categorising the important factors that need consideration. The World Health Organisation developed their International Classification of Impairments, Disabilities and Handicaps (ICIDH) in 1980 as a way of classifying the consequences of disease. This was revised and expanded into the International Classification of Functioning (ICF) in 2001.⁸

Table A1 Expanded model of illness (WHO ICF plus)

'Location' of description	Subjective/internal (experience, attributions and beliefs of the patient)	Objective/external (observations made by, and implications drawn by, others)
Level of description (term used)		
Organ within person (pathology)	<i>Disease:</i> Label attached by person, usually on basis of belief and experience.	<i>Diagnosis:</i> Label attached by others, usually on basis of investigation.
Person (impairment)	<i>Symptoms:</i> Somatic sensation, experienced moods, thoughts etc.	<i>Signs:</i> Observable abnormalities (absence or change), often elicited explicitly; <i>and</i> deficits assumed from observations.
Person in environment (behaviour/'activities')	<i>Perceived ability:</i> What person feels they can do and cannot do, and opinion on quality of performance.	<i>Disability/activities:</i> What others note person does do, quantification of that performance (not what others think should do).
Person in society (roles/'participation')	<i>Life satisfaction:</i> Person's judgement or valuation of their own role performance (what and how well).	<i>Handicap/participation:</i> Judgement or valuation of important others (local culture) on role performance (what and how well).
Context of illness		
Personal	<i>'Personality':</i> Person's attitudes, expectations, beliefs, goals, outlook, reasoning style, etc.	<i>'Past history':</i> Observed/recorded behaviour prior to and early on in this illness.
Physical	<i>Personal importance:</i> Person's attitude towards specific people, locations.	<i>Resources:</i> Description of physical (buildings, equipment etc) and personal (carers etc), resources available.
Social	<i>Local culture:</i> The people and organisations important to person, and their culture; especially family and people in same accommodation.	<i>Society:</i> The society lived in and the laws, duties and responsibilities expected from and the rights of members of that society.
Totality of illness		
Quality of life –summation of effects	<i>Contentment:</i> Person's assessment of and reaction to achievement or failure of important goals; <i>or</i> sense of being a worthwhile person.	<i>Social involvement:</i> Extent of positive interaction with society, contributing to social networks.

Appendix B: Issues for people with MS and their carers¹⁴

Table B1 Issues raised through focus groups and interviews

Issue	Links to recommendations
Diagnosis	
The time diagnosis takes – variation in services, from speedy to experiences of long delays.	Section 3.3.1 recommends the provision of ready access to a specialist neurological service for diagnosis. A local implementation point recommends that guidelines are set for how timescales for the confirmation of a diagnosis will be met locally. Diagnosis is primarily based on clinical history and examination – further tests to be carried out only if diagnosis in doubt (Section 4.1).
Misdiagnosis and the impact of this on peoples' lives.	Referral system recommended such that the diagnosis is made by a doctor with specialist neurological experience (Section 4.1).
Poor communication with or by medical staff at a devastating moment in your life.	General recommendations on communication are made in Table 2 (Section 3). Specific recommendations on communicating the diagnosis can be found in Section 4.2.
Support and information needs	
Access to support – the need for immediate access to someone knowledgeable to talk to at the time of diagnosis.	Recommendation in Section 3.1.2 to consider the provision of emotional support to the person with MS from the time of diagnosis onwards. Section 4.2 also deals with immediate needs for support and information – 'the person with MS should be put in touch with or introduced to a skilled nurse or other support worker, ideally with specialist knowledge of MS ... and counselling experience'.
Importance of a single contact point for people with MS, to provide ongoing information and support; provision of advice and sign-posting to other advice and support services. Could be an MS nurse, a GP, generic supporter or key worker knowledgeable about MS. Able to provide immediate advice and treatment in times of crisis.	Recommendation in Section 3.3.2 states that there should be someone within the MS-related services that ensures services are coordinated and collaborative. For the person with MS, they should have access to a person to assist in identifying and communicating local information sources and to facilitate access to resources and services needed.
Carers identified the need for someone to take responsibility for coordinating all aspects of care, eg organising annual review of drugs.	Recommendation to provide an annual review of support needs for people with MS who are 'severely impaired and markedly dependent', in Section 3.5.
To be in contact with people who look at physical disability in the context of the whole person, not as problems in isolation.	There are acknowledgements of the need to consider all aspects of a person with MS's situation in the introductions to sections 3, 5 and 6. It is a theme that the guideline developers have been committed to, and which runs through the whole document.
Importance of access to advice on how to stay in work, including the adaptation of the physical environment.	Recommendations in Section 5.3 includes this. Reference is made to accessing specialist advisers and services where necessary in order to stay at work.
	<i>continued</i>

Appendix B: Issues for people with MS and their carers

Table B1 Issues raised through focus groups and interviews – *continued*

Issue	Links to recommendations
Support and information needs – <i>continued</i>	
Important role of voluntary sector recognised, providing access to information.	Table 2 (Section 3) refers to the provision of information, including national sources, as does Section 4.2 – in particular recommendation R38.
GP role	
People with MS are positive about the general care provided by GPs, but acknowledge a GP isn't an expert in MS (and they need support and information themselves) – would like to see a person in each practice trained in the needs of people with MS.	This is covered by the two recommendations in Section 3.3.2.
Hospital services	
Patchy provision of neurologists – people with MS often fall through the net. Not enough emphasis on the social or practical side of having MS.	Section 3.3.1 recommends that every health commissioning authority should ensure its population has ready access to specialist neurological services for the initial diagnosis of MS and subsequent symptoms. Reference to the importance of considering leisure and social interaction is made in Section 5.4.
Problems with lack of access to case notes and full information at the time of a relapse – like starting again each time.	Importance of information sharing at the interfaces described in Section 3.3.2.
Physical problems mentioned specifically by people with MS	
There was very little discussion about specific physical problems associated with having MS. Participants recognised there is no 'cure' and were more interested in being able to get on with their lives. The following were mentioned, but not discussed: • bladder problems • mobility and balance • gait • speech • vision • hearing.	Sections 5 and 6 deal with these areas. Recommendations about bladder problems can be found in Section 6.2. Issues around mobility, balance and gait are dealt with in Sections 5.5 and 6.4. Section 6.15 makes recommendations about dealing with speech problems. Section 6.8 deals with the assessment, provision of equipment and referral to specialist ophthalmology clinic where necessary, for problems of vision.

continued

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Table B1 Issues raised through focus groups and interviews – *continued*

Issue	Links to recommendations
Psychological problems mentioned specifically by people with MS	
Cognitive problems.	Section 6.10 includes offering a cognitive assessment and specialist advice when appropriate.
Frustration/lack of confidence.	
Psychological problems mentioned specifically by people with MS – <i>continued</i>	
Mood swings.	Section 6.11 deals with emotionalism and Section 6.12 depression, each of which could be factors associated with mood swings.
Depression.	This is discussed in Section 6.12.
Isolation. For people with mild-moderate MS this was about having someone to talk to, with counselling skills. For people with more severe MS it was isolation in the home and lack of mental stimulation.	The need for access to support and counselling is referred to in Section 4.2. Section 5.4 emphasises the need for people with MS to be supported in maintaining their chosen leisure and social activities.
Relationships	
Problems with relationships with partner – including breakdown or new relationships. Family carer feels they become a nurse, rather than a partner.	Sections 3, 5.7 and 6.16 all deal with different aspects of this. Support for carers is a recurring theme.
Impact on family life, children – young carers carrying out inappropriate tasks, including missing school to provide care.	A recommendation to consider the emotional and physical health of any children in the household of a person with MS is included in Section 3.1.4.
Recognition needed of the immensely difficult task of caring, both physically and emotionally.	Recommendation in Section 3.1.4 (also Section 5).
Anxiety within the family and the person with MS about possible hereditary influences.	This should be dealt with in the information given to people with MS about the disease (Section 4.2).
Support needs of partners and families must be recognised – should include advice and information, counselling and access to respite care.	Recommendations about the provision of support to family and informal carers are given in Section 3.1.4.

continued

Appendix B: Issues for people with MS and their carers

Table B1 Issues raised through focus groups and interviews – *continued*

Issue	Links to recommendations
Respite care	
Better information needed on access to and availability of respite care – for person with MS and carer.	Reference to the provision of respite support can be found in Section 3.5 with a specific recommendation.
Variability in costs and quality of respite care highlighted – participants felt there was a need for a national benchmark.	
Need for a choice in styles and facilities of respite care, tailoring to the needs of an individual.	
Important factors for people with MS in respite care – care staff with time to talk to residents, treating the person with MS as a person.	
Treatment	
Physiotherapy – highly regarded, but strong feeling that continuous provision is needed rather than one-off sessions. Limited NHS provision criticised. Most provision currently in hospital settings – very little in the community – often stops once at home.	Section 5 (on rehabilitation) and Sections 6.4 and 6.6 (weakness and ataxia) relate to physiotherapy interventions.
Occupational therapy – long waits for assessment and provision of equipment criticised. Assessment usually only as a result of a hospital admission.	Section 5.7 deals specifically with the provision of equipment adaptations.
Speech and language therapy – regular treatment not available.	Recommendations about dealing with speech and swallowing difficulties can be found in sections 6.14 and 6.15.
Importance of adapting support and provision to individuals' needs stressed throughout.	Throughout the document/recommendations.
Need for more MS specialists (all professions) in hospital and the community – real anxiety about quality of care, particularly from carers.	Reference to the need for specific specialist members of a rehabilitation team in Section 3.3.1.

Source: Focus groups and interviews held with people with MS and their carers in July – September 2001

Appendix C: Literature searches

Table C1 Databases searched

Database	Date range searched
Cochrane Library	Pre Sept 2002
DARE	Pre Sept 2002
DARE (admin database)	Pre Sept 2002
Current Controlled Trials	Pre Sept 2002
National Research Register	Pre Sept 2002
Clinical Trials	Pre Sept 2002
Inside Conferences	1993 to September 2002
SIGLE	1976 to September 2002
Medline	1966 to September 2002
Embase	1980 to September 2002
Cinahl	1982 to September 2002
PsycINFO	1887 to September 2002
AMED	1985 to September 2002

Inclusion criteria

Studies identified by the searches were screened for relevance. Papers considered to be potentially relevant were ordered and screened for inclusion. Due to time constraints studies were assessed for relevance and inclusion by one reviewer only. Where any difficulties were encountered these were resolved by discussion between the two reviewers working on the project. All papers were assessed for inclusion using the same form and the reviewer made the decision on whether to include the study based on the criteria listed below.

Table C2 Inclusion criteria for 3.1.2 and 3.1.4

Study design	SRs and primary studies of any design
Intervention	Any intervention aimed at supporting people with MS, family members or other socially important people
Condition	People with MS, stroke, TBI or spinal cord injuries
Outcomes	Any outcomes reported

Sections 3.1.1, 3.1.3, 3.2, 3.3, 3.4 and 3.5 were not included in the review process

Appendix C: Literature searches

Table C3 Inclusion criteria for 4.1 and 4.3

Study design	SRs or diagnostic accuracy studies
Index test	Any test used for the initial diagnosis or diagnosis of a subsequent relapse, to monitor disease progression, or to determine the sub-type of MS
Reference standard	Any reported reference standard was considered acceptable (including patient follow-up)
Outcome	Studies must report at least sensitivity and specificity, the DOR or a ROC analysis
Population	Studies should aim to diagnose patients with MS

Table C4 Inclusion criteria for 4.2

Study design	SRs or primary studies of any design
Intervention	Any intervention related to the provision of information regarding the condition or on how patients should be informed of their diagnosis
Condition	Only primary studies conducted with people with MS. SRs for any condition
Outcomes	Any outcomes reported

Table C5 Inclusion criteria for 4.4 and 4.6

Study design	SRs, RCTs and CCTs
Intervention	Any intervention aimed at treating acute worsening, optic neuritis, transverse myelitis or reducing disease progression
Condition	People with MS
Outcomes	Studies must report at least one clinical outcome

Table C6 Inclusion criteria for 4.7.1, 4.7.2, 4.7.3, 5.2, 5.3, 5.4, 5.5, 5.6 and 5.7

Study design	SRs and primary studies of any design
Intervention	Any intervention related to the assessment of rehabilitation or disability or which aim to alter the environment to maximise independence and safety
Condition	People with MS
Outcomes	Any outcomes reported by the studies will be considered

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Table C7 Inclusion criteria for Section 6

Study design	<i>Assessment:</i> SRs and diagnostic accuracy studies <i>Intervention:</i> SRs, RCTs and CCTs
Intervention	Any intervention aimed at treating specific symptoms associated with MS
Condition	Only primary studies conducted with people with MS. SRs in relevant conditions for symptoms on which there is insufficient MS specific evidence available*
Outcomes	<i>Assessment:</i> studies must report at least a diagnostic outcome measure <i>Intervention:</i> studies must report at least one clinical outcome

*Insufficient MS evidence was available for the 6.2, 6.3, 6.5.2, 6.6, 6.9, 6.11, 6.13, 6.14, 6.15, 6.16, 6.17. Therefore SRs were included for the relevant conditions

Appendix D: Searching for health economics evidence

Searches and data sources

No study design criteria were imposed *a priori* as it was already known that little economic evidence was available, and it was thought best not to restrict the searches at this stage. The search strategies were designed and implemented by Catherine Beverley, Systematic Reviews Information Officer in the School for Health and Related Research at the University of Sheffield. All reviewing was carried out by the health economist. The following databases were searched: Medline, Embase, the Centre for Reviews and Dissemination (CRD) (including the Database of Abstracts of Review of Effectiveness (DARE)), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA)), the Office of Health Economics Health Economic Evaluations Database (OHE HEED) and Econlit.

► Inclusion assessment

The titles, and where available the abstracts, were screened to assess whether the study met the following inclusion criteria.

Patients – At least some of the patients had MS. After the initial searches, supplementary searches in relation to specific questions were carried out, without the requirement that some patients had MS.

Economic evidence – The study was an economic evaluation or included information on resources, costs or specific quality of life measures. Selected quality of life measures were SF-36, EQ-5D or HUI (in conjunction with EDSS). These measures are the most useful for economic analysis of outcomes since they can be used to generate utility values in a modelling framework, and since they are generic measures they are useful for comparative purposes.

Study design – No criteria for study design were imposed.

Summary results

The searches found 464 unique papers. The titles, abstracts and CRD/OHE HEED commentaries (where available) were reviewed, and 139 potentially useful papers were identified. The vast majority of these studies included only people with MS, but a small number make comparisons with other diseases. It was found that:

- 32 studies were solely concerned with quality of life (QoL) and contained no cost or resource information
- 38 studies were general resource use/cost studies, which consider the cost of MS to society and/or the individual with MS
- five studies were ‘needs assessments’.

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▷ Summary by type

Six systematic reviews (of which four were HTA reports) covered:

- one on treatments for pain and spasticity (HTA)
- one on treatments for fatigue (HTA)
- one on immunomodulatory drugs (HTA)
- one on role of specialist nurses (HTA)
- one on corticosteroids for acute exacerbations
- one on overview of azathioprine treatment.

Nine economic analyses based on RCTs included:

- three on intrathecal baclofen therapy for spasticity
- three on oral vs intravenous corticosteroids in acute relapses
- one on immunoglobulin in secondary progressive MS
- one on the effect of rehabilitation on disability
- one on reducing the period of immobilization following pressure sore surgery
- one on the effects of physiotherapy on mobility.

Thirty-eight studies considering the general costs and/or resource use of MS, all based in Europe, the US or Canada, included:

- 12 on cost of illness (COI) studies (eight using a bottom-up costing method)
- two reviews of COI studies
- a further three studies use bottom-up costing but do not consider a full COI
- 13 cost studies considering indirect costs, as well as direct costs*
- eight studies considering resource use but not including any cost information (of which five are patient surveys).

Five studies considered needs, specifically unmet needs, and included:

- three patient/carer surveys (from Europe, the UK and the US)
- one review
- one local study in Oxfordshire, which used a variety of data sources including observational data, audit and interviews.

Thirty-nine studies considered QoL as measured by the generic instruments outlined above, and included:

- 32 QoL studies containing no cost or resource data
- one study (a survey in Canada) considering QoL for carers of people with MS
- four studies making comparisons with QoL in other chronic conditions.

* 'Direct costs' are defined as all the goods, services and other resources that are consumed in the provision of an intervention, or dealing with side effects linked to the intervention. These costs can be medical and non-medical and can be incurred by the NHS, by patients and/or their carers and by wider society (eg social services). 'Indirect costs' are the lost productivity suffered by the economy as a result of an individual absence from work through illness, decreased efficiency or premature death.

Appendix E: Health economics of comparing different methods of administration of methylprednisolone in the treatment of acute relapses in multiple sclerosis

Introduction

The group were interested in finding out more about the potential costs and benefits of different methods of administering high-dose corticosteroids for the treatment of acute relapse. It is important to note that clinical practice varies widely and this document is based on 'usual' treatment, to the extent that it is possible to state what this is.

There is little clinical evidence available in this area. The evidence review (see Section 4.4) identified four trials comparing methylprednisolone with placebo and two trials comparing oral with intravenous methylprednisolone. The latter two trials are relevant to the current question and they were both carried out in the UK; unfortunately they are small and also difficult to compare given the different regimens used. Neither included any collection or analysis of resource use data. A further search for economic evidence in this area, which imposed no quality criteria on studies, found only one relevant paper. This is a survey of 212 consultant neurologists carried out in March 1997, which questioned them on their use of corticosteroids in the treatment of MS.

Formal economic modelling which attempts to systematically evaluate costs and benefits is not possible without relevant clinical data. Instead the costs and benefits of these three methods of administration were itemised in a way that facilitates comparisons.

While there are a number of choices of drugs and methods of administration, the focus here was on the use of methylprednisolone administered in three ways:

- hospital intravenous (inpatient or day case)
- home intravenous
- oral.

Background

Hospital administration of intravenous methylprednisolone is the most common treatment for relapse. In many cases the person with MS will need to be admitted to hospital as a result of the disability caused by the relapse and in these cases they will usually receive intravenous methylprednisolone during their hospital stay. Where admission for disability is not necessary, many people will still be admitted in order to administer intravenous corticosteroids.

The hospital intravenous category considered here largely refers to inpatient stays, as day case administration is rare. A recent survey suggested that only 7% of neurologists could offer administration as day case.⁴⁶² Admission to hospital is probably more common in those areas

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where specialist neurology units are not available, as there are few alternatives for administering high dose corticosteroids in these cases. Day case administration (and home intravenous) will be more common in areas with specialist units.

It is important to note that the only efficacy information considered here comparing oral and intravenous methylprednisolone comes from trials where intravenous administration was offered as a day case by the pharmacy at hospitals with specialist centres. This may not be representative of the usual method of administration of intravenous methylprednisolone across England and Wales.

Home intravenous administration is included here as it was of interest to the group. However, it is not readily available in most parts of the country. The same survey suggested that only 5% of neurologists had the facilities to offer home intravenous treatment with methylprednisolone.⁴⁶² There is no information on the number of GPs who may be able to offer this service.

The survey of neurologists may be misleading as in many parts of the country people experiencing a relapse will be managed by their GP (who would usually take advice from a neurologist). Once GP contact is established the care pathway will depend on the GP's and patient's experience of MS and relapse, the GP's relationship with the patient and local access to neurology services.

Oral corticosteroids are used by some GPs and some neurologists to treat relapse.

The Tremlett survey found that 74% of neurologists would recommend oral administration instead of intravenous methylprednisolone at sometime, although the most popular response (48%) was for 'occasional use' (<25% of cases).⁴⁶² Oral prednisolone was the most common treatment, with only 23% recommending oral methylprednisolone. There is no evidence on the comparative efficacy of prednisolone against methylprednisolone.

Making comparisons

In the absence of appropriate clinical or economic evidence Table E1 is 'think piece' in an effort to encourage full consideration of potential costs and benefits when different methods of administration are being compared.

The potential costs and benefits have been classified under six headings.

▷ Effectiveness

The methods are compared in relation to their effect on relapse. The only formal comparative clinical evidence comes from two RCTs comparing oral methylprednisolone with intravenous administration as a hospital day case;^{124,125,134} these show equal efficacy. There is no formal clinical evidence comparing home intravenous administration with either hospital intravenous or oral administration. Assuming comparable regimens there is probably no reason to expect a difference in efficacy between home and hospital intravenous administration. However, this does not take into account potential problems or side effects of treatments.

Appendix E: Health economics of comparing different methods of administration of methylprednisolone

▷ NHS resources

There is no formal evidence on the NHS resource use involved in any of the methods of administration. In terms of the pure drug cost, an intravenous course of methylprednisolone costs just over twice as much as an oral course.⁶ The costs of intravenous administration are much higher, especially if they involve an inpatient stay (although the stay may not always be solely for drug administration). Day case administration is likely to be cheaper than an inpatient stay, but this facility is probably only available at larger hospitals with specialist services.

Home intravenous administration requires equipment provision and involves staffing costs for home visits.

A study in a Toronto teaching hospital which followed 92 patients for 12 months showed that inpatient administration of methylprednisolone was more expensive than outpatient or home administration.⁴⁶³ This finding was robust to all sensitivity analysis. However there was no clear finding on the comparative costs of home against outpatient treatment, and this depended on assumptions made about the relevant overheads and staff costs.

▷ Quality of life

There is no formal evidence on the effect of alternative methods of methylprednisolone delivery on quality of life. Positive effects on quality of life would be expected to result from alleviation of the symptoms associated with relapse. It is also probably reasonable to assume that intravenous procedures would have a greater adverse affect on QoL than oral administration. It is usually assumed that QoL is adversely affected by hospital admission, but it is also important to consider the substantial burden imposed by daily hospital visits.

Home treatment is likely to be preferred in terms of QoL. An Italian study by Pozzilli *et al* comparing a home-based management program with hospital care for MS found a significant benefit in favour of home-based care for four of the eight dimensions of the SF-36:* general health, bodily pain, emotional role and social functioning.⁴⁶⁴

▷ Patient and carer costs

There is no formal evidence on the patient burden associated with alternative methods of methylprednisolone delivery. The main costs will arise from absence from work which are due to the relapse itself and also from any costs of drugs or equipment borne by the patient. In addition day case administration will require travel to hospital which involves time and possibly direct financial burden.

▷ Side effects, tolerability etc

The trials of oral *vs* intravenous administration reported similar (minor) side effects in both arms. The risk of infection is greater from intravenous treatment, but it is not clear whether there may be a greater risk at home or in hospital.

* The SF-36 is a generic health-related quality of life instrument that has been used in many studies of multiple sclerosis treatments and has been shown to be a valid and sensitive measure of QoL in the population of people with MS. The SF-36 contains 36 items covering eight dimensions of health: general health, bodily pain, physical functioning, emotional role, physical role, mental health, social functioning and vitality.

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It has been argued that oral therapy, being easier than intravenous, might be used more frequently or courses extended when clinical response is lacking. This increased 'routine' use would increase the chances of corticosteroid-induced side effects. It may also increase the chances of the therapy being used inappropriately.

▷ NHS delivery issues

There is geographical variation in the availability of home-based intravenous treatment and day case treatment at hospital. Home treatment requires equipment and the availability of appropriate staff, while day case treatment requires facilities that are unlikely to be available at DGHs.

Summary

Many factors should be considered when comparing alternative methods of methylprednisolone delivery and there is little formal evidence on any of these. There is no clearly dominant treatment in terms of clinical effectiveness or resource use.

Appendix E: Health economics of comparing different methods of administration of methylprednisolone

Table E1 Comparing methods of administering methylprednisolone (compare row with column)

	Oral	Hospital IV	Home IV
Oral		Effectiveness: equal (2 RCTs) NHS resources (no evidence) • lower drug & admin costs* • no hospitalisation • Quality of Life (no evidence) • = relief of symptoms? • non-invasive vs invasive • higher than if in hospital? Patient/carer costs (no evidence) • absence from work • prescription charges? Side effects etc (little evidence) • equal ('minor') • increased routine use? NHS delivery issues (no evidence) • no major issues?	Effectiveness: no evidence NHS resources (no evidence) • lower drug & admin costs* • Quality of Life (no evidence) • = relief of symptoms? • non-invasive vs invasive. Patient/carer costs (no evidence) • absence from work? • prescription charges ? Side effects etc (little evidence) • increased routine use? NHS delivery issues (no evidence) • no major issues?
Hospital IV	Effectiveness: equal (2 RCTs) NHS resources (no evidence) • higher drug & admin costs* • hospitalisation (or day case) Quality of life (no evidence) • = relief of symptoms? • invasive vs non-invasive • hosp. (or daily visits) Patient/carer costs (no evidence) • absence from work • travel for day case Side effects/tolerability • equal ('minor') • risk of infection NHS delivery issues (no evidence) • Avail. of day case service • appropriateness of bed use		Effectiveness: no evidence NHS resources (no evidence) • = drug costs? • hospitalisation (unless day case) Quality of life (no evidence) • relief of symptoms • hospitalisation (or daily visits) Patient/carer costs (no evidence) • absence from work • travel for day case Side effects/tolerability • no evidence • risk of infection NHS delivery issues (no evidence) • availability of day case service • appropriateness of bed use
Home IV	Effectiveness: no evidence NHS resources (no evidence) • higher drug & admin costs* • costs of monitoring • home equipment costs Quality of life (no evidence) • = relief of symptoms? • invasive vs non-invasive Patient/carer costs (no evidence) • absence from work Side effects/tolerability • risk of infection • less tendency for routine use? NHS delivery issues (no evidence) • availability of equipment • staff for home visits	Effectiveness: no evidence NHS resources (no evidence) • = drug costs? • costs of monitoring • home equipment costs Quality of life (no evidence) • relief of symptoms • home vs hospital Patient/carer costs (no evidence) • absence from work Side effects/tolerability • risk of infection NHS delivery issues (no evidence) • availability of equipment • staff for home visits	

* Drug costs have been estimated using regimens from Barnes *et al*¹³⁴ and drug costs from BNF43 (September 2002). Intravenous methylprednisolone 1000mg daily for 3 days = £41.31. Oral methylprednisolone 48mg day for 7 days, 24mg day for 7 days, 12mg day for 7 days = £18.48.

Appendix F: Economic evidence for nuclear magnetic resonance imaging scans in the diagnosis of MS

Magnetic resonance imaging (MRI) is a relatively expensive diagnostic technology (costing approximately £200 per scan*), and a relevant question is whether the benefits of MRI are worth the additional cost. While safety evaluations indicate that non-contrast MRI is safe for most people including pregnant women,⁴⁶⁵ and the procedure is not painful or invasive, many people find it uncomfortable. Benefits from MRI in diagnosis of MS may arise from the medical information it provides (which in turn informs disease management) and also from the potential psychological value of the information to the patient. In addition MRI may reduce the need for other tests, and in particular the need for EPs, CSF examination and lumbar puncture has diminished in recent years.⁴⁶⁶

How might MRI affect care?

In MS the majority of interventions are targeted at symptoms rather than the disease itself, and the extent to which symptom management is influenced by diagnosis is unclear. A review of evidence suggested that MRI has had little direct impact on therapeutics or patient outcomes.⁴⁶⁵ However, it seems sensible to suggest that errors of diagnosis, delay in diagnosis and invasive tests will all occur more often if MRI is not carried out (expert opinion).

The availability of the disease-modifying therapies (DMTs) interferon beta and glatiramer acetate under the risk-sharing scheme may have implications for the use of MRI in diagnosing MS. DMTs are available to people with a diagnosis of relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) in which relapses are the dominant feature, and who meet the Association of British Neurologists' criteria for treatment. It is estimated that between 7,500–9,000 people in England and Wales may be eligible for treatment (approximately 12.5% to 15% of the estimated total number of people with MS). The ABN criteria are not dependent on diagnosis via MRI and it is unclear how many of the eligible population would require an MRI scan to confirm diagnosis before access to treatment (the majority of people will already have had an MRI scan before this point).

Nevertheless, in countries where DMTs have been more commonly used than the UK, MRI is often used to aid the decision on whether to start, stop or modify therapy. This may mean that the risk-sharing scheme does increase the requests for MRIs.⁴⁶⁶ The new international panel criteria which recommends MRI for diagnosis on people with clinically isolated symptoms is also likely to increase demand for MRI scans.⁵⁵

Existing cost-effectiveness studies

Only two studies were identified;^{93,94} these looked at the targeting and cost-effectiveness of MRI for people with equivocal neurological symptoms who may have MS. Both studies employ

* Cost estimates vary between £155 and £286 for an MRI within the NHS.

Appendix F: Economic evidence for nuclear magnetic resonance imaging scans in the diagnosis of MS

decision analytic models, which are particularly valuable in evaluating diagnostic technologies since they enable modelling of alternative scenarios with their associated costs and benefits given available information, and they also allow identification of key areas of uncertainty around clinical utility and cost-effectiveness which can guide future research. Both studies are by the same authors and represent developments of the same piece of work; only the latest study is included in the evidence tables.⁹³

This study made good use of information available at the time (early 1990s) and also employed comprehensive sensitivity analysis to deal with the large amount of uncertainty surrounding the key model parameters. The study concluded that MRI was not cost-effective in people with low prior probability of MS (unless the diagnostic information has a very high psychological value to patients). As the probability of disease increases, further MRI use becomes cost-effective. Given the fact that this study is relatively old (in an area where the technology is developing) and that it is based in the US, there is little value in citing specific cost-effectiveness ratios. Nevertheless, the results do question the usefulness of routine use of MRI in people where the probability of MS being present is low unless there is a reasonable probability of an alternative diagnosis that can also be diagnosed using MRI being present.

The results from both studies revealed that the key areas of uncertainty were the diagnostic accuracy of MRI and the value of the diagnostic information to patients (over and above the affect of the test result on disease management); both of these factors will have an important influence on the cost-effectiveness of the technology. In addition, these studies were carried out before the availability of the DMTs interferon beta and glatiramer acetate, so they do not take account of any additional benefit arising from speeding up access to these therapies.

Increasing the relevance of this information

In an effort to update these cost-effectiveness studies and improve their relevance to our recommendations, a further comprehensive search was carried out to find economic information on the use of MRI as a diagnostic technology in MS and other neurological diseases, ie to identify the potential costs and benefits of MRI. As well as updating the original search of standard bibliographic databases (and broadening this outside of MS) the new search also focused on a number of key websites and databases. In addition information was sought from a number of relevant professional and academic organisations.

This search (and the review of the clinical evidence) revealed that evidence on the diagnostic accuracy of MRI had improved very little since the US cost-effectiveness studies of the early 1990s. As a result it was not possible to construct a cost-effectiveness model within the required time. Furthermore, this model would probably be of little value since it would be characterised by the same key uncertainties as the earlier work.

As an alternative to cost-effectiveness modelling (and after taking further advice from some members of the GDG) the focus was on providing answers to some questions, which may help to inform our recommendations.

What proportion of people with (suspected) MS receive an MRI scan at present?

There is no formal data source containing this information. Expert opinion suggests that almost all people with MS will have had an MRI scan at some point, but it is not clear how many people

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with suspected MS (ie some evidence from clinical tests) will get a scan, or how long they would have to wait (see below).

The number of MRI scans carried out for the purpose of diagnosing MS can only be estimated from incidence figures. There is uncertainty in estimating the current incidence and prevalence of MS. The HTA systematic review on the natural history and epidemiology of MS, produced to inform these guidelines,⁴ cites prevalence of 100–109 per 100,000 and incidence of 3.5 to 3.8 per 100,000. Expert opinion from Alistair Compston and David Miller suggests an incidence of 7 per 100,000. This amounts to around 2,100 to 4,200 first diagnostic scans per year, depending on which incidence figure you take and assuming that all new cases receive an MRI scan. David Miller has suggested that as many again are probably done to exclude a diagnosis of MS.

Despite much concern over extremes in geographical variation there is little formal data on this. In relation to access to a neurologist, an ABN survey in 1999 and 2001 (www.theabn.org/ukneuro/acuteneurology.html) asked consultant neurologists how long was the wait until their next appointment for a routine referral from a general practitioner for any purpose. The results show waits varying from 13 weeks in North West Thames to 51 weeks in Wales. Some areas show improvement since 1999, but in others the situation has worsened.

MRI scanning facilities in the UK are heavily used and if scanners are not used for the purposes of diagnosing MS, the machinery and staff would almost certainly be involved in scans for other purposes, so any cost savings from fewer MS scans are unlikely to be realised. However, there is a true opportunity cost from using a scanner to aid in the diagnosis of MS.

What is the value of MRI in the diagnosis of relapse?

From the research point of view there appears to be much interest in MRI results as a potentially more objective outcome measure than EDSS in measuring disease progression. However, it is not clear how MRI results can be translated into patient-based outcomes (like quality of life) and evidence on the relationship between MRI and clinical progression is not conclusive. Any recommendations on the role of MRI in the continued management of MS (ie after diagnosis) must consider the effect on waiting times for initial diagnostic scans.

Other important questions for which it was not possible to find information

- Do patients have lower/higher subsequent treatment costs if they have had more MRIs?
- Do patients have different rates of disability/relapse/death if they have had more MRIs?
- Can the cost of an MRI be equated with any clinical gain?

Appendix G: The McDonald Criteria⁵⁵

Table G1 Making the diagnosis

Clinical presentation	Additional data needed to make diagnosis	Comment
Two or more attacks; objective clinical evidence of two or more lesions.	None.	If tests (MRI scans or CSF analysis) are undertaken and are negative extreme caution must be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture.
Two or more attacks; objective clinical evidence of one lesion.	Dissemination in space demonstrated by MRI.	MRI scan must fulfil criteria for brain abnormality (overleaf).
	Two or more MRI-detected lesions consistent with MS plus positive CSF.	Positive CSF: oligoclonal bands detected by established methods, preferably isoelectric focusing, different from any such bands in serum; or by a raised IgG index.
	Await further clinical attack implicating a different site.	
One attack; objective clinical evidence of two or more lesions.	Dissemination in time demonstrated by MRI.	MRI scan must fulfil criteria for dissemination of lesions in time (overleaf).
	Second clinical attack.	
One attack; objective clinical evidence of one lesion (mono-symptomatic presentation; clinically isolated syndrome).	Dissemination in space, demonstrated by MRI scan.	MRI scan must fulfil criteria for brain abnormality (overleaf).
	Two or more MRI-detected lesions consistent with MS plus positive CSF <i>and</i> dissemination in space, demonstrated by MRI scan <i>or</i> second clinical attack.	Positive CSF: oligoclonal bands detected by established methods, preferably isoelectric focusing, different from any such bands in serum; or by a raised IgG index.
		MRI scan must fulfil criteria in the second paragraph of the criteria for dissemination of lesions in time (overleaf).
Insidious neurological progression suggestive of MS.	Positive CSF <i>and</i> dissemination in space, demonstrated by nine or more T2 lesions in brain <i>or</i> two or more lesions in spinal cord, <i>or</i> four to eight brain plus one spinal cord lesion.	Positive CSF: oligoclonal bands detected by established methods, preferably isoelectric focusing, different from any such bands in serum; or by a raised IgG index.
	Abnormal VEP associated with four to eight brain lesions, <i>or</i> with fewer than four brain lesions plus one spinal cord lesion demonstrated by MRI <i>and</i> dissemination in time, demonstrated by MRI.	Abnormal visual evoked potential of the type seen in MS (delay with well preserved wave form).
	Continued progression for one year.	MRI scan must fulfil criteria shown in criteria for brain abnormality (overleaf).

Magnetic resonance imaging criteria

▷ Magnetic resonance imaging criteria for brain abnormality

Magnetic resonance imaging criteria for brain abnormality are based on **three of four** of the following:

- one gadolinium-enhancing lesion or nine T2-hyperintense lesions if there is no gadolinium enhancing lesion
- at least one infratentorial lesion
- at least one juxtacortical lesion
- at least three periventricular lesions.

Note that one spinal cord lesion can be substituted for one brain lesion. Data from Barkhof *et al* 1999 and Tintore *et al* 2000.

▷ Magnetic resonance imaging criteria for dissemination of lesions in time

If a first scan occurs three months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but three months is recommended. A new T2- or gadolinium-enhancing lesion at this time then fulfils the criterion for dissemination in time.

If the first scan is performed less than three months after the onset of the clinical event, a second scan done three months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than three months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice.

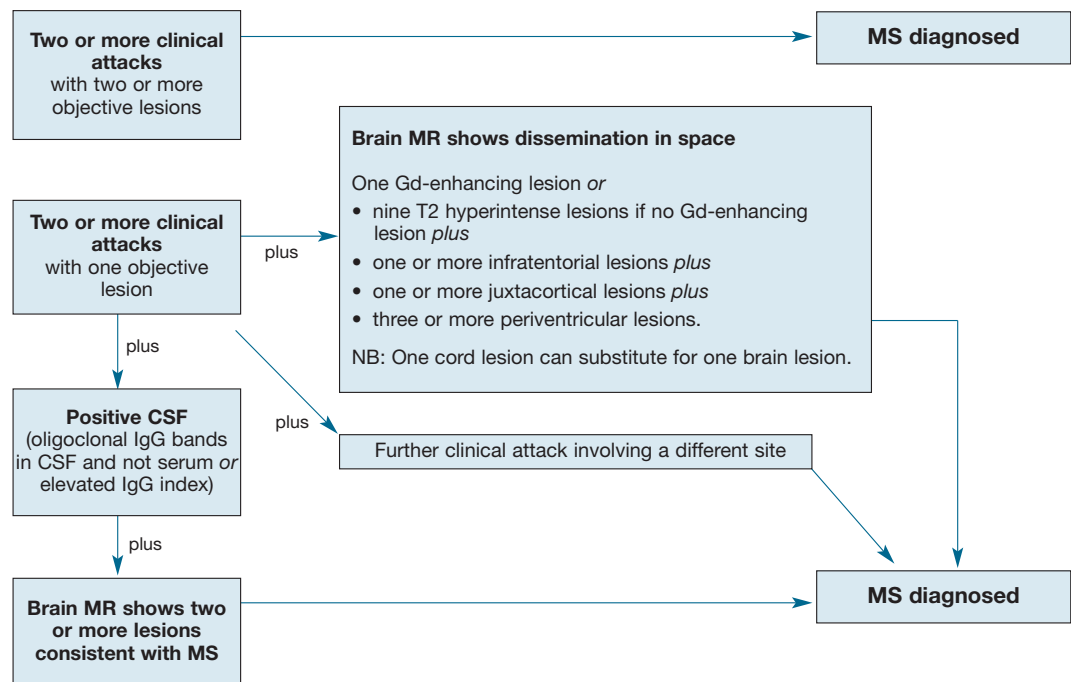
Guidelines for the accurate diagnosis of MS according to the McDonald criterias

- 1) The diagnosis should be made by an experienced clinician with expert knowledge of MS and similar neurological conditions.
- 2) The prior probability that the individual has MS depends on factors such as age, ethnicity and geographical location.
- 3) Objective evidence of dissemination in time and space of lesions typical of MS is mandatory, as is the exclusion of other, better explanations for the clinical features.
- 4) Historical reports of symptoms may suggest previous episodes of demyelination, but cannot be used without objective evidence to satisfy the requirement of lesions disseminated in time and space.
- 5) MS can be diagnosed on purely clinical evidence of lesions separated in time and space.
- 6) Radiological (MRI) and laboratory evidence is desirable and may be essential where clinical evidence is insufficient for a secure diagnosis.
- 7) The choice of investigation will be determined by the clinical situation; for example, a delayed visual evoked potential is of value in a person with a spinal cord lesion but is of little value in a person with optic neuritis.

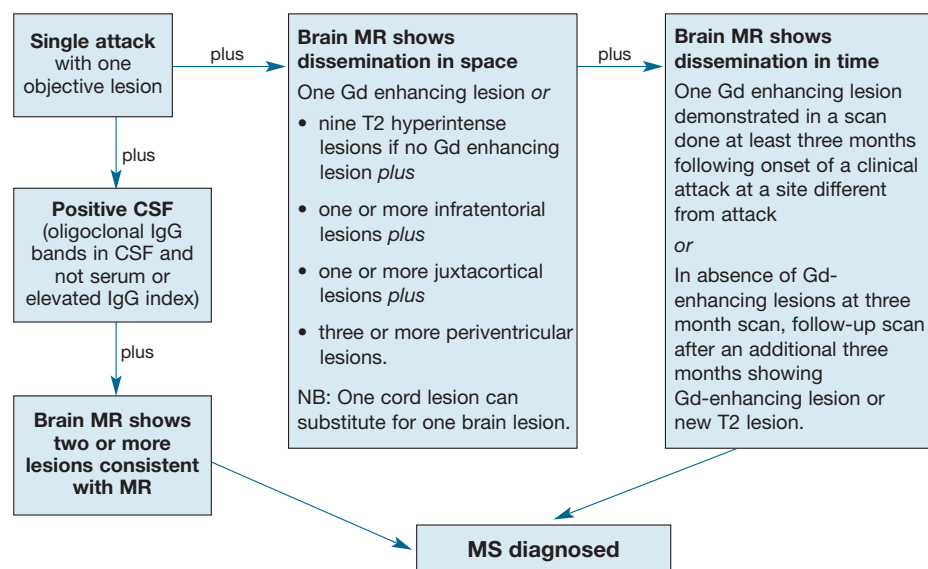
- 8) MRI is less useful in older people and in other inflammatory conditions such as acute encephalomyelitis where its specificity is lower. MRI is not applicable in people with metallic foreign bodies, pacemakers, etc or in those who cannot tolerate the procedure.

Flow charts for diagnosis of MS using McDonald criteria

- ▷ Diagnostic criteria for suspected MS (two or more attacks)

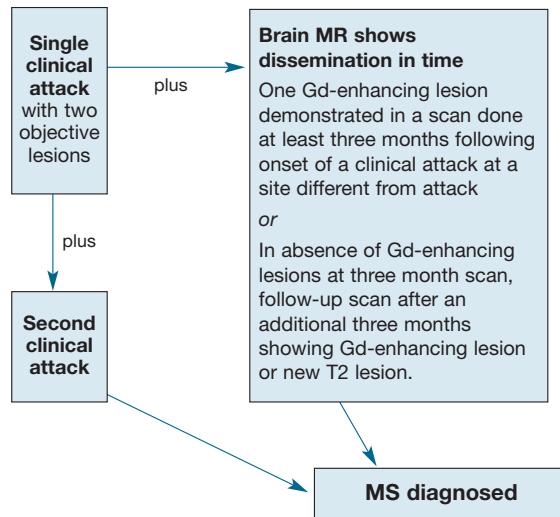


- ▷ Diagnostic criteria for suspected MS (monosymptomatic)

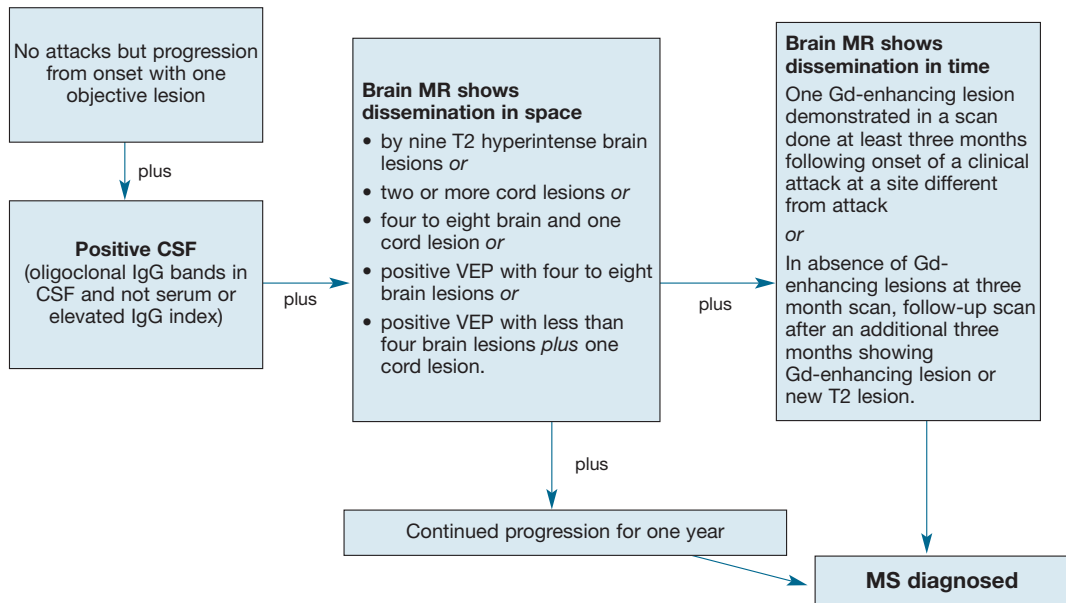


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▷ Diagnostic criteria for suspected MS (single attack)



▷ Diagnostic criteria for suspected MS (progressive from onset)



Appendix H: Assessments and measures

These guidelines do not recommend or even mention specific measures or assessments. A brief explanation is given in the introduction. This appendix gives a little more information. However, it must be emphasised that the measures mentioned here are not being recommended in any way.

First, the reader is reminded of the second paragraph in section 3.2.1:

The process of assessment refers both to the collection and to the interpretation of data needed to identify problems (screening) and to inform the solutions. The process of assessment may or may not include measurement, which is the quantification of data against some metric. In other words, an assessment procedure may be considered to have two purposes which may be distinct or combined:

- the **detection** of a phenomenon (ie diagnosis); and,
- the **measurement** of a phenomenon.

The questions faced are whether we are able to give recommendations that cover:

- how specific impairments or activity limitations should be detected
- how the severity of any impairment or activity limitation should be quantified, for example when measuring the outcome of an intervention
- what protocols should be used when first seeing a person with MS in order to detect most common or important difficulties.

In all three cases the first step is to collect data from or about the person with MS, and so the discussion is primarily concerned with whether or not the guidelines should mention or recommend specific data collection tools. These are referred to as ‘measures’ or ‘assessments’ interchangeably and loosely. A measure is a way of quantifying something; an assessment is a process of making a rehabilitation diagnosis through identifying and sometimes quantifying the presence of various abnormalities. The recommendations have emphasised the need for the process of assessment, and implied that measurement should be considered. The question is whether specific tools should be recommended.

The problems

There are several problems, especially in the context of a document that is emphasising the need to base recommendations on evidence.

The evidence searches undertaken have not been appropriate for making decisions on which data collection tools to recommend. To give reasonable evidence we would need to search for evidence on what purposes each tool might be suitable for, how reliable it is, how sensitive to change if used for that purpose, its diagnostic sensitivity and specificity if used for that purpose, its feasibility, and its comparative utility with other tools.

For almost all tools only minimal published data are available. Specifically there are very little comparative data to guide any choice between tools that collect data on the same problem.

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However, the number of tools used in research is vast. This appendix includes a list of measures mentioned in the studies tabulated in the evidence tables. This list is only a small proportion of the measures used in the totality of MS research. Moreover, in clinical practice a different set of measures is used (in as far as measures are used at all). The utility, validity etc of most of these measures is unknown.

It also needs to be recognised that many people hold strong views on what to use and will anyway disagree with and probably ignore any recommendations. The comments by stakeholders illustrated the wide variety of opinions on appropriate measures vividly – there was no agreement by stakeholders on any single measure.

At the same time those without strong views might not use any tools, whatever is recommended.

In favour of making recommendations

In the guidelines we have suggested repeatedly that specific problems (such as swallowing difficulties) are identified, but not how. This omission lessens the likelihood of the recommendations being followed. Many stakeholders suggested that we should include recommendations, but usually recommended ones that others did not.

Against making recommendations

Although we have not searched systematically for evidence on measures, there is in fact little useful evidence available and we have not searched for or found the relatively limited available evidence. Consequently any recommendations made will be arbitrary and will not be agreed. Therefore it is unlikely that any specific recommendations will be followed, making it unwise to make them.

We do not have the time or resources to undertake a proper systematic search for evidence even in one domain, let alone for the whole of neurological rehabilitation. It is wiser to make no recommendations than to make recommendations that are personal preferences, rather than based on firm evidence, and likely to be disputed by more people than agree on them.

What is available?

In the process of formulating these guidelines and collating the evidence we have, however, produced some information.

First, there is a simple list of all the measures used in the research studies referred to in this document. Many of these measures are untested and few will be useful.

List of measures

The tabulated list of measures is simply set out in order of frequency, with a brief note on some measures where known. The names given are those abstracted from the original papers, and some of the measures may have no further data available. To find further details the reader should identify the study that used the test and read the original paper.

Conclusions

Several conclusions can be drawn from this appendix.

Firstly, future search strategies should focus on investigating:

- **validity:** what purposes the measure can fulfil (or what measures can fulfil a specific purpose)
- **reliability:** how consistent the tool is when used in different circumstances by different people or in different ways
- **sensitivity:** what change or difference can it detect
- **utility:** this is a review of such factors as the time and effort needed to use the measure, the amount of equipment needed, the training needed by the assessor, and how much the information gained alters clinical decisions.

Second, a large number of measures have been used, but many only once.

A research programme should be set up to investigate simple measures for routine use, preferably not limited to MS but covering all neurological conditions.

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Table H1 Assessment tools used as outcome measures in multiple sclerosis RCTs and CCTs in evidence tables

Number of studies	Assessment tool	Number of studies	Assessment tool
84	EDSS	1	Fog scale
13	ADL otherwise unspecified	1	Global gait score
13	AI (Ambulation Index – Hauser)	1	Gottschalk and Gleser Scale
13	Ashworth scale	1	Gulick MS Specific Symptom Scale Score
12	SF-36	1	Health Attribution Test
11	FSS (Fatigue Severity Scale)	1	Hopkins Verbal Learning Test (HVLT)
10	BDI (Beck Depression Inventory)	1	HRSD
8	Alexander score	1	Imagery Assessment Tool
7	Nottingham health profile	1	Independence of activities of daily living (IADL)
6	9-HPT (Nine Hole Peg Test (manual dexterity))	1	Jebsen Test of Hand Function (JTHF)
6	Barthel Index ADL	1	Marital adjustment (Marital Adjustment Test – MAT)
6	Frenchay activities index – extended ADL		
6	Kurtske FSS (EDSS)	1	Memory concentration test
5	Rivermead mobility index	1	MFIS score
5	State Trait Anxiety Inventory (STAI)	1	MMPI D-30 scale
4	DSS (Disability Status Scale; precursor to EDSS)	1	MMSE (Mini-Mental State Examination)
4	General Health Questionnaire	1	MS self-efficacy function and control sub-scales
4	Incapacity Status Scale	1	MSIS
4	POMS (Profile of Mood States)	1	MSPSS (total social support)
4	RFSS	1	MSQOL-54
4	Scripps NRS (Neurological Rating Scale (impairments))	1	MSSE
4	FIM (Functional Independence Measure)	1	Nottingham Extended ADL index
4	HADS (Hospital Anxiety and Depression scale)	1	Oxford Handicap Scale Scores
3	GNDS (Guy's Neurological Disability Scale)	1	PASAT
3	NRS (Neurological Rating Scale Scripps)		
2	Berg Balance Test	1	Personality change (NEO-PI, Hogan Empathy Scale)
2	ERP (Evoked Response Potential (EEG))	1	Philadelphia Geriatric Center Morale Scale
2	Hamilton Rating Scale	1	Prose Memory (MAS)
2	London handicap scale	1	Rankin Scale
2	MS Symptom Checklist	1	Rehabilitation Institute of Chicago Functional Assessment Scale
2	Snellen test	1	RIC-FAS
1	Accommodation self-efficacy measure	1	Rivermead Behavioral Memory Test
1	Affect Balance Scale	1	Rivermead Motor Assessment (gross function, leg function, functional assessment)
1	AMB		
1	Anxiety Scale Score (ASQ)	1	Rosenberg Self-Esteem Scale
1	Arthritis impact measurement scale	1	SDDRE (how essential help with ADL is)
1	ASSS	1	SDDRO (help required in the last 24 hours with personal care, mobility, household tasks, leisure and employment)
1	Aulhorn Flicker Test		
1	Borg's post reading (perceived rate of exertion)	1	SDMT written (one of the attention/visuomotor search scales)
1	Boyersky Scale		
1	Brief Assessment of Social Engagement and Life Satisfaction Index scores	1	SF-36
1	Bronx scale	1	SF-54
1	CDQ	1	Shiply Institute of Living Scales
1	Cerebellar Functional System Score	1	SOMC (Short Orientation Memory Concentration Test)
1	Chalder Fatigue Scale Score	1	Spiral copying
1	Community Integration Score	1	SSEP (Somato-sensory evoked potential (EEG))
1	COP Sway Centre of Pressure	1	Standardised neurological status
1	Cyber flexion score (quadriceps spasticity)	1	Symbol Digit Modalities Test (oral version)
1	Dartmouth Co-Op Chart	1	Symptom rating questionnaire (patient assessment)
1	DRS Disability Rating Scale		
1	Environmental status score	1	Symptom Trait Scale (physical symptoms)
1	EQUISCALE	1	Tempelaar Social Experience Checklist (SET)
1	Esteem (SES)	1	Visual Faces Scale Rating (patient rating of pain and spasticity)
1	Everyday memory problems (EMQ)		
1	FAMS symptoms (Functional Assessment in MS)	1	WAIS similarities and WAIS picture arranging
1	Fatigue Impact Scale (FIS)		
1	FDS (pyramidal functions and bladder and bowel functions)		

Appendix I: Evidence tables

These are available at www.rcplondon.ac.uk/pubs/books/ms/

The evidence tables provide full details of the studies identified and critically appraised as part of the formal systematic review. They are organised according to guideline section, clinical question and study design.

Appendix J: The scope of the clinical guideline

Preamble

The National Institute for Clinical Excellence is responsible for developing, disseminating and giving advice on the implementation of clinical guidelines to provide advice on best practice for patients and health professionals in the NHS in England and Wales.

Title

Multiple sclerosis: national clinical guidelines for diagnosis and management in primary and secondary care.

Summary

The guideline will be relevant to adults of all ages with MS and will cover the full range of care that should be routinely made available from the NHS, including appropriate use of mainstream pharmacological, physical therapy, rehabilitative and psychosocial treatments.

Status

This scoping statement has been subject to a period of consultation and discussed with stakeholders. It has been approved by the Guidelines Advisory Committee and the Institute's Guidance Executive and will be posted on the Institute's website along with details of the commission and the developers of the guidelines.

Issues and objectives

- Multiple sclerosis is a progressive neurological condition. It has a variable clinical course and patients present with a variety of problems. They can present with a relapsing-remitting disorder that, after a variable time course, may evolve to a secondary progressive disorder. They may also present with a primary progressive disorder particularly in older patients.
- The guideline will cover a very broad range of care services, and the developers will need to assess how best to approach this.
- This is an NHS guideline. Although it will comment on the interface with other services, such as those provided by social services and the voluntary sector, it will not include services exclusive to these sectors.
- The guideline will incorporate the Institute's guidance on the use of interferon beta and glatiramer acetate.

Inclusions and exclusions

▷ Disease or condition

The guideline will be relevant to adults of all ages with MS. The guideline should offer best practice advice on the diagnosis of MS and on the NHS care of patients diagnosed with various forms of MS. Diagnosis, early management, relapsing-remitting and progressive stages of the disease should be considered. Severe and advanced stages of the condition, and the management of rarer symptoms and treatment side effects will also be covered. Supportive and palliative care will be covered only to the extent that they relate specifically to MS.

▷ Health care setting and professions

The guideline will cover the care provided by clinicians who have direct contact with and make decisions concerning the care of patients with MS. It will address the needs of patients and carers in whatever setting NHS care is provided.

The guideline will need to comment on the way health care services need to interact with services provided by Social Services and the voluntary sector, but will not seek to guide the practice of social care or services provided by the voluntary sector.

▷ Interventions and treatment modalities

The guidelines will cover the full range of care that should be routinely made available from the NHS, including appropriate use of mainstream pharmacological, physical therapy, rehabilitative and psychosocial treatments.

These will include:

- **the diagnosis of the disease**
- **pharmacological treatments:** the guideline will consider the long established and widely used drugs such as steroids (various forms) and azathioprine but the brief specifically excludes evaluation of the interferon betas and glatiramer acetate which are being appraised by the Institute.
- **consideration of alternative treatments that might modify disease progress:** although the evidence base is much weaker for these therapies, many patients use them. By considering them, the developers will, amongst other observations, be able to point out where more data may be needed to enable a thorough appraisal of their value.
- **prevention of secondary disease processes:** including the prevention of pressure sores, contractures, and of incidental diseases that threaten life (eg 'flu vaccination) as these pertain to MS. The guideline will take account of the guideline on pressure ulcers.
- **management of impairments and disabilities:** the following will be considered as they apply to people with MS:
 - anti-spastic treatments
 - urinary and bowel problems
 - fatigue management
 - ataxia and other movement disorders
 - visual problems

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- mood/emotions
- swallowing/feeding/diet
- pain/sensory disturbance
- mobility and function posture
- **models of care:** the guideline will consider evidence on the effectiveness of models of care required to deliver the recommendations in this guideline.

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Guideline Summary NGC-8784

Guideline Title

Use of imaging in multiple sclerosis.

Bibliographic Source(s)

Filippi M, Rocca A, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Miller DH, Wolinsky JS. Use of imaging in multiple sclerosis. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 35-51. [176 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Filippi M, Rocca MA, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Wolinsky JS. EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis. Eur J Neurol 2006 Apr;13(4):313-25.

Scope

Disease/Condition(s)

Multiple sclerosis (MS)

Guideline Category

Diagnosis

Evaluation

Technology Assessment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Radiology

Intended Users

Physicians

Guideline Objective(s)

- To define guidelines for the application of conventional and non-conventional magnetic resonance (MR) techniques for the diagnosis and monitoring of patients with multiple sclerosis (MS) in clinical practice
- To review the current status and clinical role of non-conventional MR techniques
- To update and revise previous guidelines published in 2006

Target Population

Patients with multiple sclerosis (MS) or suspected to have MS

Interventions and Practices Considered

Conventional magnetic resonance imaging (cMRI) of the brain

Note: Non-conventional MRI techniques (such as magnetization transfer MRI [MT-MRI], diffusion weighted MRI (DW-MRI); functional MRI [fMRI], and MR spectroscopy) were considered but not recommended.

Major Outcomes Considered

Sensitivity, specificity and predictive value of conventional magnetic resonance imaging (cMRI) in the management of multiple sclerosis (MS) patients

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Data for this review were identified by searches of Medline and references from relevant articles from 1965 to August 2009. The search terms 'multiple sclerosis', 'magnetic resonance imaging', 'diagnosis', 'prognosis', 'atrophy', 'magnetization transfer MRI', 'diffusion weighted MRI', 'diffusion tensor MRI', 'proton magnetic resonance spectroscopy', 'disability', and 'treatment' were used. Only papers published in English were reviewed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Good Clinical Practice Point Where there was lack of evidence but consensus was clear the task force members have stated their opinion as Good Clinical Practice Points.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Document" field).

Recommendations

Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Clinical Practice Point [GCPP]) are defined at the end of the "Major Recommendations" field.

Magnetic Resonance Imaging (MRI) Assessment of Patients at Presentation with Clinically Isolated Syndromes (CIS) Suggestive of Multiple Sclerosis (MS)

In patients at presentation with CIS suggestive of MS (i.e., neurological findings typically seen in the setting of MS) after appropriate exclusion of alternative diagnostic considerations that can mimic MS, the following recommendations should be considered:

1. Conventional MRI (cMRI) of the brain (dual-echo, fluid attenuated inversion recovery [FLAIR] and post-contrast T1-weighted scans) should be obtained as soon as possible in all patients presenting with an isolated demyelinating syndrome involving the central nervous system (CNS), not only to collect additional evidence for disease dissemination in space (DIS), but also to exclude other possible neurological conditions. As suggested by recent guidelines from the American Academy of Neurology (Frohman et al., 2003) the finding in these patients of three or more T2-hyperintense lesions with the imaging characteristics underlined by the International Panel (IP) guidelines (McDonald et al., 2001; Polman et al., 2005) (**Level A recommendation**) and the presence of two or more gadolinium (Gd)-enhancing lesions at baseline are sensitive predictors of the subsequent development of clinically definite MS (CDMS) within the next 7 to 10 years (**Level B recommendation**).
2. The presence of three or more white matter (WM) lesions on brain T2-weighted MRI in patients suspected of having MS is not diagnostic, especially when their location and appearance is non-characteristic for demyelination. In this context the IP criteria (McDonald et al., 2001; Polman et al., 2005) should be applied. Incidental WM lesions are not an infrequent observation even in the young normal population. Note that with ageing (at least >50 years) incidental WM lesions may also show progression (Longstreth et al., 2005) (**GCPP**).
3. In the case of corticosteroid treatment, which is known to dramatically suppress Gd enhancement, one of the possible markers of inflammation, cMRI should be performed before treatment or, at least, 1 month after treatment termination (**GCPP**).
4. cMRI of the spinal cord is useful in those circumstances when brain MRI is normal or equivocal, and in patients with non-specific brain T2-abnormalities (especially when older than 50 years), because, contrary to what happens for the brain, cord lesions rarely develop with ageing *per se* (Kidd et al., 1993). In patients presenting with a spinal cord syndrome, spinal cord MRI is highly recommended to rule out other conditions that may mimic MS, such as compressive lesions (**GCPP**).
5. In patients with acute optic neuritis (ON), although it will not always be required, MRI of the optic nerve can be useful in ruling out alternative diagnosis. In this case, short-tau inversion recovery (STIR) sequences should be used (**GCPP**).
6. Follow-up MRIs are required to demonstrate disease dissemination in time (DIT). In this perspective, the appearance of Gd-enhancing lesions 3 months after the clinical episode or new T2 or Gd-enhancing lesions 30 days after the clinical episode (and after a baseline MRI assessment) is highly predictive. Follow-up scans should be performed with the same machinery and scanning parameters and identical slice positions are required for exact comparison (**Level B recommendation**). A scanner with at least 1.0 Tesla should be used to optimize image quality and tissue contrast.
7. Repeat scanning beyond the two initial studies need to be considered by the neurologist individually according to the clinical circumstances that are appropriate for each patient (is not routinely recommended as the disease becomes more likely to manifest clinically in the longer term [Miller et al., 2004]) (**GCPP**).
8. Nephrogenic systemic fibrosis (NSF) is a medical condition that has come to be associated with exposure to the Gd (Kanal et al., 2007; Thomsen & European Society of Urogenital Radiology, 2007). Normal renal function has to be confirmed prior to Gd administration (**GCPP**).
9. Although non-conventional MRI techniques may provide essential and critical information in patients with CIS and their application for monitoring treatment might provide a more accurate assessment of efficacy on inflammation, axonal protection, and demyelination/remyelination, their use in clinical practice is, currently, not recommended. All these techniques are yet to be adequately compared with cMRI for sensitivity and specificity in detecting tissue damage in MS and for predicting the development of MS and disability. At present, these quantitative techniques show differences at a group level, but do not allow inferences at an individual level (**GCPP**).
10. In patients with insidious neurological progression over at least one year, primary-progressive MS (PPMS) (Thompson et al., 2000), can be diagnosed reliably in the absence of positive cerebrospinal (CSF) findings (when typical brain and spinal cord MRI changes are present). Even if in these patients a positive CSF finding increases the level of confidence for a diagnosis of MS, such a finding is not specific and may be commonly detected in patients with progressive myelopathies of other causes (**GCPP**).

MRI in Patients with CDMS

In patients with established MS, the following recommendations should be considered:

1. cMRI scans (dual-echo and post-contrast T1-weighted images) should be obtained using standardized protocols and accurate procedures for patients' repositioning to facilitate the interpretation of follow-up studies. Post-contrast T1-weighted scans should be acquired after an interval of 5 to 7 min from the injection of contrast material. Considering the weak correlation with clinical finding and the low predictive value of cMRI metrics for the subsequent worsening of clinical disability, the use of surveillance MRI for the purpose of making treatment decisions cannot be generally recommended. Serial MRI scans should be considered when diagnostic issues arise (**GCPP**).

2. Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g., mechanical compression) or atypical symptoms develop (**GCPP**).
3. Although preliminary work based on clinical trial data has suggested that presence and amount of MRI-detected disease activity may identify interferon (IFN) response status in terms of relapse rate and accumulated disability in MS patients at a group level, there are no validated methods for monitoring disease-modifying therapy in individual patients (**Class I evidence**).
4. Metrics derived from cMRI are not enough to provide a complete picture of the MS pathological process. Although cMRI has undoubtedly improved our ability to assess the efficacy of experimental MS therapies and, at least partially, our understanding of MS evolution, it provides only limited information on MS pathology in terms of accuracy and specificity and it has limited correlations with clinical metrics. This implies that the ability of a given treatment to modify metrics derived from cMRI does not mean that the treatment will necessarily be able to prevent the progressive accumulation of clinical disability, especially at an individual patient level.
5. Measurements of T1-hypointense lesions loads and brain and cord atrophy in clinical practice continue to be considered at a preliminary stage of development, as they need to be standardized in terms of acquisition and post-processing. Conversely, these metrics should be included as an end-point in disease-modifying agents trials to further elucidate the mechanisms responsible for disability (**GCPP**).
6. The application of non-conventional MRI techniques in monitoring patients with established MS in clinical practice is, at the moment, not advisable. All these techniques still need to be evaluated for sensitivity and specificity in detecting tissue damage in MS and its changes over time (**GCPP**).
7. Magnetization transfer (MT)-MRI should be incorporated into new clinical trials to gain additional insights into disease pathophysiology and into the value of this technique in the assessment of MS (**Class II evidence**). The performance and contribution of diffusion tensor MRI (DT-MRI) and MR spectroscopy (^1H -MRS) in multicenter trials still have to be evaluated.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Rating of Recommendations

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Good Clinical Practice Point Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good clinical practice points.

Clinical Algorithm(s)

None provided

Evidence Supporting the Recommendations

References Supporting the Recommendations

Frohman EM, Goodin DS, Calabresi PA, Corboy JR, Coyle PK, Filippi M, Frank JA, Galetta SL, Grossman RI, Hawker K, Kachuck NJ, Levin MC, Phillips JT, Racke MK, Rivera VM, Stuart WH. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003 Sep 9;61(5):602-11. [47 references] [PubMed](#) 

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Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol.* 2005 Dec;58(6):840-6. [40 references] [PubMed](#) 

Thompson AJ, Montalban X, Barkhof F, Brochet B, Filippi M, Miller DH, Polman CH, Stevenson VL, McDonald WI. Diagnostic criteria for primary progressive multiple sclerosis: a position paper. *Ann Neurol.* 2000 Jun;47(6):831-5. [PubMed](#) 

Thomsen HS, European Society of Urogenital Radiology. European Society of Urogenital Radiology guidelines on contrast media application. *Curr Opin Urol.* 2007 Jan;17(1):70-6. [58 references] [PubMed](#) 

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of neuroimaging in the management of multiple sclerosis (MS)

Potential Harms

Nephrogenic systemic fibrosis (NSF) is a medical condition that has come to be associated with exposure to gadolinium (Gd). Normal renal function has to be confirmed prior to Gd administration.

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Filippi M, Rocca A, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Miller DH, Wolinsky JS. Use of imaging in multiple sclerosis. In: Gilhus NE, Barnes MP, Brainin M, editor(s). *European handbook of neurological management*. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 35-51. [176 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

European Federation of Neurological Societies - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies Task Force on Use of Imaging in the Multiple Sclerosis

Composition of Group That Authored the Guideline

Task Force Members: M. Filippi, Institute of Experimental Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy; M. A. Rocca, Institute of Experimental Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy; D. L. Arnold, Montreal Neurological Institute, Canada; R. Bakshi, Partners MS Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; F. Barkhof, VU Medical Centre, Amsterdam, The Netherlands; N. De Stefano, Institute of Neurological Sciences, University of Siena, Italy; F. Fazekas, Institute of Neurological Sciences, University of Siena, Italy; E. Frohman, University of Texas Southwestern Medical Center at Dallas, USA; D. H. Miller, Institute of Neurology, Queen Square, London, UK; J. S. Wolinsky, University of Texas Health Science Center, Houston, USA

Financial Disclosures/Conflicts of Interest

D. L. Arnold has served on advisory boards for Genentech and Biogen Idec, and received speaker honoraria from Genentech, MS Forum, Biogen Idec, Serono Symposia, Teva & Sanofi Aventis, Teva Neuroscience, Bayer HealthCare Pharmaceuticals, and EMD Serono. He has received consultant's fees from Biogen Idec, Teva Neuroscience, MS Forum, Genentech, Bayer HealthCare Pharmaceuticals, Novartis, and Eisai Medical Research, and grants from Multiple Sclerosis Society of Canada and Canadian Institutes of Health Research.

R. Bakshi has received speaker honoraria and grants from Biogen Idec, Teva Neuroscience, and EMD Serono.

F. Barkhof has received consultancy fees from Bayer-Schering Pharma, Sanofi-Aventis, Biogen-Idec, UCB, Merck-Serono, Novartis, and Roche.

N. De Stefano has served on advisory boards for Merck-Serono and received speaker honoraria from Merck-Serono, Teva, Biogen, and Bayer. He has received a consultant's fee from Merck-Serono and travel grants from Merck-Serono and Biogen.

F. Fazekas has served on advisory boards and received speaker honoraria from Biogen Idec, Teva Sanofi Aventis, Merck-Serono, and Bayer Schering. He has received grants from Bayer Schering, Biogen Idec, Teva Sanofi-Aventis, Baxter, and Merck-Serono.

M. Filippi has received speaker honoraria and grants from Teva, Merck-Serono, Bayer Schering, Biogen-Dompè, and Genmab. He has received a consultant's fee from Peppen and travel grants from Teva, Merck-Serono, Bayer Schering, and Biogen-Dompè.

M. A. Rocca has received speaker honoraria and travel grants from Biogen-Dompè.

The other authors have reported no conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Filippi M, Rocca MA, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Wolinsky JS. EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis. *Eur J Neurol* 2006 Apr;13(4):313-25.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the [European Federation of Neurological Societies \(EFNS\) Web site](#).

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol*. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the [European Federation of Neurological Societies Web site](#).

Patient Resources

None available

NGC Status

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Section 5

Guidelines

Guideline for Treatment of Cancer Near the End of Life

Issue: The wording/intent of Guideline Note 12 has been determined to be in conflict with the Affordable Care Act (ACA). This was discussed at the May, 2013 VBBS meeting and a workgroup was created to work on a new guideline for treatment of cancer near the end of life. The workgroup was composed of three oncologists, an oncology nurse, a palliative care physician, an attorney in the field of healthcare law, and a healthplan representative. A patient representative was included in email discussions but was not able to attend the meetings. The highlights of these meetings are included in the packet for your reference. Additional work was done by the group via email. The meetings were public, and public testimony was heard and considered. Other stakeholder input, including health plans and DMAP, was elicited and considered.

The workgroup developed a new guideline which specifies at what point treatment of cancer would be considered futile. As part of this guideline, requirements for a documented discussion about goals of treatment, prognosis, etc. must be included, and care must be provided by evidence driven pathways when appropriate.

For reference, at the end of this document is an appendix with the relevant ACA section, the current Guideline Note 12, and the Palliative Care Statement of Intent.

Guideline for Treatment of Cancer Near the End of Life

HERC Staff Recommendations:

- 1) Adopt the new Guideline Note 12 as shown below

GUIDELINE 12 CANCER CARE NEAR THE END OF LIFE

Cancer is a complex group of diseases with treatments that vary depending on the specific subtype of cancer and the patient's unique medical and social situation. Goals of appropriate cancer therapy can vary from intent to cure, disease burden reduction, disease stabilization and control of symptoms. Cancer care must always take place in the context of the patient's support systems, overall health, and core values. Patients should have access to appropriate peer-reviewed clinical trials of cancer therapies. A comprehensive multidisciplinary approach to treatment should be offered including palliative care services (see Statement of Intent 1, Palliative Care).

Treatment with intent to prolong survival is not a covered service for patients who have progressive metastatic cancer with

- 1) severe co-morbidities unrelated to the cancer that result in significant impairment in two or more major organ systems which would affect efficacy and/or toxicity of therapy; OR
- 2) a continued decline in spite of best available therapy with a non reversible Karnofsky Performance Status or Palliative Performance score of <50% with ECOG performance status of 3 or higher which are not due to a pre-existing disability.

Treatment with intent to relieve symptoms or improve quality of life is a covered service as outlined in Statement of Intent 1, Palliative Care.

To qualify for treatment coverage, the cancer patient must have a documented discussion about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. This discussion may take place with the patient's oncologist, primary care provider, or other health care provider, but preferably in a collaborative interdisciplinary care coordination discussion. Treatment must be provided via evidence-driven pathways (such as NCCN, ASCO, ASH, ASBMT, or NIH Guidelines) when available.

Guideline for Treatment of Cancer Near the End of Life

Appendix A

ACA section 1302

CONSIDERATION.—In defining the essential health benefits under paragraph (1), the Secretary shall...

(B) not make coverage decisions, determine reimbursement rates, establish incentive programs, or design benefits in ways that discriminate against individuals because of their age, disability, or expected length of life;

(C) take into account the health care needs of diverse segments of the population, including women, children, persons with disabilities, and other groups;

(D) ensure that health benefits established as essential not be subject to denial to individuals against their wishes on the basis of the individuals' age or **expected length of life** or of the individuals' present or predicted disability, degree of medical dependency, or **quality of life**;

GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT PROVIDED NEAR THE END OF LIFE

Lines 102,103,123-125,144,159,165,166,170,181,197,198,207,208,218,220, 221,228,229,231, 243,249,252,275-278,280,287,292,310-312,320,339-341,356,459,586,622

This guideline only applies to patients with advanced cancer who have less than 24 months median survival with treatment.

All patients receiving end of life care, either with the intent to prolong survival or with the intent to palliate symptoms, should have/be engaged with palliative care providers (for example, have a palliative care consult or be enrolled in a palliative care program).

Treatment with intent to prolong survival is not a covered service for patients with any of the following:

- Median survival of less than 6 months with or without treatment, as supported by the best available published evidence
- Median survival with treatment of 6-12 months when the treatment is expected to improve median survival by less than 50%, as supported by the best available published evidence
- Median survival with treatment of more than 12 months when the treatment is expected to improve median survival by less than 30%, as supported by the best available published evidence
- Poor prognosis with treatment, due to limited physical reserve or the ability to withstand treatment regimen, as indicated by low performance status.

Unpublished evidence may be taken into consideration in the case of rare cancers which are universally fatal within six months without treatment.

The Health Evidence Review Commission is reluctant to place a strict \$/QALY (quality adjusted life-year) or \$/LYS (life-year saved) requirement on end-of-life treatments, as such

Guideline for Treatment of Cancer Near the End of Life

measurements are only approximations and cannot take into account all of the merits of an individual case. However, cost must be taken into consideration when considering treatment options near the end of life. For example, in no instance can it be justified to spend \$100,000 in public resources to increase an individual's expected survival by three months when hundreds of thousands of Oregonians are without any form of health insurance.

Treatment with the goal to palliate is addressed in Statement of Intent 1, Palliative Care.

STATEMENT OF INTENT 1: PALLIATIVE CARE

It is the intent of the Commission that palliative care services be covered for patients with a life-threatening illness or severe advanced illness expected to progress toward dying, regardless of the goals for medical treatment and with services available according to the patient's expected length of life (see examples below).

Palliative care is comprehensive, specialized care ideally provided by an interdisciplinary team (which may include but is not limited to physicians, nurses, social workers, etc.) where care is particularly focused on alleviating suffering and promoting quality of life. Such interdisciplinary care should include assessment, care planning, and care coordination, emotional and psychosocial counseling for patients and families, assistance accessing services from other needed community resources, and should reflect the patient and family's values and goals.

Some examples of palliative care services that should be available to patients with a life-threatening/limiting illness,

- A) without regard to a patient's expected length of life:
 - Inpatient palliative care consultation; and,
 - Outpatient palliative care consultation, office visits.
- B) with an expected median survival of less than one year, as supported by the best available published evidence:
 - Home-based palliative care services (to be defined by DMAP), with the expectation that the patient will move to home hospice care.
- C) with an expected median survival of six months or less, as supported by peer-reviewed literature:
 - Home hospice care, where the primary goal of care is quality of life (hospice services to be defined by DMAP).

It is the intent of the Commission that certain palliative care treatments be covered when these treatments carry the primary goal to alleviate symptoms and improve quality of life, without intending to alter the trajectory of the underlying disease.

Some examples of covered palliative care treatments include:

- A) Radiation therapy for painful bone metastases with the intent to relieve pain and improve quality of life.
- B) Surgical decompression for malignant bowel obstruction.

Guideline for Treatment of Cancer Near the End of Life

- C) Medication therapy such as chemotherapy with low toxicity/low side effect agents with the goal to decrease pain from bulky disease or other identified complications. Cost of chemotherapy and alternative medication(s) should also be considered.
- D) Medical equipment and supplies (such as non-motorized wheelchairs, walkers, bandages, and catheters) determined to be medically appropriate for completion of basic activities of daily living, for management of symptomatic complications or as required for symptom control.
- E) Acupuncture with intent to relieve nausea.

Cancer treatment with intent to palliate is not a covered service when the same palliation can be achieved with pain medications or other non-chemotherapy agents.

It is NOT the intent of the Commission that coverage for palliative care encompasses those treatments that seek to prolong life despite substantial burdens of treatment and limited chance of benefit. See Guideline Note 12: TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT PROVIDED NEAR THE END OF LIFE.

Cancer Care Near the End of Life Workgroup Summary of Work to Date

I. First workgroup meeting

The first workgroup meeting was held on June 18, 2013. In attendance were members Maccini, Gajewski, Dayton, and Ahmann (Phone), staff members Smits and Coffman and twelve in the audience. Absent were members Olson, Walsh and McWilliams. Smits and Coffman reviewed the current guideline regarding cancer care near the end of life, as well as problems with the guideline voiced by oncologist, health plans, and patients. The impact of the Affordable Care Act (ACA) on the guideline was also reviewed, particularly limitations on using expected length of life in making coverage decisions.

Several issues were identified by the workgroup. First, cancer is a disease with many subtypes, and treatment efficacy varies based on patient characteristics, disease characteristics, prior treatment, etc. The group felt that a rapid appeals process for any guideline should be developed, as treatment efficacy can be significantly affected by speed of initiation of treatment.

The group felt that a statement of intent might be more useful than a guideline. Such a SOI should focus on limiting treatment for those patients who cannot expect prolongation of quality of life or who have poor performance status. All expressed understanding of the need to not provide futile therapy, in terms of saving money and resources for treatment of other patients and conditions.

Public comment was heard suggesting the addition of a medical ethicist to the group, as well as patient representation.

A subgroup consistent of Gajewski, Maccini, and Dayton, to be staffed by Smits was delegated to work on a SOI proposal to bring back to the next meeting on July 15th.

II. Working meetings

A subgroup met twice on July 2nd and 9th, consisting of Gajewski, Maccini, and Dayton (staffed by Smits). This group drafted a new proposed guideline. They took into consideration feedback from such stakeholders as the OHP medical directors, the Oregon state oncology professional society, and others. The medical directors strongly urged the workgroup to use the guideline format, rather than the statement of intent, as SOIs are not enforceable before administrative law judges. Based on evidence in the literature of the importance of frank discussions regarding the realistic expectations of treatment, a clause requiring such a discussion was included. Other stakeholders stressed the need for evidence based treatment requirements.

Note: there is significant interest among stakeholders to have the current workgroup continue on as a permanent workgroup of the HERC to allow for ongoing reassessment of this guideline and related Prioritized List coverage.

Cancer Care Near the End of Life Workgroup Summary of Work to Date

III. Second work group meeting

The second workgroup meeting was held on July 15, 2013. In attendance were members Maccini, Gajewski, Dayton, Olson, Walsh (phone) and McWilliams, staff members Smits and Coffman and at least fifteen in the audience. Absent was member Ahmann. Smits reviewed the discussion from the first meeting, subsequent stakeholder input, and the working group draft revised guideline. Coffman reviewed the history of the HSC/HERC limiting care for cancer patients with metastatic disease with less than 5% 5 year expected survival, which was subsequently broadened by the current Guideline Note 12 to limiting care only for patients with expected length of life of 24 months or less. Essentially, the workgroup agreed that the intent should be that OHP will not cover very expensive cancer treatment with marginal benefit/trivial increase in life expectancy. The challenge for the workgroup is to create a guideline which is implementable and will result in enough monetary savings to make a meaningful difference.

There was discussion about whether the guideline encompassed all cancer care, or just cancer care near the end of life. The decision was only cancer care near the end of life. The suggestion was made to remove the statements about when cancer treatment with intent to prolong life was covered, as this made the guideline intent confusing.

There was discussion about whether the current Guideline Note 12 was workable. John Sattenspiel, an OHP medical director present in the audience, advocated for continuing the current GN12 as it was effective and could be enforced. However, the general consensus heard by the HERC to date from the oncology community and other OHP plans is that the guideline is very problematic.

Walsh suggested using the Medicare definition of hospice eligibility as a definition for what the guideline means by end of life. The ACA prohibits the use of expected length of life. The Medicare definition includes many types of metastatic disease, as well as non small cell lung cancer, pancreatic cancer, and glioblastoma. Others argued that some patients who meet the hospice eligibility criteria can have meaningful extension of life with some therapies. Walsh reiterated that this could be the definition for what is meant by near the end of life, but that patients would not have to enroll in hospice. Other members felt that this definition might have the unintended consequence of denying all care to anyone who is hospice eligible, despite possible successful treatment. Dayton argued for this definition as being likely to be acceptable to CMS.

Members of the workgroup and audience members advocated for a very rapid appeals process to be put in place with any guideline that is adopted. Smits noted that such a process is beyond the scope of the HERC.

Cancer Care Near the End of Life Workgroup

Summary of Work to Date

Public testimony included a request for another workgroup meeting to allow further public testimony/input, accounts of cancer survivors who were initially given very short life expectancies, and a perspective from a medical oncologist.

The workgroup decided to have the draft new guideline revised by staff. The clause about when cancer care is covered should be struck and the guideline focused on when such care is futile and not covered. Verbiage regarding care guidelines and use of best available evidence should be kept. Staff will circulate the draft via email for further input and comment, and then bring to the August VBBS meeting for their consideration. If the VBBS requests additional input from this workgroup, then a third meeting will be scheduled.

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Advanced Imaging for Back Pain Guideline - correction

Question: How should the Advanced Imaging for Back Pain Guideline be modified to capture coverage for cervical and thoracic imaging and for defining radiculopathy?

Question source: DMAP Staff, CCO Medical Directors

Issue: At the 10/11/12 VBBS/HERC meeting, the MRI of the spine guideline was revised based on the Coverage Guidance: Advanced Imaging for Low back Pain. DMAP let HERC staff know that previously the MRI of the Spine guideline was also used for cervical and thoracic back pain, and the current title of the guideline suggests it can only be applied to low back pain and the red flag table largely applies to low back pain alone, making there be a deficiency in direction for appropriate imaging for cervical and thoracic back pain.

Also, the CCO Medical Directors raised a concern that the new D4 Diagnostic Guideline does not define what radiculopathy is, nor that it requires a neurologic exam. They requested clarity on this.

The previous guideline was as follows.

DIAGNOSTIC GUIDELINE D4, MRI OF THE SPINE

MRI of the spine is covered in the following situations:

1. Recent onset of major or progressive neurologic deficit (objective evidence of reflex loss, dermatomal muscle weakness, dermatomal sensory loss, EMG or NCV evidence of nerve root impingement), suspected cauda equine syndrome (loss of bowel or bladder control or saddle anesthesia), or neurogenic claudication in patients who are potential candidates for surgery;
2. Clinical or radiological suspicion of neoplasm; or,
3. Clinical or radiological suspicion of infection.

GUIDELINE NOTE 94, EVALUATION AND MANAGEMENT OF LOW BACK PAIN

Lines 400,562

Procedures for the evaluation and management of low back pain are included on these lines when provided subject to the State of Oregon Evidence-based Clinical Guidelines dated 10/2011 located at:

<http://www.oregon.gov/OHA/OHPR/HERC/Evidence-Based-Guidelines.shtml>

The revised approved guideline is as follows:

DIAGNOSTIC GUIDELINE D4 ADVANCED IMAGING FOR LOW BACK PAIN

Advanced Imaging for Back Pain Guideline - correction

In patients with non-specific low back pain and no “red flag” conditions [see Table 1], imaging is not a covered service; otherwise, workup is covered as shown in the table.

Electromyography (CPT 96002-4) is not covered for non-specific low back pain.

Low Back Pain - Potentially Serious Conditions (“Red Flags”) and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	History of cancer with new onset of LBP	MRI	ESR
	- Unexplained weight loss - Failure to improve after 1 month - Age >50 years - Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	- Fever - Intravenous drug use - Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	- Urinary retention - Motor deficits at multiple levels - Fecal incontinence - Saddle anesthesia	MRI	None
Vertebral compression fracture	- History of osteoporosis - Use of corticosteroids - Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	- Morning stiffness - Improvement with exercise - Alternating buttock pain - Awakening due to back pain during the second part of the night - Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	- Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month - Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	- Radiculopathic symptoms present >1 month - Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI**	Consider EMG/NCV
Spinal stenosis	- Radiating leg pain - Older age	None	None

Advanced Imaging for Back Pain Guideline - correction

	• Pain usually relieved with sitting (Pseudoclaudication a weak predictor)		
	• Spinal stenosis symptoms present >1 month	MRI**	Consider EMG/NCV

* Level of evidence for diagnostic evaluation is variable

** Only if patient is a potential candidate for surgery or epidural steroid injection

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

HERC Staff Recommendations:

1) Re-adopt the guideline on MRI of the spine, specifically for cervical and thoracic back pain:

DIAGNOSTIC GUIDELINE DX, MRI OF THE SPINE (CERVICAL AND THORACIC)

MRI of the cervical and thoracic spine is covered in the following situations:

1. Recent onset of major or progressive neurologic deficit (objective evidence of reflex loss, dermatomal muscle weakness, dermatomal sensory loss, EMG or NCV evidence of nerve root impingement), suspected cauda equina syndrome (loss of bowel or bladder control or saddle anesthesia), or neurogenic claudication in patients who are potential candidates for surgery;
2. Clinical or radiological suspicion of neoplasm; or,
3. Clinical or radiological suspicion of infection.

2) Modify Diagnostic Guideline D4 as follows:

DIAGNOSTIC GUIDELINE D4 ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no “red flag” conditions [see Table 1], imaging is not a covered service; otherwise, workup is covered as shown in the table.

Electromyography (CPT 96002-4) is not covered for non-specific low back pain.

Low Back Pain - Potentially Serious Conditions (“Red Flags”) and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic	Lumbosacral plain radiography	

Advanced Imaging for Back Pain Guideline - correction

	deficit, night pain or pain increased in supine position		
	Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	- Fever - Intravenous drug use - Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	- Urinary retention - Motor deficits at multiple levels - Fecal incontinence - Saddle anesthesia	MRI	None
Vertebral compression fracture	- History of osteoporosis - Use of corticosteroids - Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	- Morning stiffness - Improvement with exercise - Alternating buttock pain - Awakening due to back pain during the second part of the night - Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	- Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month - Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	- Radiculopathic symptoms** present >1 month - Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI***	Consider EMG/NCV
Spinal stenosis	- Radiating leg pain - Older age - Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	Spinal stenosis symptoms present >1 month	MRI**	Consider EMG/NCV

* Level of evidence for diagnostic evaluation is variable

** [Radiculopathic symptoms are defined for the purposes of this guideline as in Guideline Note 37 with any of the following:](#)

- Markedly abnormal reflexes
- Segmental muscle weakness
- Segmental sensory loss
- EMG or NCV evidence of nerve root impingement
- Cauda equina syndrome,
- Neurogenic bowel or bladder
- Long tract abnormalities

*** Only if patient is a potential candidate for surgery or epidural steroid injection

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

Health and Behavior Assessment Guideline

Question: should the health and behavior assessment guideline be modified or eliminated?

Question source: DMAP, HERC staff

Issue: When the health and behavior assessment CPT codes were adopted, a guideline was adopted to define the provider types that could use these codes. This guideline was largely based on the CMS guideline in place at the time. Additional wording was added to allow managed care organizations to authorize other employees to deliver these services.

As the health plans transition to CCO's, the health and behavior assessment guideline has been identified as a barrier for fully integrating mental health into the physical health organizations. The CCOs believe that the CMS guideline would restrict these services to licensed psychologists.

CMS guidelines from 2010 read:

“Health and behavior assessment codes may not be used for physician (example: medical doctor, nurse practitioner, physician assistant, clinical nurse practitioner) or clinical social worker services.”

Current guideline:

GUIDELINE NOTE 1, HEALTH AND BEHAVIOR ASSESSMENT/INTERVENTION

Lines 1,6,8,10-18,20-22,25,26,28,29,33-37,39-42,46,47,50,52,53,55,57,62,64,66, 67, 69, 71,74,76,79,80,82,84,85,87,92,94,96,98,100-103, 105,108-111,113, 115,119, 122-124, 128,134,135,137,138,140,141,144,146,147,149-151,158,159,164-169,173,179,181-183,185,190,191,193,195-197,199,201,202,205,207,208,210,218,220,221,224,227-229,233,235-238,243,246,249,250,252-256,265-268,271-279,285,287,288,290,292,293, 302,304,306,310-314,320,326,331,333,338-342,352,354,356,357,360,366,370,371, 376,377,387,394,400,407,410,421-423,426,432,434,435,439,442,444,446, 447,459,466, 470-472,478,489,491,506

Health and behavior assessment and interventions (CPT codes 96150-96154) are included on these lines when provided subject to the Centers for Medicare and Medicaid (CMS) guidelines dated 2/1/06 located at:

http://downloads.cms.gov/medicare-coverage-database/lcd_attachments/30514_1/L30514_031610_cbg.pdf

In addition, Managed Care Organizations may authorize employees of organizations holding certificates or letters of approval from DHS and a Medicaid vendor number to deliver these services (i.e., not delivering services as an independent practitioner).

Recommendation:

- 1) Delete guideline note 1, Health and Behavior Assessment/Intervention
 - a. DMAP can make internal rules about provider types allowed to bill these codes

Coding and Billing Guidelines

Contractor Name

Wisconsin Physicians Service (WPS)

Contractor Number

00951, 00952, 00953, 00954
05101, 05201, 05301, 05401,
05102, 05202, 05302,
05402, 52280

Contractor Type

Carrier
Fiscal Intermediary (FI)
MAC – A
MAC – B

Article Type

LCD Companion Article

Article Title

PSYCH-015 - Health and Behavior Assessment/Intervention

Effective Date

03/16/2010

Health and Behavior Assessment

Health and behavior assessment procedures are used to identify the psychological, behavior, emotional, cognitive, and social factors important to the prevention, treatment, or management of physical health problems.

The Health and Behavioral Assessment codes, CPT 96150-96154, are used to describe services that are intended to assess factors that may affect the recovery or progression of a diagnosed physical health problem or illness. Specifically this would include assessment and treatment for biopsychosocial factors that do not directly treat the illness and the focus is not on mental health issues. If the beneficiary has a mental health diagnosis, the 96150 – 96154 codes would not be appropriate. In addition, these services do not represent preventive medicine counseling and risk factors reduction interventions.

CMS National Coverage Policy:

Title XVIII of the Social Security Act section 1862 (a)(1)(A). This section allows coverage and payment of those services that are considered medically reasonable and necessary.

Title XVIII of the Social Security Act section 1862 (a)(7). This section excludes routine physical examinations and services p

Title XVIII of the Social Security Act section §1833 (c) and §1833 (e). This section prohibits Medicare payment for any claim which lacks the necessary information to process the claim.’
Code of Federal Register

CFR Title 42, Part 410.73(b)(1) [Revised as of October 1, 2004][CITE: 42CFR410.73]
CMS) of the Act and in §2470ff

(1) *Definition*. “Clinical social worker services” means, except as specified in paragraph (b)(2) of this section, the services of a clinical social worker furnished for the diagnosis and treatment of mental illness that the clinical social worker is legally authorized to perform under State law (or

the State regulatory mechanism provided by State law) of the State in which the services are performed. The services must be of a type that would be covered if they were furnished by a physician or as an incident to a physician's professional service and must meet the requirements of this section.

Coding Guidelines

1. CPT codes 96150 - 96154 represent services offered to beneficiary who present with established illness or symptoms, the purpose of the assessment is not for the diagnosis or treatment of mental illness, and may benefit for evaluations that focus on the biopsychosocial factor related to the beneficiary's physical health status
2. Physician's must bill health and behavior assessment and/or intervention services with an Evaluation and Management or preventive Medicine service codes.
3. Medical records must document the specific underlying medical problem
4. Health and behavior assessment normally will be performed in an office or facility setting.
5. Health and behavior assessment codes may not be used for physician (example: medical doctor, nurse practitioner, physician assistant, clinical nurse practitioner) or clinical social worker services.
6. CPT codes 96150 – 96154 are to be billed as one service for each 15 minute of face-to-face contact with the beneficiary(s).
- *7. When more than four CPT codes 96150 are submitted by a provider/group the additional services will be denied. If a redetermination is requested, documentation showing the medical necessity of the additional time must be submitted.

CPT Codes

96150	Health and behavior assessment (eg, health-focused clinical interview, behavioral observations, psychophysiological monitoring, health-oriented questionnaires), each 15 minutes face-to-face with the patient; initial assessment
96151	Health and behavior assessment (eg, health-focused clinical interview, behavioral observations, psychophysiological monitoring, health-oriented questionnaires), each 15 minutes face-to-face with the patient; re-assessment
96152	Health and behavior intervention, each 15 minutes, face-to-face; individual
96153	Health and behavior intervention, each 15 minutes, face-to-face; group (2 or more patients)
96154	Health and behavior intervention, each 15 minutes, face-to-face; family (with the patient present)

Diagnoses that Support Medical Necessity

Medical diagnoses only

Reasons for Denial

1. Beneficiaries who do not have specific underlining medical condition.
2. Services for preventive medicine counseling and/or risk factor reduction intervention.
3. Services to beneficiaries who require psychiatric services (services should be billed with CPT codes 90801 – 90899).
4. Evaluation and Management services, including Preventive Medicine, Individual Counseling codes 99401 – 99404, and Preventive Medicine, Group Counseling codes 99411 – 99412 billed on the same day as 96150 – 96154.

5. Health and behavior assessment and/or intervention performed by a physician, clinical nurse specialist, nurse practitioner, physician assistant. These services should be billed using the appropriate evaluation and management CPT codes.
6. Health and behavior assessment and/or intervention performed by a clinical social worker. Per CFR Title 42, Part 410.73(b)(1) the services of a clinical social worker are limited to the diagnosis and treatment of mental illness.
7. Health and behavior assessment and/or intervention performed by physical therapist, or occupational therapist.
8. Smoking cessation; (use CPT codes G0375 - G0376).

Additional information may be found at

http://www.cms.hhs.gov/manuals/14_car/3b5111.asp#_1_5 define SW ect

http://www.cms.hhs.gov/manuals/pm_trans/R1660B3.pdf

Original Effective Date

03/16/2010,

Revision History Number/Explanation

02/01/2010, one, merge of legacy LCD into J-5 and Legacy LCD, this LCD replaces all other previous LCDs on this subject including L21749, L21751, L21753, and L21755;

Publication Date

02/01/2010,

Cystocele Repair

Question: Where should cystocele repair be prioritized compared to other causes of urinary incontinence? Should the pelvic organ prolapse guideline apply to cystoceles?

Question source: John Sattenspiel, MD, OHP Medical Director

Issue: Cystoceles (protrusion of the bladder into the vagina) is located on line 492 UTERINE PROLAPSE; CYSTOCELE. Cystoceles cause problems if the bladder protrudes to the introitus or beyond and causes discomfort, or may cause urinary incontinence or retention. Other pelvic organ prolapse diagnoses (uterine prolapse, rectoceles, etc.) are located on line 492 which has an associated Guideline Note 50 UTERINE PROLAPSE. Other types/causes of urinary incontinence such as stress and overflow incontinence are located on line 478 URINARY INCONTINENCE and are associated with Guideline Note 47 URINARY INCONTINENCE.

From Dr. Sattenspiel:

I recently reviewed a request for surgery related to stress incontinence. While the line 478 GN #47 criteria were not met, the surgical request was also submitted with diagnosis code 618.01 (cystocele, midline). That condition is found on line 492, titled Uterine Prolapse; Cystocele, where it is subject to GN #50 and pairs with the requested procedures (57240/57267/57288). My concern is that GN #50 appears to apply only when hysterectomy is intended as part of the surgical treatment and while it does require that pelvic organ prolapse to the introitus be present, it is otherwise silent with regard to surgical interventions that do not include hysterectomy as a component. Is it the intent of the HERC that if the presence of any grade of cystocele is documented, then surgery for stress incontinence does not have to meet either the criteria of GN #47 or of GN #50? What is the intent of the HERC when this type of situation arises, i.e. is it the intent of the HERC that coverage on line 492 for any of the listed procedures is dependent on the degree of pelvic organ prolapse whether or not hysterectomy is being requested? As I read the GN, at this time the request for cystocele/bladder repair must be approved even though the criteria of GN #47 have not been met and there is no documentation that member has a cystocele that prolapses to the level of the introitus as required by GN #50.

GUIDELINE NOTE 47, URINARY INCONTINENCE

Line 478

Surgery for genuine stress urinary incontinence may be indicated when all of the following are documented (A-G):

A) Patient history of (1, 2, and 3):

- 1) Involuntary loss of urine with exertion
- 2) Identification and treatment of transient causes of urinary incontinence, if present (e.g., delirium, infection, pharmaceutical causes, psychological causes, excessive urine production, restricted mobility, and stool impaction)
- 3) Involuntary loss of urine on examination during stress (provocative test with direct visualization of urine loss) and low or absent post void residual

- B) Patient's voiding habits
- C) Physical or laboratory examination evidence of either (1 or 2):
 - 1) Urethral hypermobility
 - 2) Intrinsic sphincter deficiency
- D) Diagnostic workup to rule out urgency incontinence
- E) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized
- F) Nonmalignant cervical cytology, if cervix is present
- G) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

GUIDELINE NOTE 50, UTERINE PROLAPSE

Line 492

Hysterectomy for pelvic organ prolapse may be indicated when all of the following are documented (A-E):

- A) Patient history of symptoms of pelvic prolapse such as:
 - 1) Complaints of the pelvic organs prolapsing at least to the introitus
 - 2) Low back discomfort or pelvic pressure
 - 3) Difficulty in defecating
 - 4) Difficulty in voiding
- B) Nonmalignant cervical cytology, if cervix is present
- C) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
- D) Physical examination is consistent with patient's symptoms of pelvic support defects indicating either symptomatic prolapse of the cervix, enterocele, cystocele, rectocele or prolapse of the vaginal vault
- E) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized

Recommendations:

- 1) Change GN 50 to include other pelvic organ prolapse surgeries
 - a. Should put an “AND” after A1 with “or” after A2 and A3 to clarify that the organ must be significantly prolapsed AND causing symptoms
 - b. Put in some restrictions from GN47 such as a 3 month PT trial, etc.

GUIDELINE NOTE 50, ~~UTERINE~~ PELVIC ORGAN PROLAPSE SURGERY*Line 492*

Hysterectomy, cystocele repair, and/or other surgery for pelvic organ prolapse may be indicated when all of the following are documented (A-E):

A) Patient history of symptoms of pelvic prolapse such as:

- 1) Complaints of the pelvic organs prolapsing at least to the introitus, AND
- 2) Low back discomfort or pelvic pressure or
- 3) Difficulty in defecating or
- 4) Difficulty in voiding

B) For hysterectomy:

- 1) Nonmalignant cervical cytology, if cervix is present
- ~~1~~ 2) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding

~~D~~C) Physical examination is consistent with patient’s symptoms of pelvic support defects indicating either symptomatic prolapse of the cervix, enterocele, cystocele, rectocele or prolapse of the vaginal vault

~~E~~D) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized

E) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

Smoking and Cervical Spine Fusion

Question: should non-smoking status be required for elective cervical fusion procedures?

Question source: OHP medical directors, HERC staff, community providers

Issue: In October, 2012, HERC adopted a new guideline limiting vertebral fusion surgeries to non-smokers. There have been questions raised from community providers and OHP medical directors about whether this restriction should apply to cervical fusions. The bulk of the evidence of harm from smoking is for lumbar fusions. There are other implementation issues which have been raised by providers and medical directors about the current guideline.

Guideline as adopted October, 2012:

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION

Lines 84,158,208,271,400,434,507,549,607

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking for 6 months prior to the planned procedure, as shown by three negative urine cotinine tests including testing on the day of surgery. Patients should be given access to appropriate smoking cessation therapy.

From Don Theiman, OHP Medical director

I'm gathering from surgeons, and it makes clinical sense to me, that cervical fusions are much, much less of an issue for failure in smokers because the loads on the fusion are so much smaller. We need to know if you found good literature that would disagree with that, and what literature we should review if so to see what went into the decision for GN 100. Meantime, we are viewing some requests with relative urgency and smoking, in the neck, as approvable.

From David Pass, MD

I have a couple of quick questions. The new Guideline note 100 for spinal fusions in smokers states that for smokers we need to get 3 urine cotinine tests including one on the day of surgery. We are trying to figure out how to comply with this and have the following questions:

- 1) How are we (or anyone) to manage the day of surgery testing. There is no mechanism to get that information to insurers and back to the surgeon quickly enough to make the surgery happen. Is this a primary responsibility of the surgeon to get the testing and cancel surgery if it is positive? If we don't have the testing results from the day of surgery or if they are positive and the surgery is done anyway are we to deny payment?
- 2) Those who are quitting smoking are often on an aid to help (like Nicoderm) which are nicotine containing and will likely make the cotinine testing positive even if they are not smoking (as you probably already know and we have one case of this already). Is the intention that patients are off of all nicotine products before surgery, or just that they have ceased smoking for 6 months?

Finally, I would be curious to know what literature you used to make this apply to all spine areas. We have looked at this fairly extensively in the past and came to the conclusion that smoking cessation is essential in lumbar fusions and we apply that to thoracic fusions too, but the evidence for cervical fusions seems to suggest that smoking does not play a major role in healing post op. However knowing that you have significant resources through the state's affiliation with the EPC and Med Project perhaps you have found some things that we should consider. Clearly it would be best if all payers were consistent across the State so we would be interested in looking at that information if you can share it (which I know is not possible sometimes!).

From John Sattenspiel, OHP Medical Director

Today's question is related to GN#100, Smoking and Spinal Fusion. There is some commentary that use of smokeless tobacco also impairs post-fusion healing. Is there evidence behind those assertions and if so, was it considered as this guideline was formulated. The issue came up today related to a member who uses chewing tobacco and for whom fusion is requested. Since the language in GN#100 solely and explicitly relates only to smoking, it was my interpretation that the use of chewing tobacco did not allow for a decision that coverage criteria had not been met. Please advise.

Evidence

1) Washington HTA 2013 Review of cervical spinal Fusion

- a. In the RCT comparing fusion to physical therapy and cervical collar immobilization (Persson, 2001), the improvement in VAS pain among those undergoing surgery was found to be better among smokers vs. nonsmokers ($p < .05$), although the actual data on VAS changes among these subgroups are not provided.
- b. Seven case series examined the impact of pre-operative smoking status on adverse events and clinical outcomes. While 1 study described statistically-significantly fewer cases of pseudarthrosis among non-smokers (20% vs. 50% for smokers, $p = .001$) (Goldberg, 2002), 3 found no correlation between smoking status and development of pseudarthrosis or adjacent segment disease (Matsumoto, 2009; Bindal, 2007; Emery, 1998). In terms of clinical outcomes, 3 series evaluated the effect of smoking status on treatment success using Odom's criteria. In one, data from a series of 144 patients indicated that smokers had a significantly ($p = .008$) higher rate of fair or poor outcomes (Jensen, 2009), although actually percentages were not reported. Another study ($n = 190$) found non-smokers to have a significantly higher rate of excellent outcomes (43.0% vs. 27.3%, $p < .03$) (Hilibrand, 2001). A third smaller series ($n = 66$) found no statistically-significant differences in this measure (Samartzis, 2005).
- c. No conclusions drawn regarding non-smoking requirement for surgery

2) Additional studies not included in Washington HTA

- a. **Peolsson 2003**
 - i. RCT of anterior cervical decompression and fusion with carbon fiber cage vs the Cloward procedure.
 - ii. $N = 103$

- iii. Non-smoking found to be a predictor of post-operative pain reduction and functional outcome

b. Eubanks 2011

- i. Retrospective case series of patients who had posterior cervical fusion with lateral mass instrumentation and iliac crest bone grafting
- ii. N=158
- iii. Smokers and nonsmokers had similar fusion rates (100%).
- iv. Conclusions In contrast to the effect of smoking on anterior cervical fusion, we found smoking did not decrease posterior cervical fusion with lateral mass instrumentation and iliac crest bone grafting. Posterior cervical fusion with lateral mass instrumentation should be considered over anterior procedures in smokers if the abnormality can appropriately be addressed from a posterior approach.

Summary: There is evidence, based on 1 RCT and several case series, that smoking reduces the success of cervical fusion procedures.

Related restrictions on nicotine use from GN8 Bariatric Surgery:

No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.

HERC Staff Recommendations:

- 1) Continue to include cervical fusion procedures in the smoking guideline (GN 100)
- 2) Change GN 100 as shown below
 - a. Correlates more closely with GN8
 - i. Evidence is around smoking rather than nicotine use
 - b. Will include restrictions on chewing tobacco and nicotine products if adopted as written

GUIDELINE NOTE 100 SMOKING AND SPINAL FUSION

Lines 84,158,208,271,400,434,507,549,607

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking for 6 months prior to the planned procedure, as shown by three negative urine cotinine tests.

Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from smoking. ~~including testing on the day of surgery.~~ Patients should be given access to appropriate smoking cessation therapy.

Does Smoking Influence Fusion Rates in Posterior Cervical Arthrodesis With Lateral Mass Instrumentation?

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Abstract

Background Smoking is associated with reduced fusion rates after anterior cervical decompression and arthrodesis procedures. Posterior cervical arthrodesis procedures are believed to have a higher fusion rate than anterior procedures.

Questions/purposes We asked whether smoking (1) would reduce the fusion rate in posterior cervical procedures; and (2) be associated with increased pain, decreased activity

level, and a decreased rate of return of work as compared with nonsmokers.

Methods We retrospectively reviewed 158 patients who had a posterior cervical fusion with lateral mass instrumentation and iliac crest bone grafting between 2003 and 2008. Fusion rates and Odom Criteria grades were compared among smokers and nonsmokers. The minimum followup was 3 months (average, 14.5 months; range, 3–72 months).

Results Smokers and nonsmokers had similar fusion rates (100%). Although 80% of patients had Odom Criteria Grade I or II, smokers were five times more likely to have Grade III or IV with considerable limitation of physical activity. Age, gender, and diagnosis did not influence fusion rates or the Odom Criteria grade.

Conclusions In contrast to the effect of smoking on anterior cervical fusion, we found smoking did not decrease posterior cervical fusion with lateral mass instrumentation and iliac crest bone grafting. Posterior cervical fusion with lateral mass instrumentation should be considered over anterior procedures in smokers if the abnormality can appropriately be addressed from a posterior approach.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was waived as no patients were contacted.

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Introduction

Fusion is reportedly important for successful outcomes and clinical results in cervical spine procedures [4, 5, 10, 15]. Pseudarthrosis can lead to persistent neck and arm pain syndromes as well as numbness and dysesthesias in the upper extremities [5, 23, 24]. Both local and systemic factors are important for graft healing and solid fusion.

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Predictive factors for the outcome of anterior cervical decompression and fusion

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Abstract In a prospective study, 103 patients were randomised to anterior cervical decompression and fusion (ACDF) with a cervical carbon-fibre intervertebral fusion cage or the Cloward procedure. Preoperative background variables, active range of neck motion, handgrip strength, radiological evaluation and subjective variables were used in a multiple regression model to find the strongest predictors of postoperative outcome as measured by current pain intensity and the Neck Disability Index (NDI). Male sex, greater kyphosis at the level operated on, non-smoking, a greater neck mobility in right rotation, low disability on NDI, and older age were predictors of pain reduction and explained 30% of current pain intensity at follow-up. Higher educational level, non-smoking, greater kyphosis at the level operated on, a greater flexion mobility, greater right handgrip strength and lower current pain intensity were

predictors of improvement, and explained 28% of the postoperative outcome on NDI. The most important predictor for postoperative pain intensity was the magnitude of the preoperative kyphosis. Preoperative pain intensity was the most important predictor for improved NDI. At follow-up about 70% of the patients still had deficit based on current pain intensity and NDI, and 44% had remaining dysfunction based on Odom's criteria. In conclusion, the multivariate analysis shows that male sex, non-smoking, greater segmental kyphosis and a low pain and disability level are preoperative predictors of a good outcome in ACDF. In addition, the study suggests the importance of other predictive variables than those studied for the outcome of ACDF.

Keywords Cervical spine · Intervertebral fusion · Prognostic factors · Outcome

Introduction

Many authors have reported the results of anterior cervical decompression and fusion (ACDF) in cervical radiculopathy [6, 24, 29]. The best results have been reported for young male patients with soft disc disease [3, 9, 14] at a single level [3, 9], radicular pain without additional neck or lumbar pain [12, 14], correlation between radiological and clinical findings [14], and short duration of symptoms [3, 9, 14]. The preoperative predictive value of objective variables such as radiological findings, active range of

motion (AROM) in the neck and handgrip strength has not been determined.

In previous studies of ACDF the outcomes have been determined by pain quantification or by Odom's criteria [21], and there are only limited reports on functional outcome [23, 29]. Except for Eriksen et al. [9], all previous reports have used only chi-square test or bivariate correlation analysis, with no potential to control for interdependency between variables. The present study used multivariate analysis with quantification of the relative importance of each variable studied. Determination of predictive factors may be of great importance, since a large



Cervical Spinal Fusion For Degenerative Disc Disease

Final Evidence Report

February 21, 2013

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FINAL APPRAISAL DOCUMENT

CERVICAL SPINAL FUSION FOR DEGENERATIVE DISC DISEASE

February 21, 2013

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ABOUT ICER

The Institute for Clinical and Economic Review (ICER), based at the Massachusetts General Hospital's Institute for Technology Assessment (ITA), provides independent evaluation of the clinical effectiveness and comparative value of new and emerging technologies. ICER's mission is to lead innovation in comparative effectiveness research through methods that integrate evaluations of clinical benefit and economic value. By working collaboratively with patients, clinicians, manufacturers, insurers and other stakeholders, ICER develops tools to support patient decisions and medical policy that share the goals of empowering patients and improving the value of healthcare services.

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- Blue Shield of California Foundation
- Greater Boston Chamber of Commerce
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- HealthPartners
- The John W. Rowe Family Foundation
- Johnson & Johnson
- Kaiser Permanente
- Merck & Co.
- The National Pharmaceutical Council
- Philips Healthcare
- Robert Wood Johnson Foundation
- United Health Foundation
- The Washington State Health Care Authority

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EXECUTIVE SUMMARY

Introduction

Chronic neck pain is a prevalent and costly disorder. Approximately 15-20% of adults report at least one episode of neck pain during a given year, and nearly half of these individuals seek care (Carroll, 2008). On an annual basis, it is estimated that 11-14% of workers will have some limitation in their activities due to neck pain (Côté, 2008). While no recent studies have been conducted in the US on the economic burden of neck pain specifically, the combined burden of neck and back disorders in this country has been estimated to total \$86 billion (Deyo, 2008).

One of the common causes of chronic neck pain is the progression of degenerative disc disease (DDD) of the cervical spine, a natural consequence of aging that results in gradual deterioration of cervical intervertebral discs (Emery, 2001). As the ability of these discs to absorb the shock and stress of vertebral motion declines, they become inelastic and cause a settling of the spinal column structure and abnormal spinal motion patterns. This process may in turn cause the development of abnormal bony growths and/or spurs (spondylosis), osteoarthritis, and/or herniation of one or more cervical discs. All of these conditions may in turn cause radiculopathy, or peripheral nerve root impingement. Symptoms of cervical radiculopathy include neck and arm pain, and weakness, tingling, or numbness in the upper extremities (Mayo Clinic, 2012). Less commonly, cervical DDD progression and its sequelae may directly compress parts of the spinal cord (myelopathy), affecting gait and balance in addition to causing arm and/or leg weakness and numbness.

A variety of management options are available to treat cervical neck pain and related symptoms arising from degenerative disc disease. These options are described in detail in the main body of the report. Briefly, the major options include:

- *Conservative Treatment*
 - Physical Therapy
 - Cervical Collar Immobilization
 - Spinal Manipulation (i.e., chiropractic or manual physical therapy)
 - Medication (e.g., analgesics, muscle relaxants, opioids)
 - Alternative Treatments (e.g., yoga, acupuncture)
 - Self-Care (e.g., educational materials, home stretching)

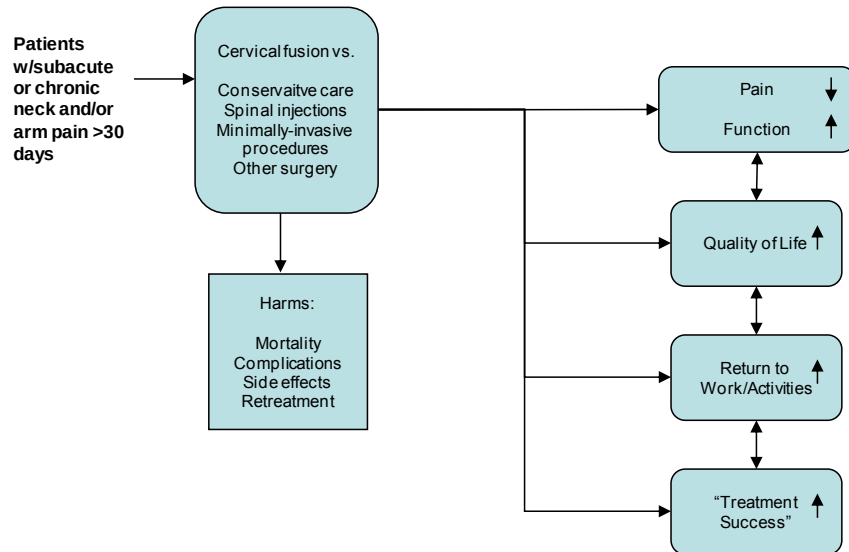
- *Spinal Injections*
 - Steroids
 - Nerve Blocks
 - Chemonucleolysis
 - Other (e.g., Botulinum toxin)
- *Minimally-Invasive Procedures*
 - Radiofrequency Denervation
 - Coblation Nucleoplasty
- *Surgical Procedures*
 - Spinal Fusion
 - Discectomy
 - Foraminotomy
 - Laminectomy/Laminoplasty

The most common surgical procedure employed in the U.S. for patients with symptomatic cervical DDD is spinal fusion (Cowan, 2006). The rate of spinal fusion has increased dramatically in recent years; an analysis of U.S. hospital discharge data from 1990-2004 showed an 8-fold increase in the utilization of anterior fusion procedures, even while the overall rate of hospital admissions for cervical DDD remained steady (Marawar, 2010). The cost of these procedures, as well as questions regarding the short- and long-term outcomes associated with fusion, have raised considerable interest in understanding the evidence on the relative effectiveness of this procedure in comparison to other management options.

Appraisal Scope

This appraisal sought to evaluate the comparative clinical effectiveness and comparative value of spinal fusion and its alternatives in patients with cervical degenerative disc disease (DDD). The scope of this appraisal is summarized in the Analytic Framework figure below.

Analytic Framework: Management Options for Cervical Degenerative Disc Disease



There are limited data directly demonstrating the impact of most cervical DDD management strategies on summary measures of “treatment success” or “successful clinical outcome”, so judgments about the effectiveness of these interventions must rest primarily upon consideration of multiple and potentially overlapping measures (e.g., pain, function, quality of life) as well as evaluation of treatment-associated risks. In addition, various stakeholders will by nature be more interested in certain outcomes than others. For example, payers and employers may be most interested in functional improvement and/or return to work, while clinicians and patients may focus more on relief of symptoms and spinal stability.

The focus of this appraisal was on adults (>17 years of age) with cervical DDD symptoms, including neck pain, arm pain, and/or radiculopathic symptoms (e.g., numbness, tingling); these symptoms could occur with or without the presence of spondylosis. We did not focus on studies that consisted primarily or in total of patients whose primary complaint was cervical myelopathy, as this is generally considered a neurologic emergency in all but the mildest cases and patients typically proceed directly to surgical intervention (McCormick, 2003); included studies may have involved a minority subgroup of patients with myelopathy, however. In all cases, the target population was focused on patients whose

symptoms have persisted despite an initial short course (i.e., 4-6 weeks) of self-care and conservative management.

Evidence was sought to answer the following key questions:

1. What is the comparative clinical effectiveness of cervical fusion for DDD relative to that of conservative management approaches, minimally-invasive procedures, and other forms of surgery?
2. What are the adverse events and other potential harms associated with cervical fusion compared to conservative management approaches, minimally-invasive procedures, and other forms of surgery?
3. What is the differential effectiveness and safety of cervical fusion according to factors such as age, sex, race or ethnicity, pre-existing conditions (e.g., smoking history), neuromuscular disease states (e.g., Parkinsonism), measurable spinal instability, technical approach to fusion, insurance status (e.g., worker's compensation vs. other), and treatment setting (e.g., inpatient vs. ambulatory surgery)?
4. What are the costs and potential cost-effectiveness of cervical fusion relative to alternative approaches?

Outcomes of interest included measures of pain, function, health-related quality of life, and employment status. In addition, information was obtained on standardized or study-specific measures of "treatment success" or "successful clinical outcome". Potential harms of interest included perioperative (occurring during the operative episode or the 30 days following) mortality, major and minor complications, and procedure revision, as well as long-term mortality, adverse events, and requirements for subsequent surgery or additional treatment.

Information was obtained from all randomized controlled trials (RCTs) and comparative cohort studies that compared fusion to one of the comparators described above. Importantly, studies that only compared different variants of fusion (e.g., according to instrumentation or graft type employed) were excluded from consideration, as numerous systematic reviews have not found evidence distinguishing these approaches. Studies that compared anterior to posterior anatomic approaches to fusion as well as single-level, 2-level, and multi-level fusion were included, however, as evidence suggests that rates of mortality and certain complications may differ between these approaches (Shamji, 2008; Riley, 2010). Additionally, the Washington HCA was interested in examining whether fusion outcomes differed by surgical setting (i.e., inpatient vs. ambulatory/outpatient).

Data on harms and/or subgroups of interest were also obtained from large (>50 patients), long-term (≥12 months of follow-up) case series evaluating cervical fusion.

Study Quality

We used standardized criteria specific to previous systematic reviews in back pain to rate the quality of each included RCT; these criteria have also been widely adopted for use in studies of neck pain (Nikolaidis, 2010). The criteria, which related to issues of study design, reporting, and minimization of bias, are presented in Appendix A. RCTs meeting a majority of criteria (i.e., 5 of 9) were deemed to be “higher quality”. We used general criteria to assess the quality of comparative cohort studies, using the categories “good”, “fair”, or “poor”, based on the criteria employed by the U.S. Preventive Services Task Force (AHRQ, 2008) to assess these studies in terms of comparability of study populations, retention of patients during follow-up, use of standardized and/or validated outcomes, and level of attention paid to confounders.

Study quality was not assessed for case series, as the focus of quality ratings was on the level of bias in assessing the *comparative* impact of fusion vs. alternative treatments on measures of effectiveness and harm.

Data on costs and potential cost-effectiveness were obtained primarily from a newly-developed decision-analytic model that simulated and compared multiple treatment pathways in patients with symptomatic cervical DDD, as described in the “Comparative Value” section on page 20.

Evidence on Comparative Clinical Effectiveness (KQ 1)

Overview of Evidence & Data Quality

Of the 14 RCTs identified (total N=1,209), nearly all (13) focused entirely on patients with symptoms and radiographic evidence of cervical radiculopathy; 1 included patients with evidence of disc herniation. Most available RCTs limited patients to those with single- or 2-level disease. ***Importantly, we found no RCT evidence for spinal fusion procedures in patients with only generalized neck pain.*** Sample sizes were generally small, ranging from 10-50 patients per treatment arm.

The 7 comparative cohort studies included 929 patients evaluated in single- and multicenter studies, as well as nearly 100,000 patients assessed in a retrospective evaluation of the Nationwide Inpatient Sample database maintained by the U.S. Agency for Healthcare Research and Quality (AHRQ) (Shamji, 2008). Of the 7 studies, 1 was prospective.

Study quality is presented in Table ES1 below by study type and fusion comparator. A total of 10 of the 14 RCTs were identified as higher quality, including 1 comparing fusion to conservative management, 3 with minimally-invasive surgery as a comparator, and 6 comparing fusion to alternative open surgical approaches. Among the 7 comparative cohort studies, none were identified as good quality. Four studies were deemed to be of “fair” quality, including 1 comparing fusion to conservative management, 1 comparing

fusion to foraminotomy, 1 comparing fusion procedures performed in inpatient vs. outpatient settings, and 1 comparing anterior to posterior fusion techniques.

Table ES1. Studies of cervical fusion: study quality, by type of study and patient population.

<i>Study Type</i>	<i>Comparator</i>	<i>Higher</i>	<i>Lower</i>
RCT	Physical Therapy/ Cervical Collar	1	0
	Discectomy	5	2
	Discectomy/Foraminotomy	1	1
	Microdiscectomy	2	0
	Endoscopic discectomy	1	0
	Endoscopic foraminotomy	0	1
Comparative Cohort	Interdisciplinary Rehabilitation	1	0
	Laminoplasty	0	1
	Foraminotomy	1	0
	Fusion (in- vs. outpatient)	1	2
	Fusion (anterior vs. posterior)	1	0

Findings are organized by type of comparator to fusion in the sections that follow. No comparative data were available comparing fusion to minimally-invasive *nonsurgical* management options such as spinal injections, radiofrequency denervation, or coblation nucleoplasty.

Spinal Fusion vs. Conservative Treatment

A total of 2 studies, an RCT (Persson, 2001) and a cohort study (Mayer, 2002) compared cervical spinal fusion to conservative management approaches. These studies are summarized by outcome and population in the sections below.

“Treatment Success”

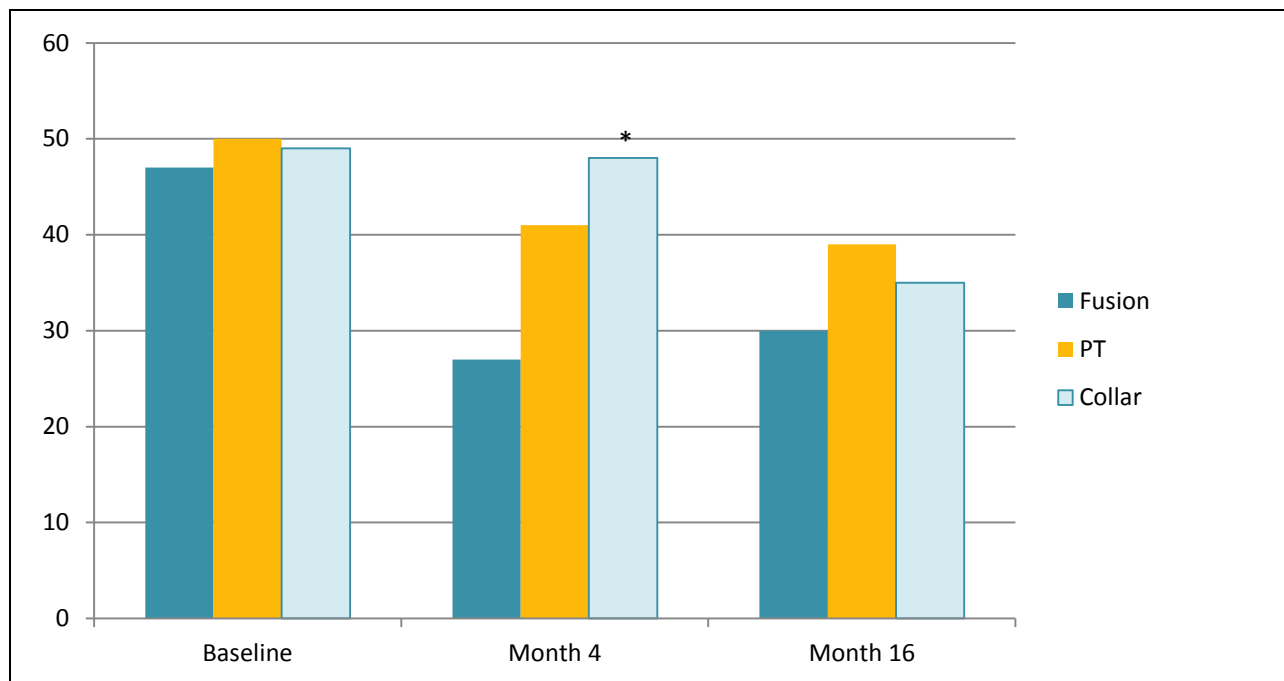
Neither of the studies comparing fusion to conservative treatment included measures of treatment success.

Pain and Function

A higher-quality RCT comparing outcomes for patients with cervicobrachial pain of > 3 months' duration and nerve root compression due to spondylitic spurs randomized 81 patients into equal groups receiving anterior discectomy with fusion, physical therapy, or cervical collar immobilization; patients were followed for 16 months (Persson, 2001). Pain

was evaluated on a 100 mm VAS scale and measured at baseline, 4 months, and 16 months. As noted in Figure ES1 below, pain was reduced at 4 months among fusion patients vs. those receiving either form of conservative management; for cervical collar immobilization, this difference was statistically significant. By month 16, however, the gap in pain scores between conservative management and fusion had narrowed, and VAS scores did not differ statistically at this timepoint. (NOTE: 5-10 point changes on VAS scores represent the minimum change that would be considered “clinically important”, and changes $\geq 30\%$ from baseline represent those that would involve significant improvements for patients).

Figure ES1. Self-rated current pain on visual analogue scale, fusion vs. physical therapy vs. cervical collar.



*: $p < .01$, fusion vs. collar; all other comparisons not statistically significant

Source: Persson et al., *Disability & Rehabilitation*;2001;23:325-35.

Data on pain and function were also available from the comparative cohort study prospectively evaluating the effects of anterior fusion in combination with an interdisciplinary rehabilitation program compared to interdisciplinary rehabilitation alone in 202 patients filing worker's compensation claims for cervical spinal disorders (Mayer, 2002). Rehabilitation consisted of medically-supervised exercise, psychological counseling, workplace and vocational services, and case management. Patients were followed for 12 months. No statistically-significant differences between groups were noted during follow-up in measures of pain, including a 10 cm VAS scale and a questionnaire-based VAS scale known as the Million VAS (Anagnostis, 2003). In addition, no statistically-significant differences were observed in either mean cumulative scores for physical function or the

percentage of patients with total cumulative functional scores demonstrating a “significant degree of pathology” (Mayer, 2002).

Quality of Life

In the Persson RCT, no statistically-significant differences between fusion and physical therapy were observed in Sickness Impact Profile or Mood Adjective Check List scores at any point during follow-up (Persson, 2001). Quality of life was also evaluated in the cohort study comparing fusion and interdisciplinary rehabilitation to rehabilitation alone (Mayer, 2002); however, such evaluation focused only on mean Beck Depression Inventory scores at 12 months without controlling for baseline levels or change from baseline.

Return to Work

Work-related outcomes were not evaluated in the Persson RCT. In the Mayer comparative cohort study of fusion vs. interdisciplinary rehabilitation, no statistically-significant differences were observed between treatment arms in the percentages of patients returning to full or modified work, returning to work at the same employer, or filing additional claims for recurrent injury at 12 months (Mayer, 2002).

Spinal Fusion vs. Discectomy or Foraminotomy

A total of 13 RCTs (9 higher-quality) examined the effects of fusion compared to discectomy or foraminotomy for cervical DDD. In 10 of these, the comparator was discectomy, microdiscectomy, or endoscopic discectomy alone. In one RCT, separate treatment arms receiving discectomy or foraminotomy were included (Wirth, 2000), and in another, comparator patients received a combination of discectomy and foraminotomy (Martins, 1976). Patients in a third RCT received endoscopic foraminotomy (Ruetten, 2008). Characteristics of all RCTs comparing fusion to these alternative surgical approaches are summarized in Table ES2 on the following page. Fusion was compared to foraminotomy in a single comparative cohort study of 292 patients who were treated for radicular symptoms and followed for 6 years (Korinith, 2006).

“Treatment Success”

Treatment success was evaluated in 6 of the 9 higher-quality RCTs. In one, 3 types of discectomy with fusion (autograft, polymethylmethacrylate [PMMA] graft, and titanium cage) were compared to microdiscectomy alone in 125 patients with single-level cervical disc disease and radiculopathy who were treated at a single institution in Switzerland and followed for 12 months (Barlöcher, 2002). Based on Odom’s criteria, a greater percentage of patients undergoing fusion with titanium cage had “excellent” or “good” results vs. microdiscectomy alone at 12 months (94.4% vs. 75.5%, $p < .02$); differences were not statistically-significant for the other fusion groups compared to microdiscectomy. No statistically-significant differences were observed for measures of treatment success in the other higher-quality RCTs.

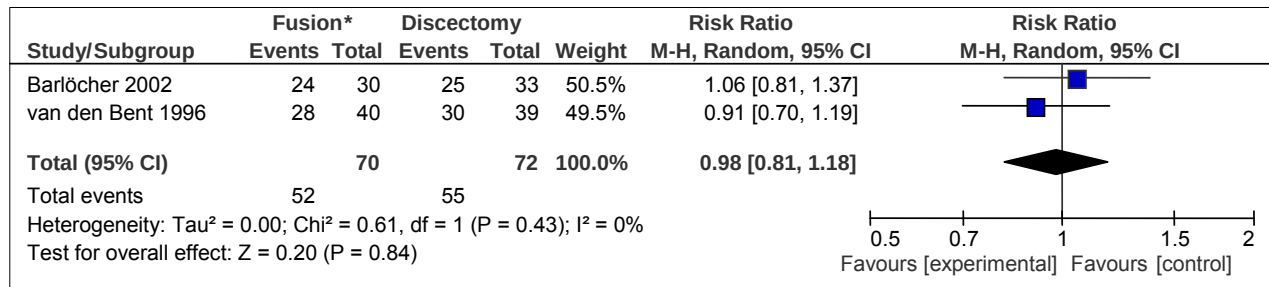
The retrospective comparative cohort study also evaluated outcome based on Odom’s criteria. In this study, an assessment of 292 patients receiving either PMMA fusion or

posterior foraminotomy (Korinth, 2006), long-term outcome was assessed after a mean of 6 years. The number of patients reporting excellent or good outcome was statistically-significantly greater in the fusion group (93.6% vs. 85.1%, $p<.05$).

Table ES2. Characteristics of RCTs comparing fusion to discectomy or foraminotomy.

Author	Year	Comparator(s)	Sample Size	Study Duration (Months)	Quality
Abd-Alrahman	1999	Discectomy	90	15	Lower
Barlöcher	2002	a--Microdiscectomy b--PMMA Fusion c -- Fusion w/ Cage	125	12	Higher
Dowd	1999	Discectomy	84	54	Lower
Hauerberg	2008	Discectomy	86	24	Higher
Martins	1976	Discectomy and foraminotomy	51	12	Higher
Oktenoglu	2007	Microdiscectomy	20	18	Higher
Rosenørn	1983	Discectomy	63	12	Higher
Ruetten	2009	Endoscopic discectomy	120	24	Higher
Ruetten	2008	Endoscopic foraminotomy	200	24	Lower
Savolainen	1998	a--Discectomy b--Fusion w/Plating	91	36	Higher
van den Bent	1996	Discectomy	81	24	Higher
Wirth	2000	a--Discectomy b--Foraminotomy	72	60	Lower
Xie	2007	a -- Discectomy b--Instrumented Fusion	45	24	Higher

We conducted a random-effects meta-analysis examining the likelihood of treatment success for fusion vs. discectomy based on data from 2 studies using Odom's criteria to assess treatment success. No statistically-significant difference was observed, as noted in Figure ES2 below (Rate ratio [RR]: 0.98, 95% CI: 0.81, 1.18; $p=.84$).

Figure ES2. Meta-analysis of treatment success, based on Odom's criteria.

*Anterior discectomy and fusion

Pain and Function

Information on pain was available from 6 of the 9 higher-quality RCTs comparing fusion to alternative surgical procedures. No significant effects of treatment on pain were observed in 4 of these RCTs. In the van den Bent RCT comparing discectomy with PMMA fusion to fusion alone (van den Bent, 1996), the percentage of patients reporting relief of neck pain was statistically-significantly greater in the fusion group at 6 weeks (78% vs. 43% for discectomy, $p=.04$). Pain relief improved in the discectomy group thereafter, however, and differences were no longer statistically-significant for the remainder of the 24-month follow-up. The percentage of patients with any improvement in VAS neck or radicular pain was assessed at 2, 6, and 12 months in the RCT comparing 3 types of fusion to microdiscectomy alone (Barlöcher, 2002). At month 12, there was a statistically-significant difference in favor of fusion with titanium cage (97.3% vs. 81.9% for microdiscectomy alone, $p<.05$); no other measures differed statistically at any timepoint.

Quality of Life

Data on quality of life were found in the Xie RCT comparing fusion with or without instrumentation to discectomy (Xie, 2007). Quality of life was assessed via the SF-36 instrument; in repeated-measures analyses, no statistically-significant differences were noted between groups in SF-36 total scores as well as scores for individual domains.

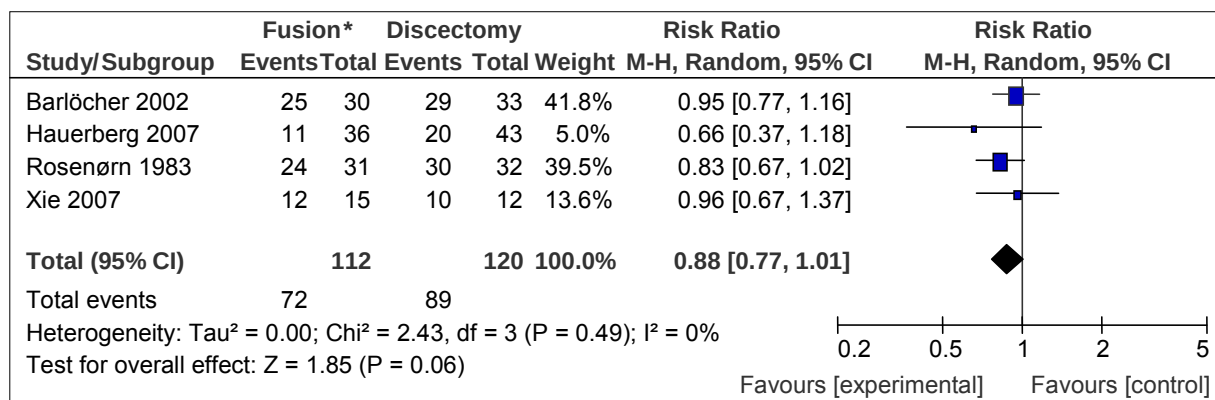
Return to Work

Data on return to work were available from 4 higher-quality RCTs. The proportion of patients returning to work did not statistically differ at any timepoint between treatment groups in the previously-described Hauerberg and Xie RCTs. In a third RCT examining 63 patients undergoing anterior cervical discectomy with and without fusion who were followed for 12 months (Rosenørn, 1983), a statistically-significantly greater percentage of fusion patients had returned to work at 2, 3, 4, 6, and 9 weeks postoperatively; differences were no longer significant when measured at weeks 12, 26, and 52, however. Finally, the percentage of working individuals not yet able to return to work was assessed in the Barlocher RCT (Barlöcher, 2002). At 6 months, a statistically-significantly lower percentage of patients undergoing fusion with titanium cage were not yet able to work as compared to

microdiscectomy alone (5.5% vs. 18.1%, $p < .05$). However, differences were nonsignificant when evaluated at 12 months.

We also assessed return to work in a random-effects meta-analysis comparing fusion to discectomy in 4 higher-quality RCTs. It is important to note that we used timepoints for return-to-work data that were uniform across all available RCTs (i.e., 12-24 months); the “early” benefits of fusion as noted in some studies above were therefore not considered in this analysis. As shown in Figure ES3 below, the pooled estimate directionally favored discectomy in terms of return to work at 12-24 months, but this difference was not statistically significant. A second analysis focused return to work at 6 months following surgery in two of these RCTs (Barl cher, 2002; Xie, 2007) also did not yield statistically-significant results.

Figure ES3. Meta-analysis of likelihood of return to work at 12-24 months, fusion vs. discectomy.



* Anterior discectomy and fusion

Potential Harms (KQ 2)

Cervical spinal fusion is associated with a number of harms, some of which are common to both fusion and other surgical alternatives, and others of which are unique to the fusion procedure itself (e.g., pseudarthrosis). Relevant harms are presented on Table ES3 on the following page, described in the sections that follow, and categorized according to their timing.

Information from the observational studies examined in this review suggests that risks of surgical interventions may be higher than reported in RCTs. For example, in the 14 RCTs examined for this appraisal, only 1 provided any data on perioperative mortality (Xie, 2007; rates were 0% in both treatment groups). In contrast, rates of in-hospital and 30-day mortality from large database studies, while $<1\%$, were certainly nonzero (Shamji, 2008; Wang, 2007). Other harms that may not be apparent until after hospital discharge, such as pneumonia or venous thrombosis, appear relatively rarely in observational studies but are not reported at all in available RCTs.

Table ES3. Reported ranges of rates of potential harms from RCTs and comparative cohort studies, by type of study and comparator.

Type of Harm	Fusion		Conservative Rx		Surgical Approaches				No. of studies reporting harms		
% of Patients with Event											
	RCT	CC	RCT [¥]	CC [¥]		RCT		CC		RCT	CC
<i>Perioperative Events</i>					Discectomy	Foraminotomy	Laminoplasty	Foraminotomy			
Mortality	0	0-0.05	NR	NR	0	NR	0	NR		1	2
<i>Complications</i>											
○ Hemorrhage	NR	NR	NA	NA	NR	NR	NR	NR		0	0
○ Hematoma	1-6.6	0-0.8	NA	NA	0	NR	NR	0		4	2
○ Nerve Damage*	2.5-8	0.8-6	NA	NA	0-8	9-14	6	0.6		3	3
○ Paralysis	NR	NR	NA	NA	NR	NR	NR	NR		0	0
○ Infection	0-13	0-0.02	NA	NA	0	4	6	0.6		2	4
○ Hoarseness	5-20	1.6	NA	NA	0-8	NR	NR	0		3	1
○ Dysphagia	3-17.5	0-10	NA	NA	15.2-25	3.3	NR	0		4	3
○ Thrombosis	NR	0.02	NA	NA	NR	NR	NR	NR		0	1
○ CSF Leak	NR	0	NA	NA	NR	NR	NR	NR		0	1
Return to OR	NR	0	NA	NR	NR	NR	10	0.6		0	2
<i>Long term Events†</i>											
<i>Complications</i>											
○ Chronic pain	4.8	NR	NR	NR	2.6	NR	NR	NR		2	0
○ ASD	6.9-16.6	NR	NR	NR	2.4-8.3	NR	NR	NR		2	0
○ Pseudarthrosis	8	3.2	NA	NR	0	NR	NR	NR		1	1
○ Neurological Decline*	3-23.3	0	14.2	NR	27.2	NR	NR	0		2	1
○ Myelopathy	NR	NR	NR	NR	NR	NR	NR	NR		0	0
○ Muscle weakness	NR	NR	NR	NR	NR	NR	NR	NR		0	0
○ Paresthesia	14.2	3	8.2	NR	NR	NR	0	NR		1	1
Subsequent Rx	0.5-21.7	0-3.2	13.8	3.7	1.1-9.8	5.1	NR	1		10	4

NR: Not reported; NA: Not Applicable; ASD: Adjacent segment disease

¥: Conservative treatment = Physiotherapy; ¥: Conservative treatment = Interdisciplinary treatment; *: Nerve damage includes numbness, weakness and nerve palsy. **: Neurological decline includes sensory loss and neurological deficit; † Rates are annualized.

Data from RCTs and Comparative Cohorts

As mentioned previously, certain types of complications and adverse outcomes were not reported in any available RCT or comparative cohort study. For example, data on perioperative paralysis or hemorrhage were not available in any RCT or comparative cohort study, and information on thrombosis was only reported in comparative cohort studies of fusion. In addition, there was a significant degree of overlap between treatment alternatives in reported rates of complications, with no clear or discernible pattern of differential rates for most complication types.

As described previously, perioperative mortality was rarely identified or reported in any RCT or comparative cohort study. Among perioperative complications, the most frequently reported for fusion included dysphagia, hoarseness, and infection. Not surprisingly, generally higher rates of dysphagia and hoarseness were reported for fusion, given the increasing use of anterior surgical approaches for this procedure (Shamji, 2008); rates were similar to those reported for discectomy in available RCTs, however. The upper end of the range of infection rates was higher with fusion relative to other procedures, which was related to 2 cases of donor site infection in a small RCT (Xie, 2007). Leakage of cerebrospinal fluid was rarely reported for any type of procedure.

Rates of longer-term events were annualized to account for differential follow-up across studies. Mortality was again rarely reported in RCTs or comparative cohort studies with a significant degree of overlap by intervention. In some fusion studies, relatively high rates of adjacent segment disease and pseudarthrosis were reported. High rates of neurological decline were also reported in 1 RCT comparing fusion to discectomy, but these included measures of unchanged or worsened sensory loss in 1 RCT (Persson, 2001). Rates of repeat surgery or subsequent therapy were more commonly reported across study types. Again, ranges of reported rates overlapped significantly between them. The highest rate of reoperation was reported in the Persson RCT, where 8 of 30 patients underwent a second surgery by 16 months of follow-up (Persson, 1997); 6 of these had surgery adjacent to the initial surgical site.

Data from Fusion Case Series

Long-term data on harms were reported in 46 reports of case series, describing events in nearly 6,000 patients. Follow-up ranged from 1 to 21 years in these studies. The most frequently-documented events included reoperation (n=23), pseudarthrosis (n=19), and adjacent segment disease (n=13), with ranges similar to those reported in RCTs and comparative cohorts. Mortality data were reported in 9 studies; rates ranged from 0-2.6% on an annualized basis.

In an effort to create an exhaustive list of long-term adverse events reported in patients undergoing cervical fusion, all reported harms from these studies are listed in Table ES4 on the following page. Recent data on risks associated with any surgical procedure are also provided for additional context within the main body of the report.

Table ES4. Reported ranges of annualized rates of potential harms from fusion case series.

<i>Type of Harm</i>	<i>Number of Studies</i>	<i>% of Patients With Event (Range)</i>
Mortality	9	0-2.6
Complications		
Adjacent segment disease	13	0-27
Arm pain	1	0.1
Donor site pain	1	8.7
Dysphagia	2	3.6-33
Dysphonia	1	2.0
Hepatitis C infection	1	0.08
Hoarseness	1	0.08
Laryngeal paresis	2	0.5-1.4
Neck pain	3	0.3-2.5
New-onset radiculopathy	2	0.8-5.0
Paresis	1	1.3
Pseudarthrosis	19	0-8.5
Ptosis	1	0.5
Tetraparesis	1	0.08
Upper limb numbness	2	0.3-2.2
Upper limb weakness	1	0.4
Worsening headache pain	1	25.5
Worsening lower extremity function	1	1.7
Worsening sensory function/strength	2	0.7-2.7
Worsening upper extremity function	1	0.4
Re-operation	23	0-6.8
Inability to return to work	2	0.5-4.3

Differential Effectiveness/Safety for Key Patient Subgroups (KQ 3)

Data examining the differential effects of cervical fusion in key patient subpopulations were obtained from RCTs, comparative cohort studies and case series where available. Findings are reported below by type of study and subgroup in the sections that follow.

Randomized Controlled Trials

Single- vs. 2-level Surgery

In an RCT comparing anterior cervical discectomy with fusion to discectomy alone in 51 patients (Martins, 1976), the percentage of patients with excellent or good results (complete relief or minimal persistence of preoperative symptoms and abnormal signs improved or unchanged) was compared by level of surgery. Among patients undergoing single-level

procedures, the percentage of those with excellent or good results was higher in the fusion group (82% vs. 66% for discectomy), while the rate for 2-level surgery was lower for fusion (26% vs. 63%). Rates were not tested statistically.

Smoking Status

In the RCT comparing fusion to physical therapy and cervical collar immobilization (Persson, 2001), the improvement in VAS pain among those undergoing surgery was found to be better among nonsmokers vs. smokers ($p < .05$), although the actual data on VAS changes among these subgroups were not provided.

Gender

In an RCT comparing anterior discectomy with and without fusion in 63 patients (40 men and 23 women) (Rosenorn, 1983), a higher percentage of males ($n=16$) undergoing fusion had excellent or good results (defined as return to previous occupation with no or minimal symptoms) at 12 months (15 [94%] vs. 19 [86%] for discectomy), while a lower percentage of females ($n=13$) had excellent or good results (5 [38%] vs. 8 [89%] for discectomy). While statistical testing was not performed for the stratified analysis across treatment groups, the percentage of patients with treatment success in the fusion group was greater ($p < .005$) among males vs. females.

Comparative Cohort Studies

Data were available from 4 comparative cohort studies; the focus of attention in the descriptions below is on the 2 studies that were fair-quality. In these studies, the subgroups of interest defined the study comparators (i.e., inpatient vs. outpatient fusion, posterior vs. anterior fusion).

Inpatient vs. Outpatient Fusion

The effects of fusion performed in inpatient vs. ambulatory care settings were assessed in a single fair-quality comparative cohort study. In this study, a comparison of 50 consecutive day-surgery patients to 53 retrospectively-analyzed inpatient controls (Silvers, 1996), no statistically-significant differences by setting were noted for functional outcomes, VAS pain, performance of activities of daily living, or return to work or normal activities. The rate of reoperation was numerically higher in the inpatient group (9.4% vs. 4.0% for outpatient), but this difference was not statistically tested.

Anterior vs. Posterior Fusion

Comparisons of anterior vs. posterior fusion techniques were performed in 1 fair-quality retrospective cohort study. This study examined differences between anterior and posterior fusion techniques using the U.S. Nationwide Inpatient Sample (NIS) database (AHRQ, 2012), and assessed hospital outcomes among nearly 100,000 patients undergoing anterior or posterior fusion for cervical DDD between 1988 and 2003 (Shamji, 2008). Patients were further stratified by whether their record included a diagnosis of myelopathy (approximately 75% of patients did *not* have such a diagnosis). On an unadjusted basis, patients undergoing posterior fusion experienced higher rates of death and major complications ($p \leq .001$), regardless of the presence of myelopathy on the record. Length of

stay and inflation-adjusted cost was also significantly increased, as shown in Table ES5 on the following page (data on myelopathy patients are displayed for context). After adjustment for differences in patient characteristics between groups, patients undergoing posterior fusion had significantly higher rates of all complications except for thrombophlebitis when compared to anterior fusion.

Table ES5. Outcomes of anterior vs. posterior fusion surgery, stratified by neurological status (n=96,773).

<i>Outcome</i>	<i>Anterior</i>		<i>Posterior</i>		<i>p-value</i>
	No Myelo	Myelo	No Myelo	Myelo	
Death (%)	0.05	0.52	0.36	0.67	<.001
Pulmonary embolism (%)	0.02	0.06	0.14	0.12	<.001
Pneumonia (%)	0.14	0.62	1.04	1.10	<.001
Transfusion (%)	0.34	1.02	3.33	5.64	<.001
Thrombophlebitis (%)	0.02	0.07	0.04	0.16	.001
Infection %	0.02	0.10	0.36	0.55	<.001
Length of stay (mean days)	1.95	3.42	4.37	5.76	<.001
Inflation-adjusted cost (\$)	20,639	28,581	34,963	40,313	<.001

Source: Shamji et al., J Neurosurg: Spine, 2008;9:10-16

Myelo: Myelopathy diagnosis on inpatient record

While the results of this study suggest higher rates of complications with posterior fusion, it is often the case that contemporary posterior techniques are reserved for patients with greater disability and/or spinal instability who require multi-level intervention (Caridi, 2011). Information from administrative databases is understandably limited in controlling for differences in clinical presentation.

While not considered a “comparative cohort” study per se, an earlier study analyzing data from the NIS also showed higher rates of complications and mortality for posterior vs. anterior fusion (Wang, 2007); in multiple logistic regression analyses, posterior fusion was significantly associated with a higher risk of in-hospital complications (but not mortality).

Fusion Case Series

A total of 28 fusion case series stratified data according to key patient subgroups of interest; findings are presented in Appendix C, Table C23 and described in further detail below.

Single- vs. Multi-Level Surgery

Subgroup analyses of patients undergoing single- and multi-level fusion procedures were analyzed in 17 case series. In most of these studies, increases in the number of levels involved were associated with increased rates of pseudarthrosis, although the statistical significance of any observed differences was often not tested. Reoperation rates and

development of adjacent segment disease were assessed in 3 studies (Matsumoto, 2009; Heidecke, 2000; Bishop, 1996); no statistically-significant differences in these rates according to number of levels involved were observed. In one series, rates of dysphagia were reported for patients undergoing 1-, 2-, and 3+ level anterior fusion; these rates increased according to the number of levels involved (11% vs. 24% vs. 43%, significance not tested) (Riley, 2005). Findings from a later systematic review by the same author were similar in nature (Riley, 2010).

Smoking Status

Six case series examined the impact of pre-operative smoking status on adverse events and clinical outcomes. While 1 study described statistically-significantly fewer cases of pseudarthrosis among non-smokers (20% vs. 50% for smokers, $p=.001$) (Goldberg, 2002), 2 found no correlation between smoking status and development of pseudarthrosis or adjacent segment disease (Matsumoto, 2009; Bindal, 2007). In terms of clinical outcomes, 3 series evaluated the effect of smoking status on treatment success using Odom's criteria. In one, data from a series of 144 patients indicated that smokers had a significantly ($p=.008$) higher rate of fair or poor outcomes (Jensen, 2009), although actual percentages were not reported. Another study ($n=190$) found non-smokers to have a significantly higher rate of excellent outcomes (43.0% vs. 27.3%, $p<.03$) (Hilibrand, 2001). A third smaller series ($n=66$) found no statistically-significant differences in this measure (Samartzis, 2005).

Gender

Clinical outcomes and adverse events did not statistically differ according to patient gender in 4 case series (Chen, 2009; Matsumoto, 2009; Bindal, 2007; Javid, 2001). Data from an additional series did find statistically-significantly greater rates of dysphagia (41.2% vs. 22.9% for women vs. men, $p<.05$) and dysphonia (28.2% vs. 8.6%, $p<.05$) among women (Yue, 2005b).

Anterior vs. Posterior Fusion

Fusion approach was evaluated in a single case series of 120 patients undergoing revision procedures for pseudarthrosis (Carreon, 2006). Over 3-4 years of follow-up, the rate of subsequent reoperation was lower among patients undergoing posterior revision (2.2% vs. 44.4%), although this difference was not tested statistically.

Duration of Symptoms

Four case series analyzed the impact of symptom duration on clinical prognosis and long-term outcomes. While 1 study found no correlation (Chen, 2009), 3 case series demonstrated significantly better outcomes in patients with shorter duration of symptoms (Kadoya, 2003; Hamburger, 2001; Heidecke, 2000). In one study, patients with a symptom duration of less than 3 months had a statistically-significantly higher rate of excellent outcomes based on Odom's criteria as compared to those with symptoms > 12 months (48.9% vs. 33.3%, $p<.03$) (Hamburger, 2001). In a study of anterior microdiscectomy with fusion, no significant difference in the percentage of patients with a self-reported "good" outcome was seen in patients with radiculopathy symptoms; however, patients with

myeloradiculopathy symptoms for < 1 year had a significantly higher rate of good outcome (78.9% vs. 50.0%, $p < .01$) (Heidecke, 2000). Finally, a significant ($p = .01$) correlation was observed between outcome scores derived from the Neurological Cervical Spine Scale and duration of symptoms. Those with symptom duration of 6 months or less had the highest mean score (3.3); scores declined with increasing symptom duration, culminating with score of 1.2 among patients with symptom duration > 4 years (Kadoya, 2003).

Age

Seven case series provided data on patient subgroups based on age. While 3 studies described no correlation between age and clinical outcomes such as the Neck Disability Index and the Hirabayashi recovery rate (Chen, 2009; Matsumoto, 2009; Bindal, 2007), 3 other case series demonstrated statistically-significant differences based on patient age in rates of adverse events and neurologic outcomes (Cabraja, 2011; Kadoya, 2003; Heidecke, 2000). For example, the rate of neurologic improvement significantly declined with increasing age, from 71.0% among those age < 40 years to 11.1% among patients age 70 years or older ($p = .014$) (Kadoya, 2003). An additional case series found a greater incidence of dysphagia in younger (mean age 48 years) vs. older (mean age 55 years) patients (Yue, 2005b); differences were not tested statistically, however.

Workers' Compensation

Goldberg et al. evaluated outcomes in 80 patients with and without worker's compensation (Goldberg, 2002). Patients underwent anterior discectomy and fusion with a mean follow-up of 4 years. There were no statistically-significant differences in outcome based on Odom's criteria; incidence of donor site pain and the development of pseudarthrosis also did not differ. Seventy percent of patients with workers' compensation returned to work without restriction vs. 80% of patients without workers' compensation, although this difference was not tested.

In a case series involving 66 patients undergoing anterior discectomy and fusion, a subgroup analysis of work- and non-work-related injuries demonstrated no significant differences in outcome based on Odom's criteria at 22 months of follow-up (Samartzis, 2005).

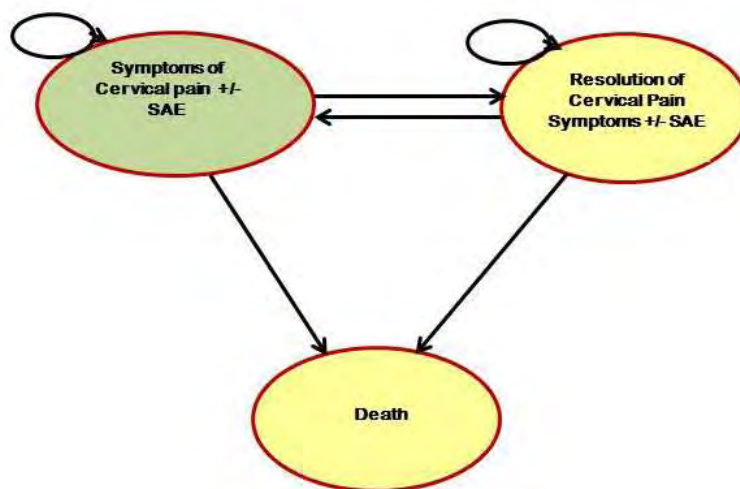
Analysis of Comparative Value (KQ 4)

The comparative value of cervical fusion was assessed through a review of existing literature on cost-effectiveness and the development of a *de novo* decision analytic model and subsequent performance of cost-utility analyses. Decision analysis is a systematic quantitative approach for assessing the relative value of one or more different decision options. To structure the analysis a simulation model is constructed. In the kind of model used for our analysis, called a Markov model, patients with the condition in question are assumed to be in one of a limited number of distinct clinical "states", e.g. "without symptoms". Each state is assigned a "utility", which represents an estimate of the relative quality of life of patients in that state. The probability of patients transitioning from one

state to another is estimated from the clinical literature and/or expert input. The model is then used to compare clinical outcomes and costs over time across different “pathways” of care using different clinical interventions. One pathway is termed the “reference” pathway as it serves as the general comparator for all other interventions. Comparisons can be made of cumulative clinical events, such as complications; of cumulative mortality and quality of life; and of costs.

The basic outline of the decision model designed for this evaluation is shown in Figure ES4 below. The model was structured so that, as time passes, the clinical status of patients with cervical DDD is represented by one of the three mutually exclusive states shown. The model shifted patients between the different model states at three-month intervals over a 1-3 year time horizon.

Figure ES4. Markov Disease State Diagram for Cervical Degenerative Disc Disease



SAE = Serious adverse event.

Anterior cervical discectomy and fusion (ACDF) was chosen as the primary approach of spinal fusion for the analysis. The reference case analysis compared spinal fusion with conservative management and assumed that fusion would initially have more pronounced effects versus conservative management but the effects for conservative therapy “catches up” over time (fusion 40% better at 6 months; 20% better at 12 months, 10% better at 24 months; equal at 48 months), based on data from a randomized study judged to be the most reliable source for this purpose (Persson, 2001). Baseline transition probabilities for spinal fusion were derived using data from an RCT which compared fusion with cervical arthroplasty (Sasso, 2011). Physical therapy was the chosen conservative management

modality in the reference case. Comparisons of spinal fusion with other potential treatment alternatives of interest are also reported, as follow below:

- Manual therapy with spinal manipulation
- Epidural steroid injections
- Posterior laminoforaminotomy
- Anterior discectomy without fusion

Outcome Measures

This evaluation assessed key clinical outcomes related to the diagnosis of cervical DDD including the proportion of patients who had resolved cervical pain symptoms, the proportion of patients who had cervical pain symptoms, and the occurrence of rare but important adverse events such as perioperative complications and longer-term complications such as adjacent segment disease, and death. Costs related to treatments, total costs to the payer, and the impact of different treatment pathways on quality of life (as reflected by QALYs) were also calculated.

Key Assumptions

Listed in Table ES6 below are the key assumptions made in designing the model for this evaluation. Our model was based to some degree on past decision models associated with the management of cervical DDD (Carreon, 2012; Van der Velde, 2008) as well as on clinical studies comparing spinal fusion with conservative treatment or cervical arthroplasty (Persson, 2001; Sasso, 2011).

Table ES6. Key Model Assumptions

Prior to entering the model patients have had an initial trial of conservative management lasting between 6-12 weeks which did not resolve symptoms.

The gap in clinical benefit between spinal fusion and conservative treatment narrows over time as patients with conservative treatment reach similar pain and function levels, consistent with observations from clinical studies.

All forms of conservative management (e.g., physical therapy, spinal manipulation) have approximately equal clinical effectiveness.

Patients who do not resolve symptoms of cervical pain will have a reduction in health related quality of life and will incur costs equivalent to approximately \$1,983 per cycle (~ equal to cost of ongoing physical therapy).

Summary Model Results

Spinal Fusion vs. Conservative Treatment

Table ES7 on the following page provides the results for adult patients with severe cervical pain who have failed an initial conservative therapy course of 6-12 weeks' duration. A greater percentage of patients using spinal fusion resolved their cervical pain symptoms than patients treated with conservative therapy, although conservative therapy "catches up" over time; the absolute difference in this percentage was 14.8% after 1 year, but only 3.6% after 3 years.

Table ES7. Clinical Results from Reference Case Analyses

Time Horizon	Symptoms of Cervical Pain	Resolution of Symptoms of Cervical Pain	Death
Spinal Fusion			
1 year	25.8%	74.0%	0.2%
2 year	26.3%	73.2%	0.5%
3 year	26.5%	72.9%	0.7%
Conservative Treatment			
1 year	40.6%	59.2%	0.2%
2 year	33.7%	65.9%	0.5%
3 year	30.1%	69.2%	0.7%
Absolute Difference			
1 year	-14.8%	14.8%	0.0%
2 year	-7.3%	7.3%	0.0%
3 year	-3.6%	3.6%	0.0%

Following the pattern of clinical benefit, the incremental cost to achieve 1 additional treatment response (i.e., a patient with resolution of symptoms) increased from \$174,515 in year 1 to \$677,917 in year 3, as shown below in Table ES8.

Table ES8. Results of Reference Case Cost-Effectiveness Analysis

	Spinal Fusion		Conservative Therapy		Difference		Cost per Additional Responder
	Cost	% With Resolution of Symptoms	Cost	% With Resolution of Symptoms	Cost	% With Resolution of Symptoms	
1 year	\$31,981	74.0%	\$6,153	59.2%	\$25,828	14.8%	\$174,515
2 year	\$33,957	73.2%	\$8,895	65.9%	\$25,062	7.3%	\$342,380
3 year	\$35,897	72.9%	\$11,204	69.2%	\$24,693	3.6%	\$677,917

From a cost-utility perspective, spinal fusion produced more QALYs than conservative therapy, albeit an increased cost (range \$24,693 - \$25,828 across horizons) (Table ES9 on the following page). The incremental cost per QALY gained for spinal fusion versus conservative therapy ranged from \$347,473 to \$579,428 depending on the time horizon considered.

Table ES9. Results of Reference Case Cost-Utility Analysis

	Spinal Fusion		Conservative Therapy		Difference		Cost per QALY, Spinal Fusion versus Conservative Treatment
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
1 year	\$31,981	0.6609	\$6,153	0.6163	\$25,828	0.0446	\$579,428
2 year	\$33,957	1.3060	\$8,895	1.2435	\$25,062	0.0625	\$401,306
3 year	\$35,897	1.9303	\$11,204	1.8592	\$24,693	0.0711	\$347,473

Spinal Fusion vs. Other Treatments

Table ES10 below and on the following page provides a summary of comparisons of spinal fusion with the other treatments. Spinal fusion was slightly more effective and slightly less expensive than laminoforaminotomy (based on Washington HCA reimbursement amounts), but was more expensive than discectomy. Fusion was most cost-effective when compared to initial therapy with epidural steroid injections, as we assumed that such injections would only be one-third as effective as fusion at a constant rate over time.

Table ES10. Comparisons of Spinal Fusion to Other Treatments

Comparator	Incremental Cost for Fusion	Incremental QALYs for Fusion	Incremental Response (% Improvement) for Fusion vs. Comparator	Incremental Cost per QALY Gained (ICER)	Incremental Cost per Responder for Fusion
Manual therapy with spinal manipulation	\$28,465	0.0711	3.6%	\$400,544	\$781,460
Laminoforaminotomy (relative risk (RR) of cervical pain resolution, 0.98 vs. spinal fusion, mean cost, \$29,556)	-\$328	0.0115	2.2%	Less expensive and more effective	Less expensive and more effective

Table ES10. Comparisons of Spinal Fusion to Other Treatments

Comparator	Incremental Cost for Fusion	Incremental QALYs for Fusion	Incremental Response (% Improvement) for Fusion vs. Comparator	Incremental Cost per QALY Gained (ICER)	Incremental Cost per Responder for Fusion
Discectomy (RR of cervical pain resolution, 0.98 vs. spinal fusion, mean cost, \$22,284)	\$6,945	0.0115	2.2%	\$603,558	\$317,757
Epidural steroid Injection (RR of cervical pain resolution, 0.39 vs. spinal fusion, mean cost, \$443 and 2 per cycle)	\$18,831	0.2340	44.4%	\$80,488	\$42,375

Sensitivity and Alternative Analyses

Due to the uncertainty around clinical evidence, a substantive number of sensitivity analyses were conducted to explore the impact of varying parameter values and assumptions within the model. Across a range of assumptions and variation of key model parameters, including discount rate, inclusion of work-loss costs, assumptions regarding treatment effects, subsequent treatment, and specific consideration of side effects, the cost-utility values for spinal fusion exceeded thresholds of \$100,000 per QALY. As one example, when the employer perspective is taken and estimated productivity losses/gains are included for the 3-year time horizon, the incremental cost-effectiveness of spinal fusion versus conservative therapy was \$322,429 indicating that considering productivity has relatively small impact on estimates of the incremental cost-effectiveness of surgery vs. conservative management.

Limitations

There were considerable gaps in available clinical evidence. As a result, findings from the economic evaluation should be interpreted with caution. There was a limited body of clinical evidence comparing spinal fusion with alternative treatments other than surgery. Further, there was considerable variation in patient populations, study design, and outcome definitions across studies, which limits the comparability of evidence. As a result, effect estimates are based on assumptions around the clinical effects of conservative treatment versus spinal fusion, using data derived from the Persson, 2001 study. Because of the underlying uncertainty around clinical effects of fusion versus conservative treatment, we conducted numerous sensitivity analyses where efficacy for surgery versus conservative

treatments was varied. Nonetheless, to obtain more robust comparative clinical and cost-effectiveness estimates, more clinical studies are needed comparing fusion with alternative conservative therapies after patients have had a trial of conservative therapy.

Comparison to Other Economic Studies of ACDF

Carreon et al. conducted a cost-effectiveness analysis of single level ACDF in the United States (Carreon, 2012). Carreon reported cost per QALY estimates of \$106,256 at year 1, \$54,622 at year 2, \$38,836 at year 3, \$29,454 at year 4 and \$24,479 at year 5, and concluded that single-level instrumented ACDF is both effective and durable resulting in QALY gained as compared to other widely accepted healthcare interventions. The results from Carreon differ from those reported in our study largely because the Carreon study *did not compare fusion's costs and effects to any alternative treatment strategy*. Standard guidelines for economic evaluation recommend that a comparator be used when conducting economic evaluations when they are available. Further, Carreon *applied a cost of \$15,714 which is almost half the cost of fusion in the Washington State Health Care Authority*. If the cost of surgery (~\$30,000) in the Washington State Health Care Authority were applied in the Carreon analysis, the cost per QALY estimates in the Carreon study would approximately double.

Although the Carreon study applied similar utility gains for resolving cervical pain to those applied in this report (0.18), it is important to note that assumed utility gains are equivalent to gaining 67.5 days of perfect health each year. These estimates exceed those reported for severe complications such as stroke or myocardial infarction (Sullivan, 2006). Consequently, the utility gains in the Carreon analysis (and our reference case analysis) may not be generalizable to patients with less severe forms of cervical DDD, where utility gains may be less pronounced. These aforementioned issues (no comparator, assumed cost of fusion of \$15,714, and assumed utility gain of 0.18) limit the generalizability of findings from the Carreon analysis to patient populations with more severe forms of cervical DDD in which conservative treatments are not an option. Indeed, we were able to produce findings similar to those reported in the Carreon analysis (~\$40,000 per QALY gained at year 3) when we: 1) did not use a comparator (i.e., assumed conservative treatment costs \$0 and fusion is 100% more effective), 2) assumed fusion costs \$15,714, and 3) applied utility gains of 0.185 for resolution of cervical pain symptoms.

Our analysis is more generalizable to the Washington State Health Care Authority – we consider alternative treatment strategies; use Washington State Health Care Authority specific costs; and our analysis considers multiple sources of utilities, some of which may be more generalizable to broader patient populations such as those less severe forms of disease where an alternative conservative treatment remains an option despite a previous trial of conservative treatment. Nonetheless, further research is needed exploring how gains in health related quality of life vary by disease severity.

The only other study identified compared the cost-effectiveness of various types of fusion (i.e., plating and allograft vs. autograft) (Angevine, 2005). Because this type of comparison was outside the scope of our systematic review, it is not discussed in detail here.

Summary ICER Integrated Evidence Ratings

The ICER integrated evidence rating matrix is shown below; a detailed explanation of the methodology underpinning this rating system can be found beginning on page 30. Separate ratings are provided for cervical fusion in comparison to conservative management (i.e., physical therapy or cervical collar immobilization) and discectomy or foraminotomy respectively.

ICER Integrated Evidence Rating™:

Spinal Fusion vs. Conservative Management (Physical Therapy/Cervical Collar) for Patients with Cervical Degenerative Disc Disease

With Radiculopathic Symptoms: 
Without Radiculopathic Symptoms: 

Comparative Clinical Effectiveness	Superior: A	Aa	Ab	Ac
	Incremental: B	Ba	Bb	Bc
	Comparable: C	Ca	Cb	Cc
	Inferior: D	Da	Db	Dc
	Promising/Inconclusive: P	Pa	Pb	Pc
	Insufficient: I	I	I	I
		a	b	c
		High	Reasonable/Comp	Low
		Comparative Value		

Rationale for ICER Rating

As noted previously, there were no randomized controlled trials focusing only on patients with generalized neck pain only. In fact, most comparative cohort studies also required some documentation of radiculopathic or myelopathic symptoms. Therefore, the evidence for fusion's comparative clinical effectiveness in relation to conservative management in patients without radiculopathy is "Insufficient".

Even for patients with clinical symptoms of radiculopathy and radiographic evidence of nerve root compression there is not a large evidence base comparing outcomes between spinal fusion and conservative management. We identified only 1 RCT and 1 comparative cohort study, neither of which stood out for their methodologic rigor, size, or generalizability.

Nevertheless, despite variability in study design, entry criteria, and outcomes measured, findings were reasonably consistent. Specifically, spinal fusion appeared to provide faster relief of pain and symptoms than conservative management (i.e., physical therapy or cervical collar immobilization) in the short term. Over time, however, these differences diminished and no material differences in outcome were observed by 12 months after intervention. Because of this, and because spinal fusion may cause relatively rare but significant complications, we deemed the overall comparative clinical effectiveness of fusion to conservative management "Comparable". In some patients, however, neck pain and related symptoms may be so severe and disabling that the faster relief potentially afforded by fusion surgery would also allow a quicker return to work and other normal activities. For such patients, fusion might in fact be considered "Incremental" in comparison to ongoing conservative management.

However, fusion is a high-cost intervention; as illustrated by our decision analysis, even the greater short-term clinical and return-to-work benefits assumed for fusion cannot offset its much higher costs relative to conservative management, particularly because these benefits wane over longer time horizons; as such, fusion is associated with high cost-effectiveness ratios and costs per treatment responder at 1 year that only increase over time. As such, the comparative value of fusion vs. conservative management is deemed to be "Low".

**ICER Integrated Evidence Rating™:
Spinal Fusion vs. Discectomy or Foraminotomy
for Patients with Cervical Degenerative Disc Disease**

With Radiculopathic Symptoms

Vs. Discectomy:

Vs. Foraminotomy:



Without Radiculopathic Symptoms:



Comparative Clinical Effectiveness	Superior: A	Aa	Ab	Ac
	Incremental: B	Ba	Bb	Bc
	Comparable: C	Ca	Cb	Cc
	Inferior: D	Da	Db	Dc
	Promising/Inconclusive: P	Pa	Pb	Pc
	Insufficient: I	I	I	I
		a	b	c
		High	Reasonable/Comp	Low
		Comparative Value		

Rationale for ICER Rating

As in comparisons to conservative management, there is insufficient evidence to evaluate the clinical benefits of spinal fusion relative to other major surgical procedures in patients with only generalized neck pain and no confirmatory evidence of radiculopathic symptoms.

In patients with clinical symptoms of radiculopathy and radiographic evidence of nerve root compression, a moderate level of RCT- and cohort-based evidence exists that suggests that clinical outcomes do not materially differ between these types of surgery, either over

the short- or long-term. Differences in rates of complications and subsequent surgery have been observed in some studies, but findings have not been consistent. We therefore chose to rate the comparative clinical effectiveness of spinal fusion to discectomy or foraminotomy as “Comparable”.

However, data from the Washington HCA suggests that, while average payments for cervical fusion and foraminotomy are similar (approximately \$30,000), payments for discectomy procedures are lower (\$22,000). Given that equivalent clinical outcomes would be expected with all of these procedures, we chose to rate the comparative value of spinal fusion relative to foraminotomy as “Reasonable/Comparable”, and the comparative value of spinal fusion relative to discectomy as “Low”.

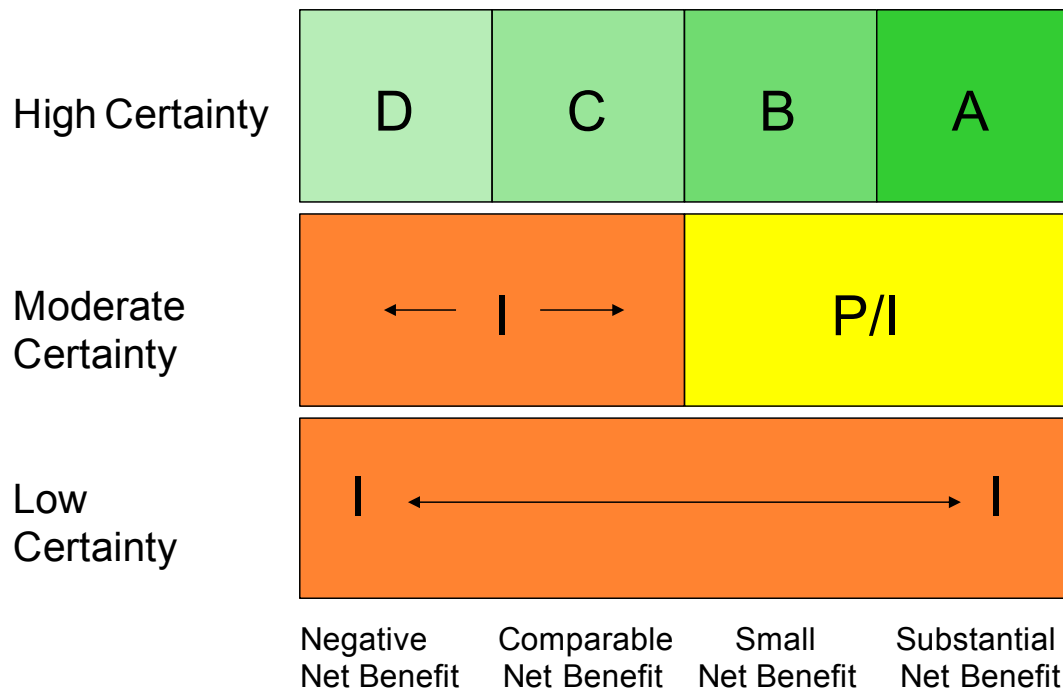
Methodology: ICER Integrated Evidence Rating™

The ICER Integrated Evidence Rating™ is constructed as a matrix, with a vertical axis denoting the possible categories for a rating of comparative clinical effectiveness, and the horizontal axis divided into 3 possible rating categories for comparative value (Ollendorf, 2010). It is important to note that these ratings are specified as comparing specific uses of medical interventions; that is, there may be different ratings for different uses of a test, treatment, or other intervention depending on the specified indication and patient population(s).

Level of Certainty in a Comparative Net Health Benefit

The underlying approach to ICER’s rating of comparative clinical effectiveness evolved from an earlier model developed by a multi-stakeholder workgroup convened in 2007 by America’s Health Insurance Plans (AHIP). The rating matrix, depicted in the graphic below, is used to rate the comparative clinical effectiveness of one or more interventions relative to a comparator of interest (Ollendorf, 2010, and is designed with the flexibility to compare multiple types of interventions, including drugs, devices, procedures, programs, and healthcare system processes. The rating matrix relies on a joint judgment of:

- a) The **magnitude** of the difference between an intervention and its comparator in “net health benefit” – the balance between clinical benefits and risks and/or adverse effects (horizontal axis); AND
- b) The level of **certainty** that one has in the best point estimate of net health benefit (vertical axis).



A = “**Superior**” - High certainty of a moderate-large net health benefit

B = “**Incremental**” - High certainty of a small net health benefit

C = “**Comparable**” - High certainty of a comparable net health benefit

D = “**Inferior**” - High certainty of an inferior net health benefit

P/I = “**Promising but Inconclusive**” - Moderate certainty of a small or moderate-large net health benefit

I = “**Insufficient**” - The evidence does not provide high certainty that the net health benefit of the technology is at least comparable to that provided by the comparator(s).

The term comparative “net” health benefit is used because of the importance attached to an explicit judgment of the overall balance of benefits and risks between an intervention and its selected comparator(s). The rating of net health benefit on the horizontal axis of the Comparative Clinical Effectiveness Matrix represents the best conceptual “point estimate” ICER can make given its interpretation of the existing evidence. There is no set definition of the boundaries between “comparable,” “small,” and “substantial” comparative net health benefit. For example, if the results of the appraisal include an estimate of a small lifetime quality-adjusted life year (QALY) advantage for one intervention compared with another, balanced against known greater short-term risks, whether or not these findings should be judged as conferring a comparative net health benefit will depend on many features of the relative certainty of the benefits and harms, as well as value judgments of the importance to patients of small QALY gains over a lifetime.

Despite the variability that will attend these judgments, presenting a categorical judgment of net health benefit serves an important goal: it enhances understanding of the underlying evidence by forcing the review team to justify its rating. The review team must describe

more concretely than they might otherwise their view of how the disparate findings of a systematic review and decision model sum up. The review team's justification can be debated and disagreed with, but in all cases it will give decision makers a more clear insight into the key issues they should consider when summing up the evidence and applying it to particular clinical actions or policies.

The vertical axis of the comparative clinical effectiveness matrix rates the level of certainty that the evidence provides in the precision of the net health benefit. There are 3 categories: high, moderate, and low. While the vertical axis represents a judgment of certainty, the horizontal axis of the Comparative Clinical Effectiveness Matrix displays gradients of the estimated net health benefit provided by a health intervention compared with the net health benefit of the selected comparator intervention. The categories for comparative net health benefit begin at the far left with "negative"; as the estimate of net health benefit increases, the rating moves to "comparable," then to "small net benefit," and culminates with a rating of "substantial" comparative net health benefit.

When assigning a level of certainty, it may be useful to consider that "conceptual confidence intervals" around a point estimate of comparative net health benefit that do not extend beyond a single box on the matrix represent a "high" level of certainty. Thus, if the point estimate of comparative net health benefit is "comparable," and you feel that the reasonable bounds of your conceptual confidence interval do not extend into either "negative" or "small," then you have high certainty in a "comparable" net health benefit. At the other end of the spectrum, no matter where your point estimate of comparative net health benefit is, if you feel that the conceptual confidence interval extends across multiple boxes such that there is a reasonable chance that the comparative net health benefit could be "negative," then there is "low" certainty. Finally, "moderate" certainty is used to imply that the conceptual confidence interval could extend one, or perhaps even two boxes in either direction. Essentially, for both low and moderate certainty, the possibility exists that the introduction of new evidence might move the estimate of comparative net health benefit in either direction.

Summary Rating of Comparative Clinical Effectiveness

As shown in the figure above, the Comparative Clinical Effectiveness Matrix maps the 3 categories of certainty upon the categories of comparative net health benefit to define a summary rating of comparative clinical effectiveness. Here, the relationship between level of certainty and magnitude of net health benefit comes into sharper relief. With a high level of certainty, the point estimate of net health benefit in one category is relatively assured, and therefore each cell in the matrix on the row of high certainty has a distinct label. A technology whose evidence base provides high certainty of a moderate-to-high net health benefit is rated to have "superior" comparative clinical effectiveness. As the net health benefit diminishes, the rating of comparative clinical effectiveness shifts to "incremental," then "comparable," and finally "inferior."

When the level of certainty in the point estimate is only moderate, however, the summary ratings change to reflect that the conceptual confidence interval stretches 1-2 boxes in either direction. The “P/I” (promising but inconclusive) category describes an intervention with evidence suggesting that it provides either a small or substantial net benefit over the comparator (i.e., the “point estimate”). This point estimate, however, is relatively uncertain – further evidence may change the estimate of comparative net health benefit, and the conceptual confidence interval may extend one box into the “comparable” net health benefit box, and even includes a small but not unreasonable chance that the true comparative net health benefit is “inferior.” The P/I rating is a particularly important one for emerging interventions with some evidence of benefit over alternative treatments, but limitations in the evidence, particularly on longer-term safety and effectiveness, usually reduce certainty in the true magnitude of comparative net health benefit.

The final rating category is “I” (insufficient). This is used in two situations: (a) when there is moderate certainty that the best point estimate of an intervention’s comparative net health benefit is comparable or inferior; and (b) any situation in which the level of certainty in the evidence is low, indicating that no matter what the point estimate is for comparative net health benefit, limitations in the body of evidence are so severe that the conceptual confidence interval extends across multiple categories in the ICER matrix, representing a reasonable likelihood that the true net benefit is inferior.

Rating Comparative Value

The rating of comparative clinical effectiveness can stand alone, to be discussed and applied by decision makers, but it also forms the first of the 2 parts of the ICER Integrated Evidence Rating. The second component is a rating of “comparative value.” ICER rates the use of interventions for particular patient populations as having “high,” “reasonable or comparable,” or “low” comparative value.

ICER does not employ a single measure of cost effectiveness, such as the incremental cost-effectiveness ratio, for assignment of a rating of comparative value, and therefore does not rely on a formal cost-effectiveness threshold. Instead, the rating of comparative value is informed by multiple measures of potential economic impact.

To determine a final rating of “high,” “reasonable/ comparable,” or “low” value, ICER considers all of the economic findings, including the relative uncertainty of model findings as explored through multiple deterministic sensitivity analyses and a probabilistic sensitivity analysis. To aid transparency, ICER provides general guidance that incremental cost per QALY ratios of less than approximately \$50,000 will often be considered as indicative of a “high” value intervention; incremental cost per QALYs from about \$50,000 to \$150,000 would often fit within a designation as “reasonable” values; and incremental cost per QALYs above \$150,000 would be more likely to suggest “low” value interventions. This general guidance is based upon previous academic work benchmarks modified by ICER’s interpretation of evidence on the role medical inflation and societal willingness to pay

should have in creating cost-effectiveness thresholds (Braithwaite, 2008; King, 2005). While there is a limited normative or empiric basis for the loose boundaries ICER presents, these boundaries also reflect input from stakeholders in today's health care system on how best to present incremental cost-effectiveness ratios within broad categories that can be widely understood, gain relative consensus, and be actionable.

Integrated Ratings

The ICER Integrated Evidence Rating™, as presented on the following page, combines the individual ratings given for comparative clinical effectiveness and comparative value. The overall purpose of the integrated ratings is to highlight the separate considerations that go into each element but to combine them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system (Ollendorf, 2010).

The ICER Integrated Evidence Rating™

Comparative Clinical Effectiveness	Superior: A	Aa	Ab	Ac
	Incremental: B	Ba	Bb	Bc
	Comparable: C	Ca	Cb	Cc
	Inferior: D	Da	Db	Dc
	Promising/Inconclusive: P	Pa	Pb	Pc
	Insufficient: I	I	I	I
		a	b	c
		High	Reasonable/Comp	Low
		Comparative Value		

Final Scope

Chronic neck pain due to the progression of cervical degenerative disc disease (DDD) is a prevalent condition that results in high rates of disability and work loss as well as substantial costs to the U.S. medical system. This appraisal focuses on cervical spinal fusion procedures and their major alternatives, including conservative treatments (e.g., physical therapy), spinal injections and other minimally-invasive procedures, and other surgical procedures. The final scope of this appraisal, described using the Populations, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS) format (Counsell, 1997), is described in detail in the sections that follow. Patients receiving cervical fusion are generally stratified according to the presence of specific symptoms:

- Radiculopathy (pain due to nerve root compression)
- Myelopathy (pain due to spinal cord compression)
- Axial neck pain (musculoskeletal or soft tissue pain due to muscle strain, whiplash, or non-specific reasons)

These symptoms can be present in patients with or without spondylosis, the presence of abnormal growths or bony spurs on the vertebrae caused by the progression of cervical DDD and the development of osteoarthritis.

Objective and Methods:

The objective of this report is to appraise the comparative clinical effectiveness and comparative value of spinal fusion for cervical DDD. To support this appraisal we report the results of a systematic review of published randomized controlled trials, systematic reviews, and observational studies as well as the findings from a *de novo* decision analysis.

Key Questions:

1. What is the comparative clinical effectiveness of cervical fusion for DDD relative to that of conservative management approaches, minimally-invasive procedures, and other forms of surgery?
2. What are the adverse events and other potential harms associated with cervical fusion compared to conservative management approaches, minimally-invasive procedures, and other forms of surgery?
3. What is the differential effectiveness and safety of cervical fusion according to factors such as age, sex, race or ethnicity, pre-existing conditions (e.g., smoking history), neuromuscular disease states (e.g., Parkinsonism), measurable spinal instability, technical approach to fusion, insurance status (e.g., worker's compensation vs. other), and treatment setting (e.g., inpatient vs. ambulatory surgery)?

4. What are the costs and potential cost-effectiveness of cervical fusion relative to alternative approaches?

FULL APPRAISAL REPORT

1. Background

1.1 The Condition

Chronic neck pain is a prevalent and costly disorder. Approximately 15-20% of adults report at least one episode of neck pain during a given year, and nearly half of these individuals seek care (Carroll, 2008). On an annual basis, it is estimated that 11-14% of workers will have some limitation in their activities due to neck pain (Côté, 2008). While no recent studies have been conducted in the US on the economic burden of neck pain specifically, the combined burden of neck and back disorders in this country has been estimated to total \$86 billion (Deyo, 2008).

One of the common causes of chronic neck pain is the progression of degenerative disc disease (DDD) of the cervical spine. DDD is not in fact a disorder, but a natural consequence of aging that results in gradual deterioration of cervical intervertebral discs (Emery, 2001). As the ability of these discs to absorb the shock and stress of vertebral motion declines, they become inelastic and cause a settling of the spinal column structure and abnormal spinal motion patterns. This process may in turn cause the development of abnormal bony growths and/or spurs (spondylosis), osteoarthritis, and/or herniation of one or more cervical discs. All of these conditions may in turn cause radiculopathy, or peripheral nerve root impingement. Symptoms of cervical radiculopathy include neck and arm pain, and weakness, tingling, or numbness in the upper extremities (Mayo Clinic, 2012). Less commonly, cervical DDD progression and its sequelae may directly compress parts of the spinal cord (myelopathy), affecting gait and balance in addition to causing arm and/or leg weakness and numbness.

A variety of options are available to manage chronic neck pain associated with cervical DDD. Many patients benefit from conservative management, which may include pain medication, immobilization, exercise and/or physical therapy, or spinal manipulation (Korin, 2008). Patients not responding to these initial measures may receive therapeutic injections of anesthetic, nerve blocks, or steroids, as well as other minimally-invasive procedures such as radiofrequency ablation. Patients with ongoing neurologic symptoms

not responding to initial management or minimally-invasive options are considered possible candidates for surgical treatment (Korinth, 2008).

The most common surgical procedure employed in the U.S. for patients with symptomatic cervical DDD is spinal fusion (Cowan, 2006). The rate of spinal fusion has increased dramatically in recent years; an analysis of U.S. hospital discharge data from 1990-2004 showed an 8-fold increase in the utilization of anterior fusion procedures, even while the overall rate of hospital admissions for cervical DDD remained steady (Marawar, 2010). The cost of these procedures, as well as questions regarding the short- and long-term outcomes associated with fusion, have raised considerable interest in understanding the evidence on the relative effectiveness of this procedure in comparison to other management options.

Health Technology Assessment

February 21, 2013

1.2 Washington State Agency Data

Figure WSAD1: Cervical Fusion Paid Amounts by Agency and Year, 2008-2011

PEB ²	2008	2009	2010	2011	4-Yr Overall ¹	Average % Change	
Agency Population	204,804	210,501	213,487	212,596		1.3%	
Patient Count ³	141	167	189	160	647	5.2%	*
Procedure Count	148	186	193	163	690	3.1%	*
Amount Paid	\$3,215,634	\$5,610,920	\$4,515,666	\$2,952,639	\$16,294,859	4.9%	*
Average Per Procedure⁴	\$21,727	\$30,166	\$23,397	\$18,114	\$23,616		
% Reoperations	1.4%	8.4%	8.5%	6.5%	6.6%		
Per Procedure							
95% Upper Limit	\$61,963	\$91,863	\$69,768	\$54,184	\$72,099		
Per Procedure Maximum	\$98,035	\$230,485	\$179,028	\$109,214	\$230,485		
Labor & Industry (L&I)	2008	2009	2010	2011	4-Yr Overall ¹	Average % Change	
Agency Pop. (Total Claims)	147,445	125,611	122,712	121,043		-6.2%	
Patient Count ³	347	370	381	344	1,341	7.4%	*
Procedure Count	361	381	393	351	1,486	6.7%	*
Amount Paid	\$8,305,384	\$9,094,202	\$9,800,454	\$8,785,734	\$35,985,774	9.9%	*
Per Procedure Average ⁴	\$23,007	\$23,869	\$24,938	\$25,031	\$24,217		
% Reoperation ⁵	4.6%	9.5%	14.2%	17.4%	12.3%		
Per Procedure							
95% Upper Limit	\$51,366	\$45,590	\$48,807	\$58,420	\$51,264		
Per Procedure Maximum	\$202,175	\$91,148	\$108,393	\$166,773	\$202,175		
Medicaid	2008	2009	2010	2011	4-Yr Overall ¹	Average % Change	
Agency Pop. (Fee for Service)	392,808	416,871	424,230	435,187		3.5%	
Patient Count ³	313	335	295	326	1269	-1.6%	*
Procedure Count	313	335	299	331	1278	-1.2%	*
Amount Paid	\$3,752,673	\$3,905,816	\$1,544,595	\$1,090,176	\$10,293,260	-31.4%	*
Per Procedure Average ⁴	\$11,989	\$11,659	\$5,166	\$3,294	\$8,054		
% Reoperation ⁵	0%	0%	2.0%	3.7%	1.4%		
Per Procedure							
95% Upper Limit	\$36,043	\$33,330	\$17,757	\$10,012	\$27,367		
Per Procedure Maximum	\$92,762	\$85,450	\$49,034	\$27,457	\$92,762		
All Agencies	2008	2009	2010	2011	4-Yr Overall ¹	Average % Change	
Agency Combined Population	745,057	752,983	760,429	768,826		1.1%	
Patient Count ³	801	872	872	835	3,258	0.5%	*
Procedure Count	822	902	885	845	3,454	0.1%	*
Amount Paid Total	\$15,273,691	\$18,610,938	\$15,860,715	\$12,828,549	\$62,573,893	-5.0%	*

Figure WSAD1 Notes:

* Average Annual % Change adjusted for population.

¹ Patients who receive treatment in multiple years are counted only once in the “4 Yr Overall” total.

² Public Employee Benefits.

³ Patients undergoing cervical fusion for trauma or cancer are not included. For L&I 34 patients were excluded, for PEB 32 patients were excluded and for Medicaid, 85 patients were excluded. Patients may be counted in more than one year for multiple procedures or treatment courses that span two years.

⁴ For Medicaid and PEB, procedures consist of all charges during the hospitalization or day of service (outpatients), pre-operative cardiovascular and respiratory examinations, postoperative surgical care, and head, neck and spine specific imaging 30 days pre-operative and 90 days post-operative. For L&I, the analysis is similar, including all charges paid under the claim.

⁵ Medicaid patient claims were under-reported for CPT code 22554 for years 2008-2010.

Figure WSAD2a. PEB Cervical Spinal Fusion by Age and Gender, 2008-2011

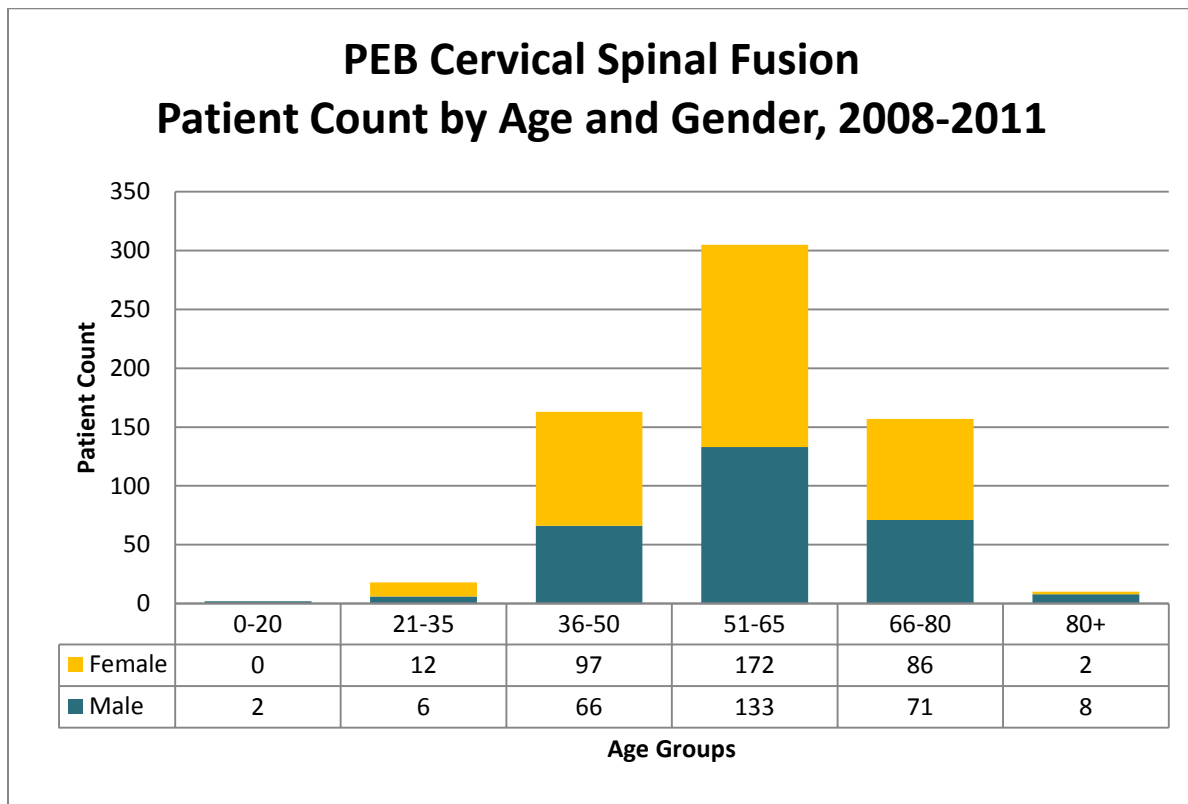


Figure WSAD2b. L&I Cervical Spinal Fusion by Age and Gender, 2008-2011

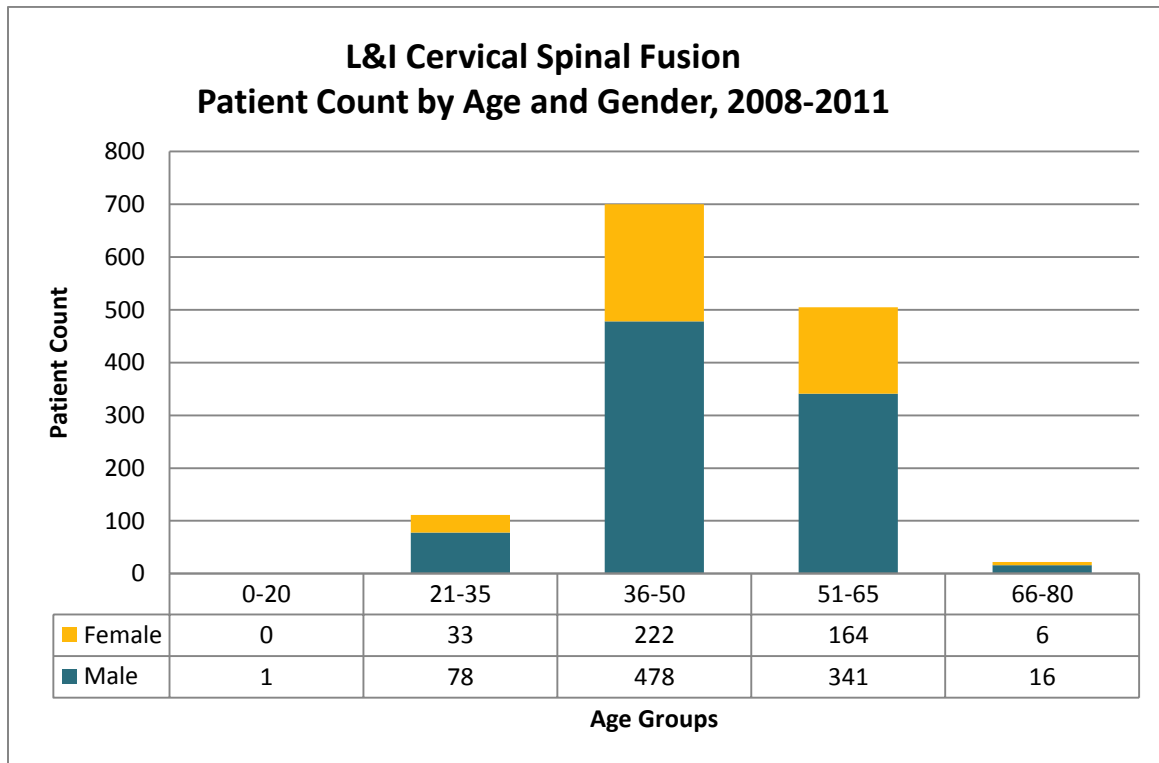


Figure WSAD2c. Medicaid Cervical Spinal Fusion by Age and Gender, 2008-2011

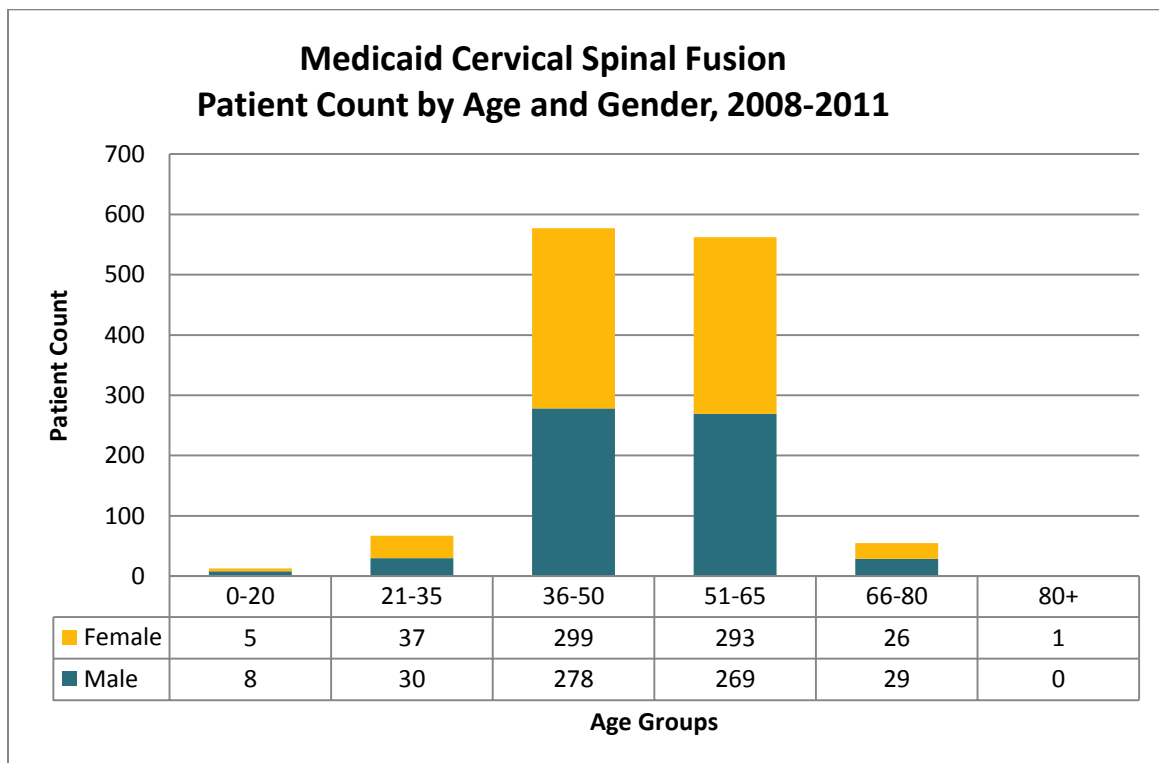


Figure WSAD3: Agency Average Allowed Amount per procedure, 2008-2011

Per Procedure Avg Charges by Agency	PEB Primary (no Medicare)	PEB Medicare*	L&I	Medicaid Primary (no Medicare)	Medicaid Medicare Crossover
Breakdown 1					
Professional Services	\$8006	\$3207	\$9262	\$3757	\$1730
Facility	\$26,006	\$41,016	\$14,955	\$8333	\$1779
Breakdown 2					
Preop Charges	\$62	\$141	\$1094	\$26	\$26
Imaging	\$533	\$613	\$320	\$280	\$92
Cervical Fusion Procedure	\$33,387	\$43,461	\$20,427	\$11,696	\$3321
Post op	\$30	\$56	\$2375	\$88	\$84
Avg Allowed/Fusion	\$34,011	\$44,270	\$24,217	\$12,090	\$3509

*The higher per patient allowed amount for PEB Medicare vs PEB Primary may be due to the frequency of procedures with complications in the Medicare population (see pie charts below).

Figure WSAD4: PEB Non-Medicare/Medicare Cervical Spinal Fusion Procedure Type comparison

**PEB Non-Medicare Cervical Fusion Procedures,
Patient Counts by Procedure Types, 2008-2011**

Abbreviations:

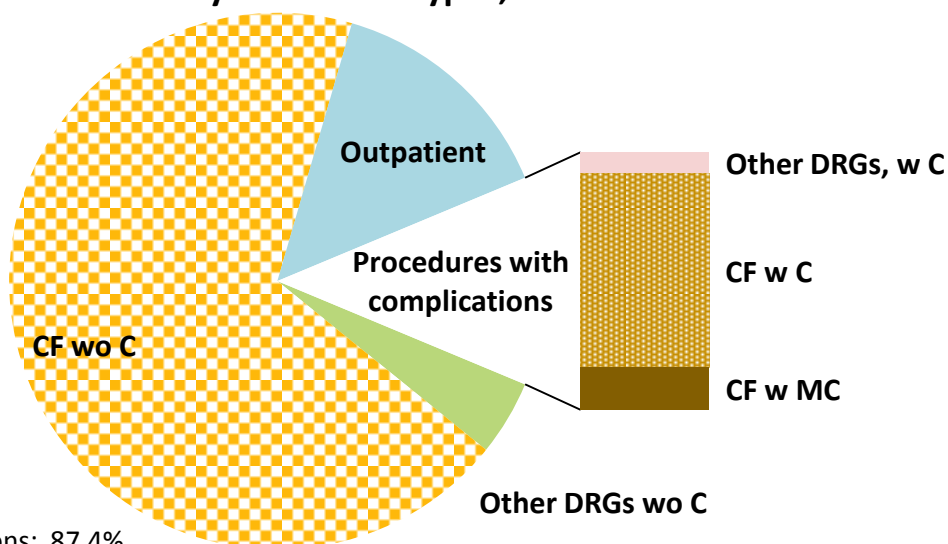
CF - Cervical Spinal Fusion DRG

DRG - Diagnosis-Related Group

wo C - without Complication

w C - with Complications

w MC - with Major
Complications



**PEB Medicare Cervical Fusion Procedures,
Patient Counts by Procedure Type, 2008-2011**

Abbreviations:

CF - Cervical Spinal Fusion DRG

DRG - Diagnosis-Related Group

wo C - without Complication

w C - with Complications

w MC - with Major
Complications

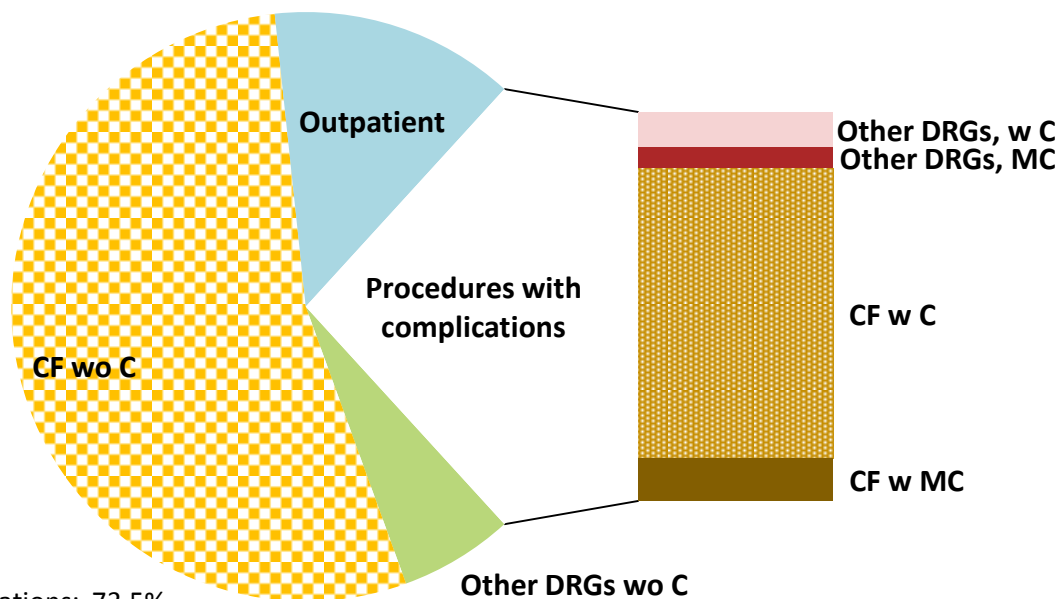


Figure WSAD5a: PEB Radiculopathy/Myelopathy Diagnosis

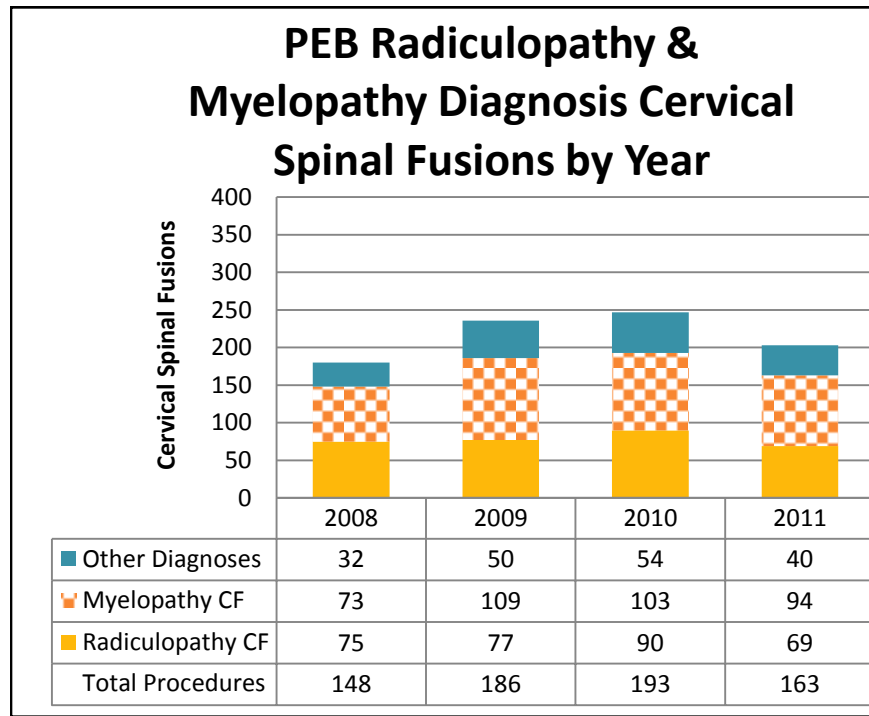
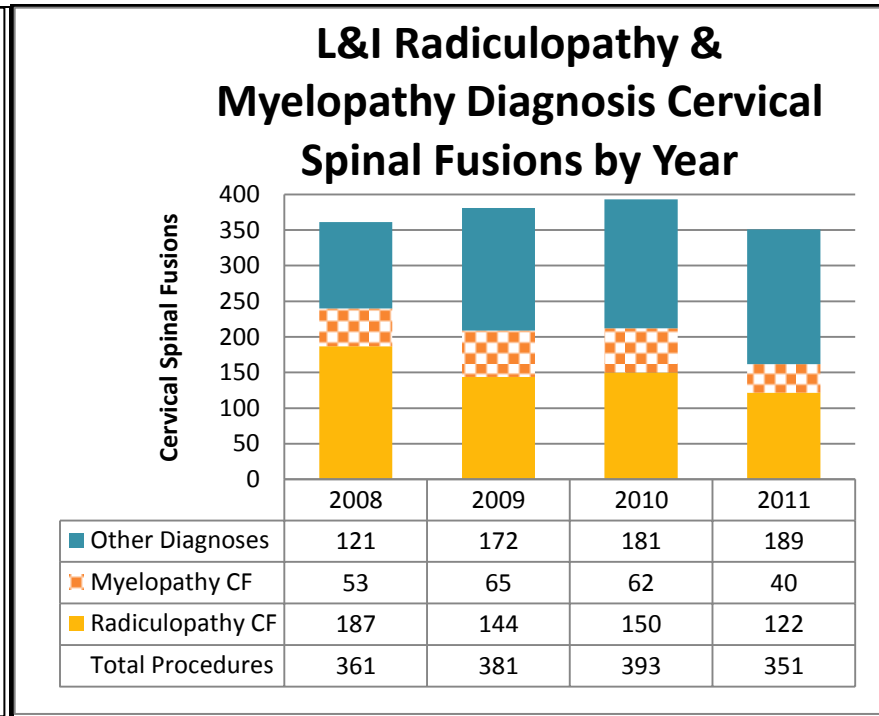


Figure WSAD5b: L&I Radiculopathy/Myelopathy Diagnosis

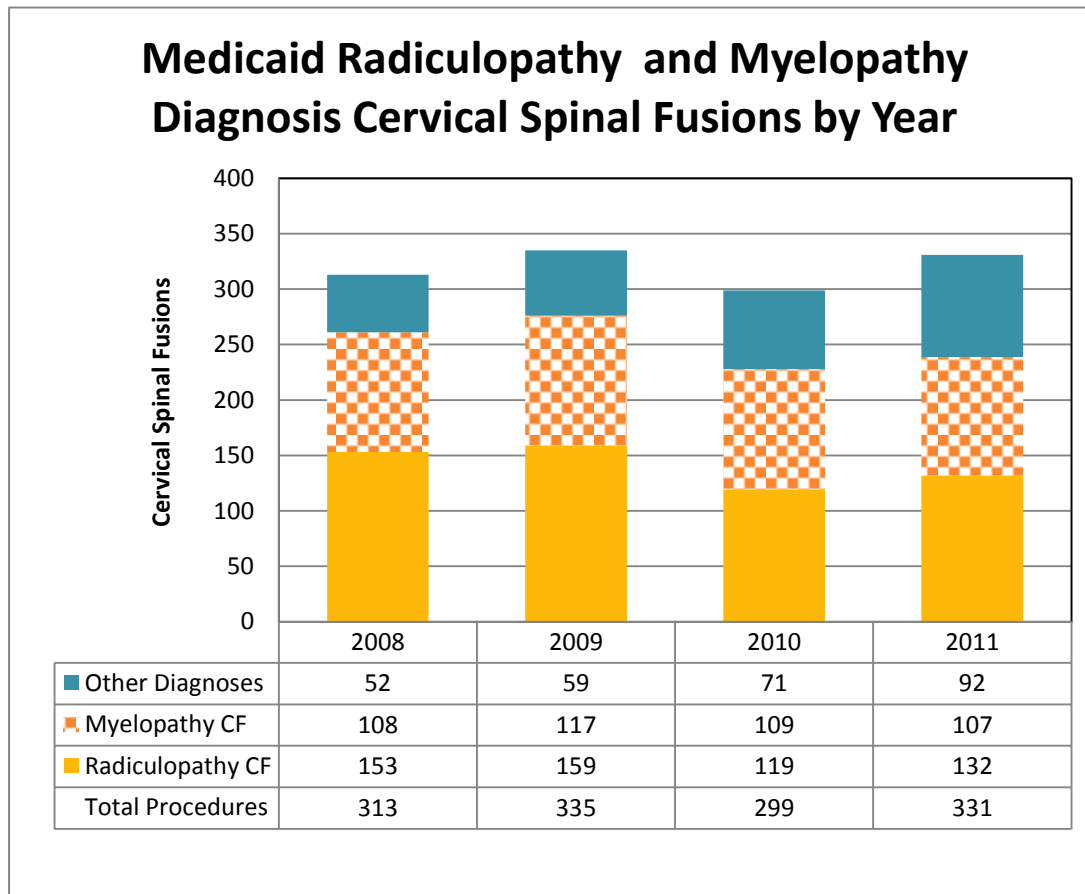


Radiculopathy diagnoses were identified by ICD9 codes: 722.0, 722.1, 722.2, Disk displacement with radiculopathy/neuropathy, 723.4 Brachial neuritis, 24.3 Sciatica, and 724.4 Lumbosacral neuritis NOS. Myelopathy diagnoses were identified by codes 721.1, Cervical Spondylosis with myelopathy, 721.91 Spondylosis NOS with myelopathy, and 722.71 Cervical disc disease with myelopathy

PEB	
Top 5 Non-Radiculopathy/ Non-Myelopathy Diagnoses	Patient Count
Cervical Spinal Stenosis	63
Cervical Spondylosis	62
Cervical Disc Degen	22
Nonunion Of Fracture	6
Lumb/Lumbosac Disc Degeneration	4

L & I	
Top 5 Non-Radiculopathy/ Non-Myelopathy Diagnoses	Patient Count
Cervical Spinal Stenosis	313
Cervical Spondylosis	264
Cervical Disc Degeneration	137
Cervicalgia	84
Cervical Disc Displacement	77

Figure WSAD5c: Medicaid Radiculopathy/Myelopathy Diagnosis



Medicaid Top 5 Non-Radiculopathy/ Non-Myelopathy Diagnoses		Patient Count
Cervical Spinal Stenosis		149
Cervical Spondylosis		117
Cervical Disc Degeneration		47
Jt Derangement Nec – Oth Jt		29
Disc Dis Nec/Nos - Cerv		10

Figure WSAD6a: PEB Top 10 Diagnosis Categories for ER Visits

Diagnosis Category	Patient Count
Back/Skeletal	13
Neurologic Symptoms	11
Respiratory Symptoms	9
Urinary Tract Symptoms	8
Abdominal Symptoms	8
Cardiac Symptoms	8
Esophageal Symptoms	6
Complication	5
Infection	3
Allergic Reaction	3

**PEB ER Visits -
Within 90 Days of Cervical Fusion**
108 ER visits for 75 patients
(11.6% of patients)

Figure WSAD6b: L&I Top 10 Diagnosis Categories for ER Visits

Diagnosis Category	Patient Count
Back/Skeletal	76
Acute Pain	32
Musculoskeletal	30
Respiratory	29
Neurologic Symptoms	27
Head and Neck	26
Abdominal Symptoms	25
Wound Disruption	21
Cardiac Symptoms	20
Infection	19

**L&I ER Visits -
Within 90 Days of Cervical Fusion**
365 ER visits for 184 patients
(13.7% of patients)

Figure WSAD6c: Medicaid Top 10 Diagnosis Categories for ER Visits

Diagnosis Category	Patient Count
Back/Skeletal	330
Abdominal Symptoms	89
Neurologic Symptoms	83
Infection	73
Acute Pain	71
Injury	66
Other Pain	53
Cardiac Symptoms	41
Head & Neck	41
Headache	40

**Medicaid ER Visits -
Within 90 Days of Cervical Fusion**
704 ER visits for 360 patients
(28.4% of patients)

Figure WSAD7a: PEB Cervical Fusions Re-Operations, 2008-2011

Cervical Fusion Re-Operations	Unique Patient Count	Avg. Days from Previous Fusion
1	35	352
2	1	185
3	1	432
4	1	511

43 re-operations in 38 patients
(5.8% of patients)

Figure WSAD7b: L&I Cervical Fusions Reoperations, 2008-2011

Cervical Fusion Re-Operations	Unique Patient Count	Avg. Days from Previous Fusion
1	138	447
2	19	398
3	4	156
4	2	257

196 re-operations in 163 patients
(12.2% of patients)

Figure WSAD7c: Medicaid Cervical Fusions Reoperations

Cervical Fusion Reoperations	Patient Count	Avg. Days from Previous Fusion
1	17	319
2	1	4

19 reoperations reported:
17 patients with 1 re-operation;
1 patient with 2 re-operations

Figure WSAD8a: PEB Non-Back/Skeletal Clinical Diagnoses Post-Operation

Top 15 Diagnosis Categories	Unique Patients	% Total Patients
Respiratory Symptoms	67	10.3%
Cardiac Symptoms	37	5.7%
Neurologic Symptoms	35	5.4%
Abdominal Symptoms	33	5.1%
Dysphagia	31	4.8%
Headache	18	2.8%
Acute Pain	15	2.3%
Head and Neck	13	2.0%
Graft Complication	11	1.7%
Infection	11	1.7%
Vocal Loss	11	1.7%
Paralysis	7	1.1%
GU	6	0.9%
Hematoma	6	0.9%
Feeding Problems	4	0.6%

Figure WSAD8b: L&I Non-Back/Skeletal Clinical Diagnoses Post-Operation

Top 15 Diagnosis Categories	Unique Patients	% Total Patients
Graft Complication	65	4.8%
Head and Neck	64	4.8%
Respiratory	52	3.9%
Psych Disturbances	47	3.5%
Cardiac Symptoms	44	3.3%
Acute Pain	43	3.2%
Dysphagia	34	2.5%
Neurologic Symptoms	34	2.5%
Infection	29	2.2%
Wound Disruption	26	1.9%
Abdominal Symptoms	23	1.7%
Headache	20	1.5%
Vocal Loss	18	1.3%
Spinal Fractures	11	0.8%
Circulation	8	0.6%

Figure WSAD8c Medicaid Non-Back/Skeletal Clinical Diagnoses Post-Operation

Top 15 Diagnosis Categories	Unique Patients	% Total Patients
Non-Acute Pain	224	17.7%
Respiratory	206	16.2%
Neurologic Symptoms	183	14.4%
Infection	182	14.3%
Cardiac Symptoms	125	9.9%
GU	108	8.5%
Injury	92	7.2%
Psych Symptoms	92	7.2%
Acute Pain	91	7.2%
Drug/alcohol abuse	67	5.3%
Debility	64	5.0%
Abdominal Symptoms	63	5.0%
Gastrointestinal Symptoms	63	5.0%
Dysphagia	55	4.3%
Head and Neck	54	4.3%

Figure WSAD9a: PEB Event Rates by Hospital Type, 2008-2011

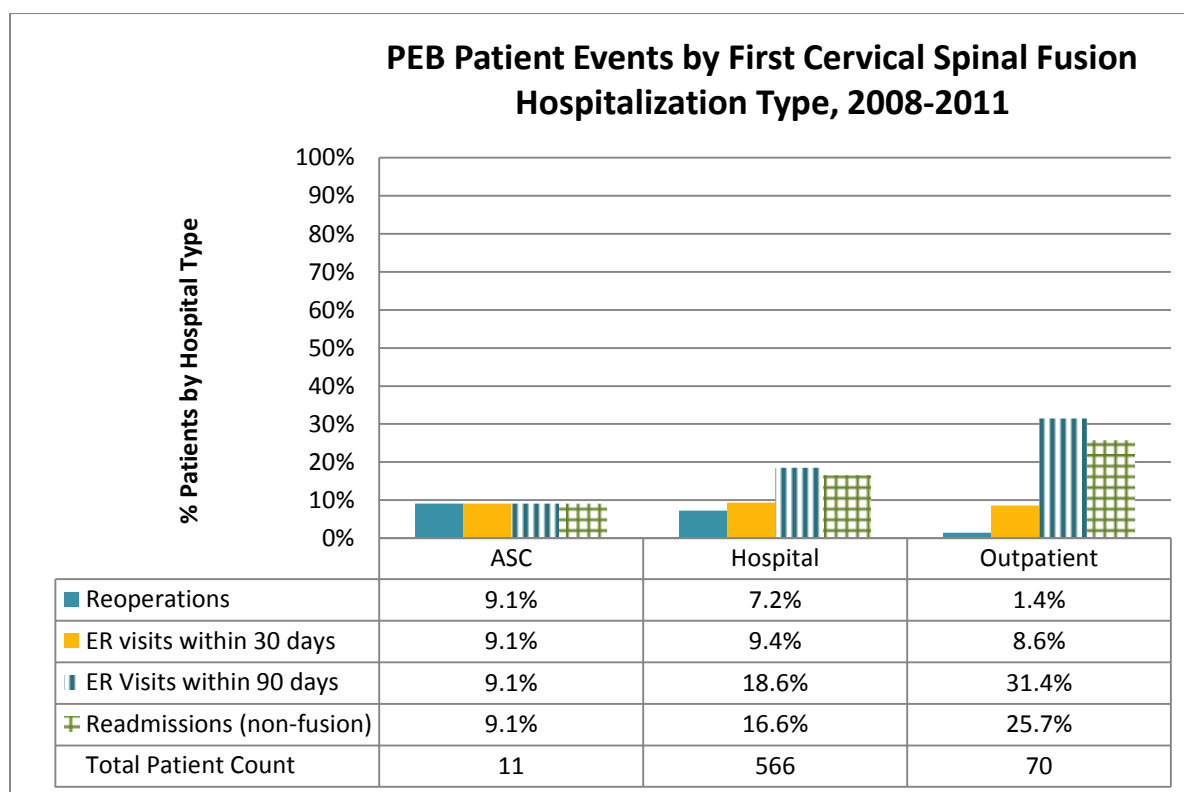


Figure WSAD9b: L&I Event Rates by Hospital Type, 2008-2011

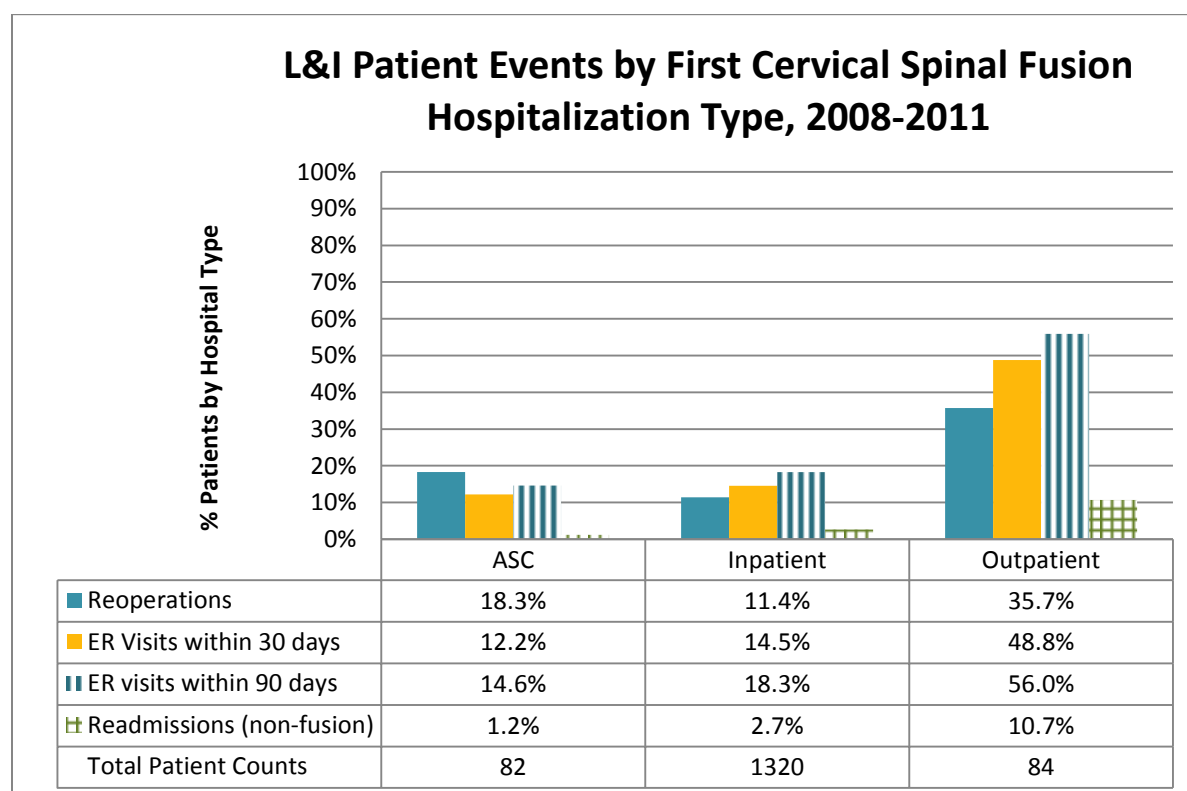
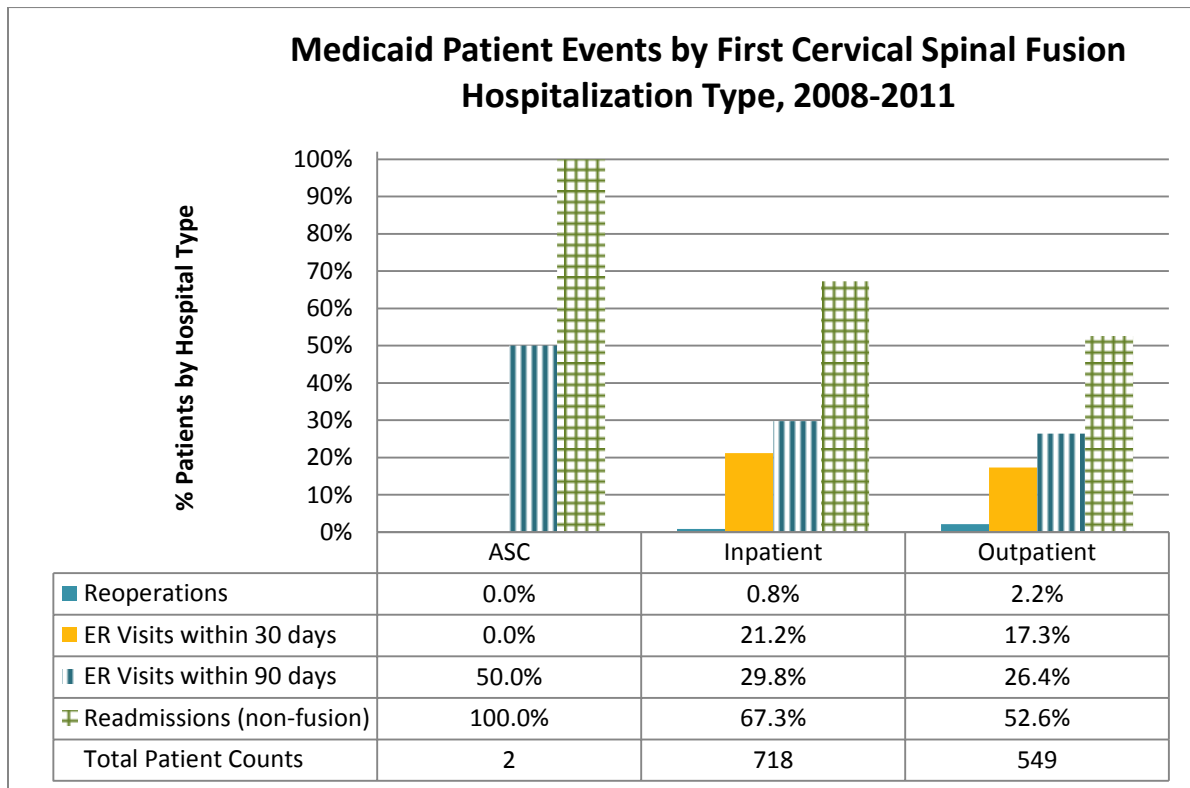


Figure 9c: Medicaid Event Rates by Hospital Type, 2008-2011



Washington State Agency Data Related Medical Codes

CPT Code	Description	Type	Fusion Type
22548	Arthrodesis, anterior transoral or extraoral technique, clivus-C1-C2 (atlas-axis), with or without excision of odontoid process	Added code	Cervical Fusion
22551	Arthrodesis, anterior interbody, including disc space preparation, discectomy, osteophytectomy and decompression of spinal cord and/or nerve roots; cervical below C2	Added code 2011	Cervical Fusion
22552	Cervical below C2, each additional interspace (List separately in addition to code for separate procedure)	Added code 2011	Cervical Fusion
22554	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); cervical below C2	CPT	Cervical Fusion
22590	Arthrodesis, posterior technique, craniocervical (occiput-C2)	CPT	Cervical Fusion
22595	Arthrodesis, posterior technique, atlas-axis (C1-C2)	CPT	Cervical Fusion
22600	Arthrodesis, posterior or posterolateral technique, single level; cervical below C2 segment	CPT	Cervical Fusion
22849	Reinsertion of spinal fixation device	Removal	All Fusions
22850	Removal of posterior nonsegmental instrumentation (eg, Harrington rod)	Removal	All Fusions
22852	Removal of posterior segmental instrumentation	Removal	All Fusions
22855	Removal of anterior instrumentation	Removal	All Fusions
63075	Discectomy, anterior, with decompression of spinal cord and/or nerve root(s), including osteophytectomy; cervical, single interspace	2008-2010	Cervical, disk removal
63076	Cervical, each additional interspace (List separately in addition to code for primary procedure)	2008-2010	Cervical, disk removal
DRG Code	Description	Type	Complications, Fusion Type
M029	Spinal Pxs W Cc Or Spinal Neurostim	DRG	Other, complications
M030	Spinal Procedures W/O Cc/Mcc	DRG	Other, complications
M453	Combined Ante/Post Spinal Fusion Wm	DRG	Other, complications
M454	Combined Ante/Post Spinal Fusion Wc	DRG	Other, complications
M455	Combined Ante/Post Spinal Fusion Wo	DRG	Other, no complications
M457	Spinal Fus W Curv/Mal/Inf Or 9+ Wcc	DRG	Other, complications
M459	Spinal Fusion Except Cervical W Mcc	DRG	Other, complications
M460	Spinal Fus Exc Cervical W/O Mcc	DRG	Other, no complications
M471	Cervical Spinal Fusion W Mcc	DRG	Cervical Fusion, major compl.
M472	Cervical Spinal Fusion W Cc	DRG	Cervical Fusion, complications
M473	Cervical Spinal Fusion W/O Cc/Mcc	DRG	Cervical Fusion, no complications
M490	Back/Neck Proc W/O Spinal Fus Wcc	DRG	Other, complications
M491	Back/Neck Proc W/O Spinal Fus W/O Cc	DRG	Other, no complications

2. The Alternative Management Strategies

A plethora of management options is available for patients with neck pain due to cervical DDD, from conservative approaches, including cervical immobilization and physical therapy, to spinal injections and other minimally-invasive procedures, to several surgical options. The management options of primary interest for this appraisal are described in detail in the sections that follow.

2.1 Conservative Treatment

Conservative treatment for chronic neck pain consists of a number of pharmacological and non-pharmacological therapies as well as self-care interventions. Frequently used as an initial treatment strategy for patients presenting with neck pain, the individual options can take many forms.

The most frequently-studied forms of conservative management for neck pain include cervical immobilization, physical therapy, and spinal manipulation. Immobilization can be accomplished using a range of devices, including soft and hard collars, body jackets, and braces. Cervical immobilization is intended to provide short-term pain relief sufficient for the patient to attempt other forms of therapy, and are typically used for no longer than 1-2 weeks (Muzin, 2008). Potential disadvantages of immobilization include muscle atrophy after long-term use, as well as restricted breathing and aspiration risk in patients using hard collars (Muzin, 2008).

Physical therapy typically includes both exercise-based approaches to strengthen supporting muscle groups as well as postural support, with the ultimate goal of increased range of motion and relief of pain. Chiropractic spinal manipulation, which is known as “manual therapy” when performed by physical therapists, involves both thrust and non-thrust techniques to adjust the cervical spine and correct any postural abnormalities (Childs, 2008). The intensity and duration of both types of therapy can vary based on patient symptoms, but most courses of therapy involve 1-3 visits per week followed by evaluation at 4 weeks; therapy can then be continued if pain and symptoms persist (University of Maryland Medical Center, 2012). Risks of physical therapy and spinal manipulation include emergence or re-emergence of pain or other radicular symptoms; manipulation techniques in particular also carry small but nonzero risks of serious complications, including vertebral artery dissection, dural tear, phrenic nerve injury, and stroke (Ernst, 2007). Other forms of conservative management may include, but are not limited to:

Self-Care

- Books, handouts
- Ice and/or heat
- Gentle stretching
- Positional support during work and/or sleep

Pharmacologic Therapy

- Acetaminophen
- NSAIDs
- Tricyclic antidepressants
- Benzodiazepines
- Tramadol, opioids

Non-pharmacologic Therapy

- Massage
- Acupuncture
- Yoga
- Cognitive-behavioral therapy

2.2 Minimally-Invasive Procedures*Spinal Injections*

Spinal injections deliver medication to the anatomic location that has been identified as the likely source of pain (Falco, 1998). Several types of spinal injections are used in practice today. They can be classified as either intraspinal injections or injections outside the spine. Intraspinal injections are further categorized into one of three categories: steroid injections, nerve blocks, or chemonucleolysis, as shown below (Chou, 2009).

- Steroid injections
 - Epidural steroid injection
 - Facet joint steroid injection
 - Intradiscal steroid injection
- Nerve blocks
 - Medial branch blocks
 - Sympathetic nerve blocks
 - Selective nerve root blocks
- Chemonucleolysis

Epidural steroid injections deliver the steroid into the epidural space, the space between the dura and the spine. The injection typically includes both a long-lasting steroid and a local anesthetic. Additional types of steroid injections have other anatomic targets. Facet joint steroid injections deliver corticosteroids into the facet joints, joints that are located

between and behind adjacent vertebrae. Intradiscal steroid injections involve injecting a corticosteroid into an intervertebral disc to treat what is believed to be “discogenic” pain.

Nerve block injections include an anesthetic and may also include a corticosteroid. These injections are intended to target specific areas thought to be the source of pain, temporarily blocking pain signals. Most commonly, these injections target the medial branch nerves, which emanate from the facet joints and in turn carry pain signals from these joints. Nerve-blocking injections may also target the sympathetic nervous system, which control some of the body’s involuntary functions. Nerve blocks may target selective nerve roots. These injections are intended primarily to diagnose the source of pain, not to treat it.

Chemonucleolysis uses a proteolytic enzyme, usually chymopapain, to dissolve the inner part of a herniated disc, in an effort to resolve radicular pain.

Injections outside the spine may include Botulinum toxin (Botox) injections, local injections, and prolotherapy. Botox injections are injected into the muscles of the neck to control muscle spasms. Local injections utilize a local anesthetic, injected into the muscles or soft tissues of the neck to treat inflammation. Prolotherapy, which may also be referred to as sclerotherapy, is a procedure in which a chemical irritant is injected into the soft tissues of the neck. This promotes an inflammatory response, which is thought to lead to a natural healing that will strengthen the injured soft tissue and thus reduce neck pain.

Each type of injection procedure may last between 15 and 30 minutes. Spinal injections are often done under fluoroscopic (live X-ray) guidance, although controversy exists over whether such guidance improves outcomes (Murtagh, 2000). Once the needle is in the proper position, a contrast dye is injected to confirm the position of the needle. Following confirmation, the steroid/anesthetic solution is injected.

Risks associated with these procedures include misplacement of the needle (either advancing the needle too deeply or placing it in the wrong position). The outcomes of incorrect needle position include nerve damage, infection, bleeding, and headaches. Risks associated with the medications include elevated blood glucose, arthritis, stomach ulcers, and weight gain. Chemonucleolysis may also cause anaphylactic reactions in some patients. One risk specifically associated with epidural steroid injections is wet tap, in which the needle penetrates the spinal sac and enters the cerebrospinal fluid. This causes the fluid to leak, resulting in severe headaches. Other rare complications associated with epidural steroid injections include epidural hematoma and abscess. In addition, a recent outbreak of fungal meningitis has been tied to nonsterile preparation of methylprednisolone for spinal injection by a large compounding pharmacy in the Northeast; the most recent data available indicate 656 confirmed cases in 19 U.S. states, 39 of which have been fatal (Centers for Disease Control, 2012).

Radiofrequency Denervation

Radiofrequency denervation (also known as radiofrequency neurotomy) is a type of procedure that uses heat to cauterize the affected nerve(s) thought to be associated with

neck pain (Niemisto, 2003). This procedure attempts to interrupt pain signals from these nerves, thereby reducing pain perception by the brain.

The physician uses fluoroscopy to help advance the placement of the needle into the desired location. A small amount of current is passed through the needle to ensure that it is next to the target nerve; this may briefly cause facet joint pain. The nerves are then numbed to minimize joint pain while the lesion is being created. The process is repeated for up to 1-5 additional nerves. The entire procedure can last between 30 and 90 minutes and is performed in an outpatient setting. Patients are usually able to resume their normal activities in a short period. Risks associated with this procedure include pain or discomfort around the injection site, worsened joint pain, permanent nerve pain, infection, and bleeding.

Coblation Nucleoplasty

Coblation nucleoplasty (also known as percutaneous disc decompression) is a relatively new minimally-invasive procedure used to treat cervical and lumbar disc herniation. The procedure uses radiofrequency energy to create small channels within the herniated disc, which is then thermally treated, producing an area of thermal coagulation. Channels are then formed in the nucleus in order to decompress the herniated discs (Sim, 2011).

Similar to radiofrequency denervation, this procedure usually takes 20 to 30 minutes and is performed in an outpatient setting. Patients are typically able to resume normal activity within a short time after the procedure.

2.3 Surgical Procedures

In order to better visualize the effects of different surgical procedures for cervical DDD, the cervical spinal anatomy is displayed in Figure 1 on the following page.

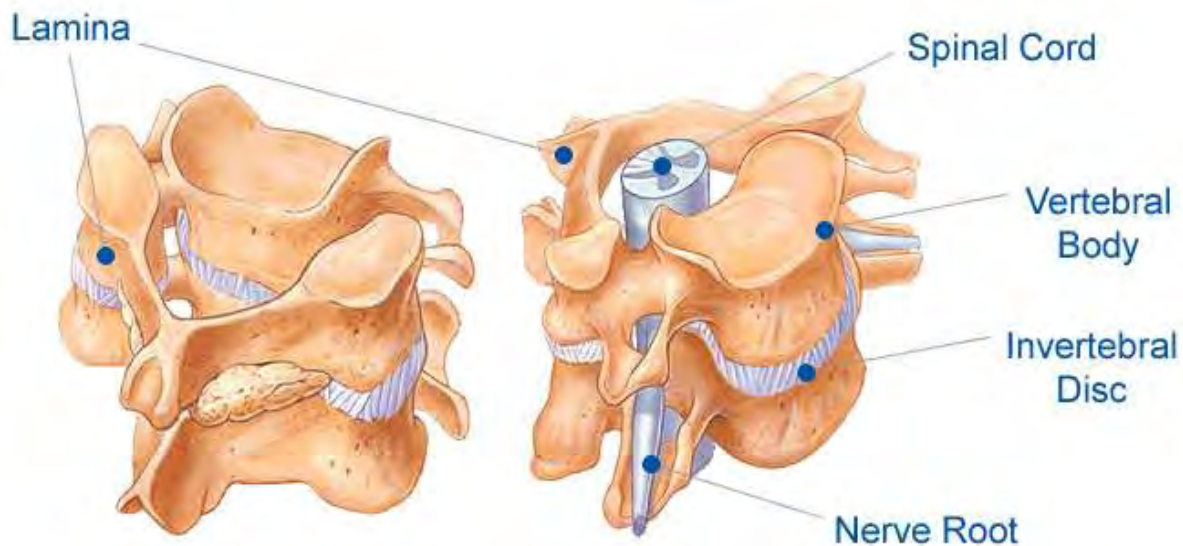
Spinal Fusion

Spinal fusion may be performed in addition to discectomy or laminectomy (see below) in order to achieve adequate decompression of the nerve root or the spinal cord or in patients with significant spinal instability.

The spine is stabilized by fusing two or more vertebrae together, using bone grafts from the patient or bone bank; in some cases, bone-related products such as bone morphogenetic proteins (BMP) or synthetic products such as polymethylmethacrylate (PMMA) may be used as graft material instead (American Academy of Orthopaedic Surgeons, June 2010). Fusion also may or may not use instrumentation such as screws, plates, or cages. Instrumentation is generally used as an internal or external splint to hold the vertebrae together while the grafts heal. Fusion may be performed on one, two, or multiple disc levels. The surgical approach may be from the back (posterior) or front (anterior); anterior approaches have become the predominant form of fusion surgery in recent years due to concerns of nerve or spinal cord injury with posterior fusion.

During the operation, the surgeon removes the lamina to help relieve the pressure on the nerve. The surgeon then removes any additional bone that may impinge upon the affected nerve. Grafts are then added to the spine; these will eventually fuse with the spine to form a solid union. Patients usually stay in the hospital for at least 3-4 days post-procedure. Completion of the fusion process takes some time to achieve and the healing process varies from person to person. Because of this, assessment of fusion “success” via radiographic images is not attempted until at least 6 weeks following the procedure. Patients are often asked to limit their activities before fusion is deemed to be complete so as not to prolong the process (Mayo Clinic, 2012). Return to work tends to be discouraged during this period, as even sedentary work may affect recovery (Medical Disability Guidelines, 2012). Following the completion of the fusion process, the surgeon may recommend a rehabilitation program to strengthen the muscles around the fused area (Mayo Clinic, 2012).

Figure 1. Illustration of cervical spinal anatomy.



Source: <http://www.spineinfo.co.uk>

Risks associated with spinal fusion include nerve root damage, cerebrospinal fluid leakage, bleeding, and infection. While the major risks are relatively rare, the odds of injury increase with increasing complexity of surgical approach and use of instrumentation (Deyo, 2010). Other complications, common to all types of major surgery, may include blood clots, myocardial infarction, pulmonary embolism, and pneumonia. Patients undergoing cervical fusion may have reduced range of neck motion due to relative inflexibility of the fusion material in comparison to a cervical disc. Finally, there are concerns that fusion can cause long-term adverse effects, most prominently adjacent segment disease, in which discs adjacent to the fusion location degenerate and cause a return of symptoms, necessitating further surgery (American Association of Neurological Surgeons, 2012).

Discectomy

Cervical discectomy is a surgical procedure to remove part of a bulging or herniated disc in an attempt to alleviate pressure on the surrounding nerve roots (American Academy of Orthopaedic Surgeons, June 2010). Open discectomy involves making a small incision in the skin over the spine, removing some of the ligament and bone to access the disc, and removing some of the disc material; discectomy can be performed alone or in combination with cervical fusion.

Open discectomy is performed under general anesthesia and typically requires a one-day hospital stay. The surgeon makes an incision in the skin over the affected area of the spine. The muscle is removed from the bone. Once the surgeon can visualize the lamina, disc, and other surrounding structures, he or she will remove the section of the disc that is protruding from the disc wall. No material is used to replace the removed disc. After the procedure, patients should avoid strenuous activity and heavy lifting for some time. Sedentary work may be resumed within 1-2 weeks.

In addition to the open procedure, there are several alternative approaches to discectomy. Microdiscectomy is a form of discectomy where only the ruptured portion of the disc is removed. The surgeon makes a very small incision in the neck over the problem disc. A small portion of the vertebra is removed. An X-ray is used to help guide the surgeon to the right disc. Once the bony material has been removed, the surgeon locates the area near the pinched nerve root. With the aid of a microscope or endoscope, the ruptured portion of the disc is removed as well as any disc fragments that have broken off in the process.

Discectomy is generally a safe procedure but it is associated with some risks. These risks include infection, bleeding, injury to surrounding blood vessels or nerves, leaking cerebrospinal fluid, and injury to the dura mater, the outer layer of the spinal cord.

Laminectomy and Laminoplasty

Laminectomy and laminoplasty are surgical procedures used to alleviate pain that is believed to be caused by neural impingement (Mayo Clinic, 2012). Laminectomy involves the removal of the lamina bone, a thin bony layer that covers and protects both the spinal canal and spinal cord. Surgeons may also remove bone spurs from the facet joints during laminectomy; this also helps to remove pressure from the spinal nerves. In laminoplasty, the lamina bone and its associated membranes are preserved, but freed from positions that impinge on the nerves and repositioned (Medscape, 2012). Both procedures are typically performed under general anesthesia. Hospital stays may range from one to 3 days.

Activities such as lifting and bending should be avoided for a few weeks after these procedures. Procedural complications of laminectomy and laminoplasty are similar to those of other cervical procedures. In addition, manipulation of the lamina can cause nerve root deficits, and over the long term, the consequences of this surgery may result in atrophy of the posterior cervical muscles, which may in turn cause spinal deformity and instability (Korinath, 2008). Preservation of the laminae with laminoplasty was thought to

prevent some of these complications, but long-term follow-up studies suggest comparable outcomes with these procedures (Nurboja, 2012).

Foraminotomy

Cervical foraminotomy is performed in patients with radiculopathy symptoms and focuses on widening the area where the spinal nerve roots exit the spinal column in order to relieve pressure on the affected nerve roots. Foraminotomy is considered less likely to be effective in patients with significant spondylosis or disc protrusion (Korinth, 2008). Foraminotomy may be performed on one side of the spinal column at single or multiple levels, on both sides at single and multiple levels, or in combination with laminectomy or laminoplasty (Epstein, 2002). In contrast to discectomy and laminectomy/laminoplasty, foraminotomy is an alternative to cervical fusion rather than a procedure that can be performed with or without fusion.

This surgery is usually done with through a posterior approach. The surgeon may use a small, rotary cutting tool (a burr) to shave the inside edge of the facet joint. This opens up the outer rim of the neural foramen. The burr is sometimes used to shave a small section of the bony ring on the back of the vertebra above and below the affected nerve root. Small cutting instruments are used to carefully remove soft tissues within the neural foramen. The surgeon takes out any small disc fragments that are present and scrapes off nearby bone spurs. In this way, tension and pressure are taken off the nerve root (Orthogate.org, 2012).

As with discectomy, foraminotomy may be performed using an open approach or employing microscopic and/or endoscopic techniques. Foraminotomy is generally a safe and straightforward procedure, with most patients able to leave the hospital after an overnight stay. Risks are similar to other forms of surgery for cervical DDD (Korinth, 2008).

3. Clinical Guidelines

Major guideline statements regarding cervical fusion can be found in the sections that follow below.

- **North American Spine Society (NASS, 2010)**

http://www.spine.org/Documents/Cervical_Radiculopathy.pdf

Anterior cervical discectomy with fusion (ACDF) is recommended in the treatment of 1-level cervical radiculopathy from degenerative disorders and is considered a comparable treatment strategy to anterior cervical discectomy (ACD) based on long-term follow-up. ACDF or posterior laminoforaminotomy (PLF) are recommended for the treatment of 1-level cervical radiculopathy secondary to foraminal soft disc herniation, while ACDF is recommended over PLF in patients with 1-level disease from central and paracentral nerve root compression and spondylotic disease. Evidence suggests that ACDF results in comparable short-term success relative to ACD, PLF, and reconstruction with total disc replacement.

- **American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves (AANS/CNS 2009)**

http://thejns.org/doi/abs/10.3171/2009.2.SPINE08727?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

For patients with cervical spondylotic myelopathy (CSM) or ossification of the posterior longitudinal ligament (OPLL), cervical laminectomy with fusion is recommended as an equivalent strategy to laminectomy or laminoplasty and is associated with postoperative neurological improvement. Laminectomy and fusion consistently results in ventral and dorsal cord decompression.

http://thejns.org/doi/abs/10.3171/2009.2.SPINE08721?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

ACD and ACDF produce equivalent clinical outcomes for patients with 1-level cervical disc degeneration. ACDF is recommended over ACD to reduce risk of kyphosis and increase fusion rate for patients with 1-level disease. ACDF is also considered superior to ACD in achieving quicker relief of neck or arm pain, though functional outcomes may be similar.

Anterior cervical plating (ACDFI) does not improve long-term outcomes in patients with level-1 disease but is considered superior to ACDF in improving arm pain for patients with 2-level cervical disc degeneration. Plating does not improve other clinical outcomes with respect to 2-level disease. For patients with 1-level cervical degeneration, plating is recommended to reduce risk of pseudarthrosis, incidence of graft-related complications, and improve cervical lordosis, but not to improve clinical outcomes alone. Plating may increase surgical blood loss.

http://thejns.org/doi/abs/10.3171/2009.3.SPINE08720?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Anterior surgical nerve root decompression via ACDF is recommended with patients with cervical radiculopathy for fast relief (3–4 months) of arm or neck pain and/or sensory loss over physical therapy (PT) or immobilization with a cervical collar. Anterior surgical nerve root decompression may also improve long-term functional outcomes relative to PT, including wrist extension, elbow extension, shoulder abduction, and internal rotation. However, recurrent symptoms are common.

- **American College of Occupational and Environmental Medicine (ACOEM, 2011)**

<http://guideline.gov/content.aspx?id=35207&search=fusion#Section442>

Cervical discectomy and fusion is recommended to speed recovery in patients with chronic cervical radiculopathy or symptomatic spinal stenosis who continue to have significant functional limitations after 6 weeks of appropriate non-operative therapy. All forms of decompressive surgery, with or without fusion, are recommended in patients with symptoms of cervical myelopathy. Cervical fusion is recommended in patients with degenerative spondylolisthesis or in patients undergoing discectomy for this condition if during the same operative episode as the discectomy.

Cervical fusion is not recommended for chronic non-specific cervical pain.

- **Work Loss Data Institute (WLDI, 2011)**

<http://guideline.gov/content.aspx?id=33185&search=fusion>

Anterior cervical fusion procedures are considered an option for a variety of chronic neck conditions. Posterior fusion remains under study and is not specifically recommended. Multi-level corpectomy with fusion is considered equivalent to other procedures in patients with cervical myelopathy, although the complication rate with fusion may be somewhat higher. Patients undergoing fusion at the C1-C2 level should refrain from returning to any activity with a risk of reinjury.

- **UpToDate (2012)**

http://www.uptodate.com/contents/treatment-of-cervical-radiculopathy?source=see_link

ACDF and other decompressive procedures should be considered in patients with (1) signs and symptoms of radiculopathy; (2) MRI or CT myelographic evidence of nerve root compression; and (3) persistence of radicular pain despite conservative management of at least 6-12 weeks' duration. There is little convincing evidence that any one surgical option is superior to another, or that any improve upon the natural history of the condition.

http://www.uptodate.com/contents/cervical-spondylotic-myelopathy?source=see_link#H14

Surgical consultation is warranted in patients presenting with cervical myelopathy and disabling neurologic deficits, or in patients with mild symptoms who are at risk of neurologic deterioration. There is no evidence to distinguish the relative benefits and risks of fusion techniques, laminoplasty, laminectomy, or corpectomy in patients with cervical myelopathy.

4. Medicare and Representative Private Insurer Coverage Policies

Centers for Medicare and Medicaid Services (CMS): Medicare does not have a National Coverage Determination (NCD) for any form of fusion surgery. Local coverage decisions (LCDs) are limited to the use of spinal fusion for *lumbar* degenerative disc disease only.

Similarly, few private payers have explicit coverage policies in place for cervical fusion surgery; those that were found are summarized below.

Humana: Patients are eligible for cervical fusion surgery when radiographic evidence confirms any of the following:

1. As a concurrent stabilization procedure with corpectomy or laminectomy;

2. Degenerative spinal segment adjacent to a previously decompressed or fused spinal segment with symptomatic myelopathy or radiculopathy corresponding to the adjacent level;
3. Disc herniation with radiculopathy with failure of conservative treatment and unremitting radicular pain secondary to nerve root compression;
4. Multilevel spondylotic myelopathy or radiculopathy;
5. Ossification of the posterior longitudinal ligament;
6. Symptomatic pseudoarthrosis from a prior procedure;
7. Symptomatic spondylosis with instability

Aetna: Cervical laminectomy (with or without anterior fusion) is considered medically necessary for individuals with a herniated disc or other causes of spinal cord or nerve root compression (osteophytic spurring, ligamentous hypertrophy) when all of the following criteria are met:

1. All other reasonable sources of pain have been ruled out; *AND*
2. Presence of neck or cervico-brachial pain with findings of weakness, myelopathy, or sensory deficit; *AND*
3. Imaging studies (e.g., CT or MRI) indicate nerve root or spinal cord compression at the level corresponding with the clinical findings; *AND*
4. Member has failed at least 6 weeks of conservative therapy (unless there is evidence of cervical cord compression, which requires urgent intervention); *AND*
5. Member has physical and neurological abnormalities confirming the historical findings of nerve root or spinal cord compression (e.g., reflex change, sensory loss, weakness) at or below the level of the lesion and may have gait or sphincter disturbance (evidence of cervical radiculopathy or myelopathy); *AND*
6. Member's activities of daily living are limited by persistent neck or cervico-brachial pain.

5. Previous Systematic Reviews/Technology Assessments

No recent technology assessments focusing on cervical spinal fusion were identified from national or international organizations other than an assessment from the National Institute for Health and Clinical Excellence that focused on a specific type of screw used during fusion. Two recent systematic reviews are available from the Cochrane Collaboration, however, and are summarized below.

- **Surgery for Cervical Radiculopathy or Myelopathy (Nikolaidis, 2010)**
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001466.pub3/pdf/abstract>
 There is low quality evidence that surgery may provide pain relief faster than physiotherapy or hard collar immobilization in patients with cervical radiculopathy; but there is little or no difference in the long-term. There is very low quality evidence that patients with mild myelopathy feel subjectively better shortly after surgery, but there is little or no difference in the long-term.

- **Single or Double-Level Anterior Interbody Fusion Techniques for Cervical Degenerative Disc Disease (Jacobs, 2011)**

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004958.pub2/pdf/abstract>

Among discectomy alone, discectomy with interbody fusion, and discectomy with interbody fusion and anterior plating, there is no evidence that any one technique is better than another for clinically significant pain relief for patients with chronic cervical degenerative disc disease or disc herniation. There was no statistically-significant difference in complication rates in studies comparing discectomy alone to fusion procedures. There is moderate quality evidence that the use of a bone graft (bone transplanted from another part of the body) is more effective than discectomy alone in achieving fusion.

6. Ongoing Clinical Studies

Information on ongoing clinical studies that have been submitted to the U.S. National Institutes of Health's registry of publicly- and privately-supported studies (www.clinicaltrials.gov) is presented in the table below and on the following page.

Title/ Trial Sponsor	Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Anterior vs. posterior procedures for cervical spondylotic myelopathy: prospective randomized clinical trial NCT00876603 The University of Hong Kong	RCT	Anterior decompression and fusion Posterior cervical laminoplasty	• n = 100 • 40 to 80 years • Patients with cervical spondylotic myelopathy requiring surgery of 1-3 levels	JOA score at 3, 6, 12 months, and 3, 5, 10 years	December 2020
PureGen: a radiographic analysis of rate and quality of fusion in patients undergoing anterior cervical discectomy and fusion NCT01291134 Alphatec Spine, Inc.	Prospective single-arm cohort	N/A	• n=50 • 18 years and older • Symptoms of cervical degenerative disc disease in 1-4 levels • Persistent neck/arm pain • Unresponsive to ≥6 weeks of conservative treatment	Fusion at 12 months	NR (study start date: February 2011)

Source: www.clinicaltrials.gov

Title/ Trial Sponsor	Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Outcome analysis for minimally invasive spine surgery NCT01751841 Weill Medical College of Cornell University	Retrospective single-arm cohort	N/A	• n=200 • Patients with degenerative disc disease • Procedures include posterior cervical fusion and anterior discectomy and fusion using silicate-substituted calcium phosphate ceramic graft material	VAS up to 2 years	April 2013
Bone graft materials observational registry (APPROACH-001) NCT00974623 Apatech, Inc.	Prospective single-arm cohort	N/A	• n=300 • 18 years and older • Failed conservative treatment, and potential candidate for spinal fusion surgery	Evidence of successful radiographic fusion at 6, 12 & 24 months	December 2013
Evaluation of DTRAX graft in patients with cervical degenerative disc disease NCT01616719 Providence Medical Technology	Prospective single-arm cohort	N/A	• n=100 • 35 to 80 years • Patients with degenerative disc disease, including arm/shoulder pain and disc herniation • Single- or multi-level disease • Unresponsive to ≥ 6 weeks of conservative treatment • NDI ≥ 30	Clinical outcome data (NDI, VAS and quality of life questionnaire) at baseline and up to 12 months	February 2015

Source: www.clinicaltrials.gov

7. The Evidence

Objectives

The primary objectives of the systematic review were to:

- Evaluate and compare the published evidence on the effects of cervical spinal fusion procedures relative to comparator treatments on pain, function, and health-related quality of life in patients with neck pain and other symptoms (e.g., radiculopathy) arising from cervical degenerative disc disease (DDD) with or without spondylosis;
- Evaluate and compare the clinical benefits of these therapies in terms of other outcomes, including rates of return to work and rates of “successful” outcomes;
- Evaluate and compare the potential harms of these therapies, including procedure-related fatalities and major and minor complications as well as requirements for repeat surgery;
- Examine the differential effectiveness and safety of cervical fusion according to factors such as age, sex, race, ethnicity, pre-existing conditions (e.g., smoking history), neuromuscular disease states (e.g., Parkinsonism), measurable spinal instability, technical approach to fusion, insurance status (e.g., worker’s compensation vs. other), and treatment setting (e.g., inpatient vs. ambulatory); and
- Assess the costs and potential cost-effectiveness of cervical spinal fusion in multiple patient populations relative to alternative approaches.

As discussed in greater detail in the sections that follow, the target population for this appraisal was patients with chronic neck pain and related symptoms due to cervical DDD, implying that these patients were treated conservatively at initial presentation and continued to have persistent symptoms. Our focus was therefore on management options available to these patients following 4-6 weeks of conservative therapy. As described in further detail in Section 7.6, we focused attention on evidence for cervical spinal fusion and the management options to which it has been compared in randomized controlled trials (RCTs) or comparative cohort studies, and did not therefore evaluate comparisons of other management options to non-fusion controls (e.g., laminectomy vs. laminoplasty). Case series of cervical fusion were also abstracted for long-term data on harms as well as information on key patient subgroups. We did not include for evaluation studies comparing cervical disc arthroplasty to fusion, as the Washington HCA has previously evaluated this evidence (Washington Health Care Authority, 2008).

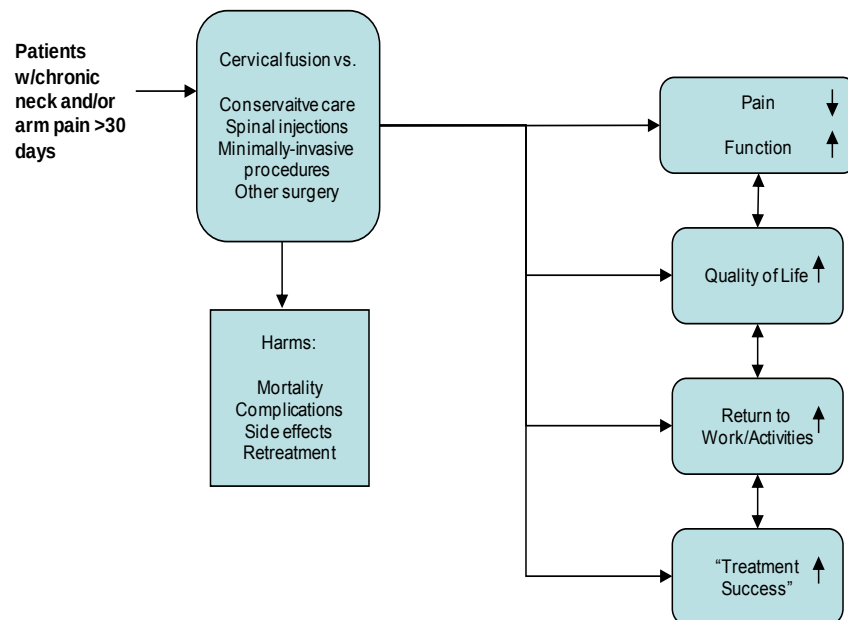
Our recording of data on potential harms of fusion and other surgical procedures included “peri-procedure” fatalities and complications occurring during the procedure or within 30 days following, as well as longer-term adverse events observed throughout the remainder of follow-up. We abstracted each type of complication in detail in order to understand the universe of specific complications reported for fusion and its comparators.

While not part of the systematic review, published studies of the economic impact of cervical fusion are summarized in Section 8 to provide additional context for the ICER decision analytic model.

Analytic Framework

The analytic framework for this review is shown in the Figure below. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of cervical fusion and its alternatives, and is not intended to depict a clinical pathway through which all patients would flow. This framework also does not represent the clinical pathways as they were constructed for the decision analytic model (see Section 8).

Analytic Framework: Management Options for Cervical Degenerative Disc Disease



There are limited data directly demonstrating the impact of most cervical DDD management strategies on summary measures of "treatment success" or "successful clinical outcome", so judgments about the effectiveness of these interventions must rest primarily upon consideration of multiple and potentially overlapping measures (e.g., pain, function, quality of life) as well as evaluation of treatment-associated risks. In addition, various stakeholders will by nature be more interested in certain outcomes than others. For example, payers and employers may be most interested in functional improvement and/or return to work, while clinicians and patients may focus more on relief of symptoms and spinal stability.

There is considerable debate about how much credence to place in comparisons across studies of multiple outcome measures for the management of cervical DDD. As has been observed in studies of both chronic neck pain and low back pain, patient populations may differ significantly in terms of baseline severity of their condition and degree of impairment, which can then in turn affect the sensitivity of measurement instruments to detect clinically important differences, even when these instruments are standardized and validated (Carey, 2007). In addition, the primary research questions and goals of

management may differ substantially by approach. For example, interventions with a goal of functional restoration may show little to no effects on pain and quality of life measures.

7.1 Patient Populations

The focus of this appraisal was on adults (>17 years of age) with cervical DDD symptoms, including neck pain, arm pain, and/or radiculopathic symptoms (e.g., numbness, tingling); these symptoms could occur with or without the presence of spondylosis. We did not focus on studies that consisted primarily or in total of patients whose primary complaint was cervical myelopathy, as this is generally considered a neurologic emergency in all but the mildest cases and patients typically proceed directly to surgical intervention (McCormick, 2003). These studies are nevertheless included in evidence tables (see Appendix C), shaded to distinguish them from the studies of primary interest.

It was also recognized that some studies enrolled a mix of patients that might have included those with myelopathic symptoms. We did not therefore exclude any study purely on the basis of the presence of a subgroup with myelopathy, as long as this subgroup constituted the minority of subjects.

Studies of patients receiving intervention for acute trauma or systemic disease affecting the spine (e.g., malignancy, autoimmune conditions) were excluded. It was also noted that surgical studies would likely include patients with a variety of prior attempts at treatment, including conservative management for varying lengths of time. While these factors were noted in summaries of study and patient characteristics, all studies were included regardless of the nature, duration, and intensity of prior treatment received.

Certain patient subpopulations were also identified as of interest in evaluating whether treatment effects and/or harms differed in these groups. These included subpopulations defined by demographic characteristics (e.g., age, sex, race/ethnicity), pre-existing conditions (e.g., smoking history), neuromuscular comorbidities (e.g., Parkinsonism), measurable spinal instability, anatomic approach to fusion (i.e., anterior vs. posterior fusion, single- vs. multi-level procedures), insurance status (e.g., worker's compensation vs. other), treatment setting (e.g., inpatient vs. ambulatory), and other subgroups as defined in available studies.

7.2 Interventions

The interventions of interest included the major approaches to cervical fusion. All forms of fusion were considered, regardless of type of decompressive surgery coupled with fusion (e.g., discectomy, laminectomy), use of instrumentation and type of hardware utilized, or graft material; these factors were nevertheless used as procedure descriptors. In addition, fusion studies were categorized by anatomic approach (i.e., anterior vs. posterior) and number of disc levels involved (single, 2-level, or >2-level) where feasible, as benefits and risks are thought to vary according to these aspects (Shamji, 2008; Riley, 2010). Studies

were also sought comparing outcomes for fusion performed in inpatient vs. ambulatory/outpatient settings.

7.3 Comparators

Potential comparators of interest in this review included all management options compared to fusion in RCTs and comparative cohort studies. These included conservative management approaches such as physical therapy, spinal manipulation, immobilization (i.e., via a cervical collar or brace), medication, and other approaches; minimally-invasive procedures such as spinal injections, radiofrequency denervation, and percutaneous procedures; and other forms of surgery, including decompressive procedures such as discectomy or laminectomy without fusion, laminoplasty, and foraminotomy. Importantly, we did *not* include studies comparing only one type of fusion to another (e.g. with vs. without plating), as recent systematic reviews have concluded that data are not sufficient to distinguish the performance of these approaches (Jacobs, 2011; Nishizawa, 2012; Gebremariam, 2012) and the focus of this review was on comparing fusion to alternative treatment modalities. Exceptions to this rule included studies where the comparison was of anatomic approach or number of levels fused, as well as the setting in which fusion was performed (i.e., inpatient vs. ambulatory/outpatient).

7.4 Outcomes

In order to adequately compare effectiveness across management options within each patient population, we prioritized for abstraction data from the most widely-used and validated outcome instruments; if other measures represented primary or key secondary outcomes, however, we also abstracted these. For example, some studies may have captured self-reported improvements in pain or other outcomes using a measure developed specifically for that study. Outcome measures of interest are described in more detail on the following pages, by type. Outcomes recorded at multiple timepoints were abstracted separately for each timepoint.

Operative Outcomes

A variety of data was abstracted as reported during the procedure and related hospital stay, including procedure duration, anesthesia duration, blood loss, number of disc levels, and length of stay in hospital. Any harms or unexpected events during the procedure or 30 days following also were recorded (see “Potential Harms” below).

Pain

Pain outcomes were evaluated based on visual analogue (VAS), numeric, or Likert rating scales, as well as the North American Spine Society (NASS) cervical questionnaire, which examines a variety of domains of pain and neurogenic symptoms (Stoll, 2004). Data were abstracted as recorded, including repeated-measures means and standard deviations or standard errors at multiple timepoints, “change scores” (i.e., mean or median change from baseline), and both univariate and multivariate measures of treatment effect. The statistical

significance of all findings was also abstracted as reported. While data were abstracted as reported for the systematic review, data transformations were performed for meta-analysis and simulation modeling if warranted. For example, VAS results using a different scale (e.g., 100 mm) may have been converted to 10 mm scales for the purpose of consistency. When examining changes in VAS pain, it is important to consider that influential clinical guideline and consensus statements consider 5-10 point changes on a 100-point VAS to be the minimal level of “clinically important” improvement (Chou, 2007). Improvements of $\geq 30\%$ from baseline levels are considered clinically-meaningful to patients (Dworkin, 2008).

Functional Status

Findings with regard to patient functional status were assessed from studies employing well-known indices for measuring function in cervical disorders, including the Neck Disability Index, a 50-point scale derived from the Oswestry Low Back Pain Disability Index (Vernon, 1991); and the 17-point Japanese Orthopaedic Association (JOA) score (Keller, 1993). Further information on these measures can be found in Appendix A. Results from generic disability scales such as the Disability Rating Index (Salén, 1994) were also considered, as were subjective measures of functional ability and timed tasks such as handling everyday items and walking. Data were abstracted as described above for pain. As above, transformations of data were considered in modeling and/or meta-analysis where warranted.

Health-related Quality of Life

We sought data on all reported quality-of-life measures, whether from generic instruments such as the SF-36 or Sickness Impact Profile, condition-specific measures correlated with neck pain (e.g., the Beck Depression Inventory), or study-specific measures. Data were abstracted as described for pain and function above. We abstracted data for all reported domains on these instruments as well as summary scores where available.

Successful Clinical Outcome

The frequency or likelihood of “successful clinical outcome” or “treatment success” was abstracted where reported. A variety of standardized versions of these measures are available, including Odom’s criteria (Odom, 1958), Hilibrand’s criteria (Hilibrand, 1999), Hirabayashi’s recovery rate (Hirabayashi, 1981), as well as study-specific measures. While all data were abstracted, patients with either an “excellent” or “good” outcome on Odom’s or Hilibrand’s criteria were considered to be treatment successes, while those with a positive Hirabayashi value were categorized as having a successful outcome. Detailed descriptions of standardized measures can be found in Appendix A.

Return to Work

Multiple measures of return to work were recorded, including the frequency of successful return to work and total amount of sick leave/absenteeism. Where available, time-to-event measures of return to part- or full-time employment were also recorded.

Potential Harms

Peri-Procedure Mortality and Complications

Peri-procedure deaths were classified as those occurring during the procedure or within 30 days following. Procedure-related complications were recorded as described in order to obtain an

exhaustive list of reported events. No attempt was made to further categorize the complications in terms of severity, as this information was typically lacking in most study reports. Examples of complications recorded are listed below.

- Nerve damage/palsy
- Wound infection
- Hemorrhage
- Cerebrospinal fluid leak
- Thrombosis
- Pneumonia
- Hardware failure
- New-onset numbness or weakness
- Dysphagia (difficulty swallowing)
- Hoarseness
- Donor site pain (for autologous bone grafts)

In addition, recent data on risks associated with any surgery, while not specific to fusion procedures, were nevertheless sought to provide further information on the spectrum of possible surgical risks.

Retreatment

Rates of repeat treatment were abstracted where reported, and categorized separately as follows. First, rates of return to the operating room during the initial hospital stay (e.g., for hardware failure, control of hemorrhage, etc.) were recorded. In addition, rates of repeat surgery with the same procedure following the peri-procedure period also were recorded. Finally, rates of repeat surgery with a different procedure at any point during follow-up (e.g., for adjacent segment disease) also were abstracted if recorded as such.

Longer-term Adverse Events

In addition to peri-procedure complications, complications and adverse events as well as death from any cause also were recorded over the remaining duration of follow-up. In addition to the complication types described above, examples of adverse events recorded following the peri-procedure period are listed below:

- New-onset radiculopathy or myelopathy
- Neurological decline
- Symptomatic pseudarthrosis (non-union of fusion)
- Adjacent segment degeneration or disease (ASD)

7.5 Timeframe

The timeframe for evaluation of clinical benefits and potential harms differed by study design (see Section 7.7 below). Data from RCTs and comparative cohorts were considered from baseline through a period of follow-up that typically did not extend beyond 2 years.

Case series data were focused on outcomes recorded at timepoints 12 months or later following intervention.

7.6 Study Designs

Data from both RCTs and observational studies were considered. However, only data from RCTs and, secondarily, comparative cohort studies involving cervical fusion and another form of active treatment were used to evaluate measures of clinical effectiveness, given the significant risks of placebo effects inherent in other study designs. Case series of cervical fusion were also utilized based on the following criteria:

- Sample size >50 cases; AND
- Follow-up $\geq$ 12 months; AND
- Data available on repeat surgery and/or other harms; OR
- Study population defined by a patient subgroup of interest as described in Key Question 3 (e.g., patients in a worker's compensation program)

7.7 Literature Search and Retrieval

Because previous systematic reviews and guideline statements have cited a dearth of available RCTs comparing cervical fusion to alternative treatments, we did not put explicit time limits on our RCT search. The general timeframe for literature search and retrieval for other study designs was January 1996 – September 2012. We focused on English-language reports only. As noted previously, RCTs and comparative cohort studies were limited to those comparing fusion to an alternative management option or comparing posterior to anterior or single- to multi-level fusion; there was no minimum sample size or duration of follow-up in these studies. Case series were limited by both sample size and duration of follow-up, as described in Section 7.6 above.

The electronic databases we searched as part of the systematic review included MEDLINE, EMBASE, and *The Cochrane Library* (including the Database of Abstracts of Reviews of Effects [DARE]) for health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies were also searched. The strategies used for MEDLINE, EMBASE, and *The Cochrane Library* are shown in Appendix B.

Studies were not further restricted by instrumentation, manufacturer, or treatment approach. Figures 1 and 2 on the following pages show flow charts of the results of all searches for RCTs (n=14), comparative cohorts (n=7), and case series (n=56).

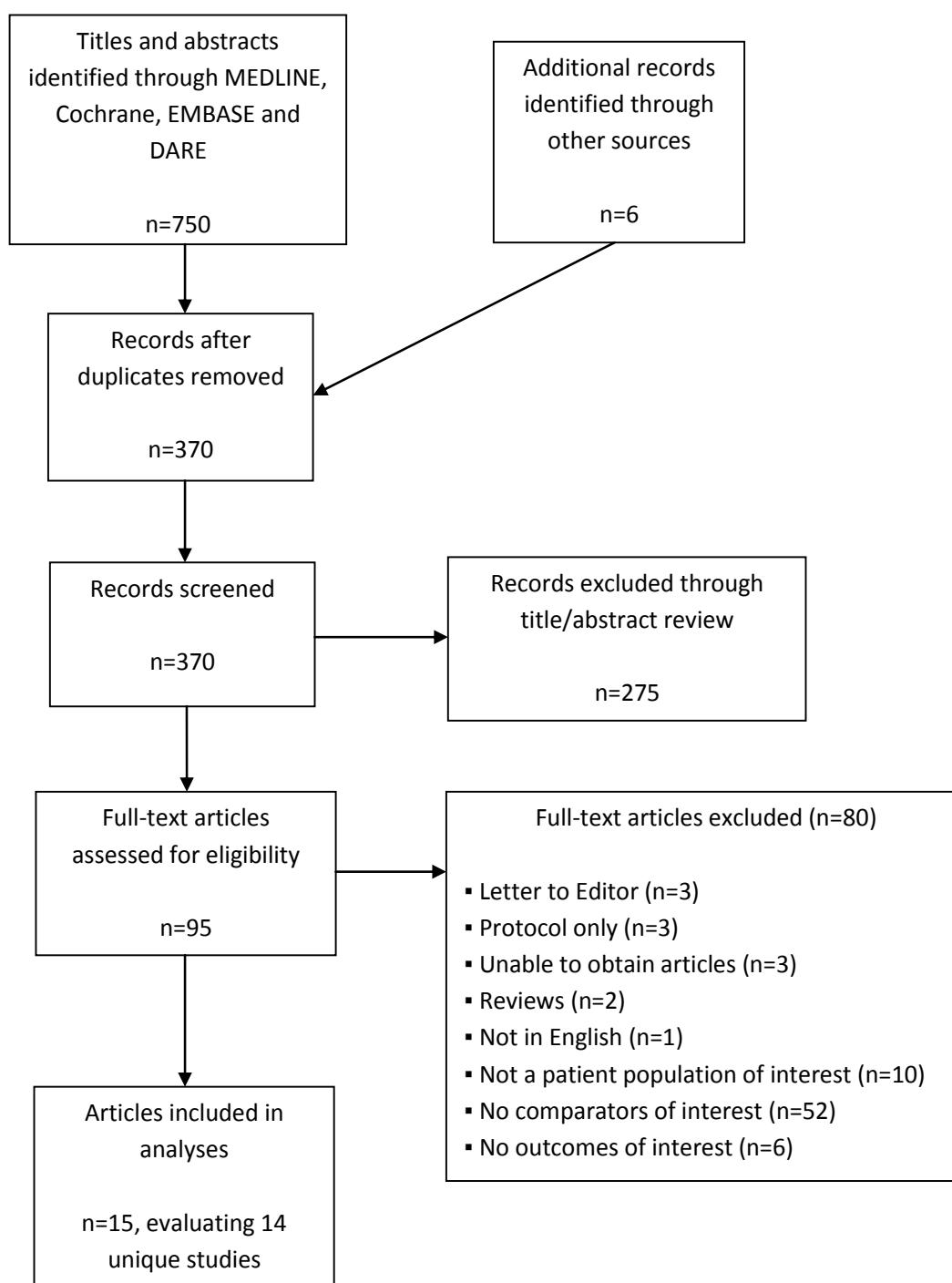
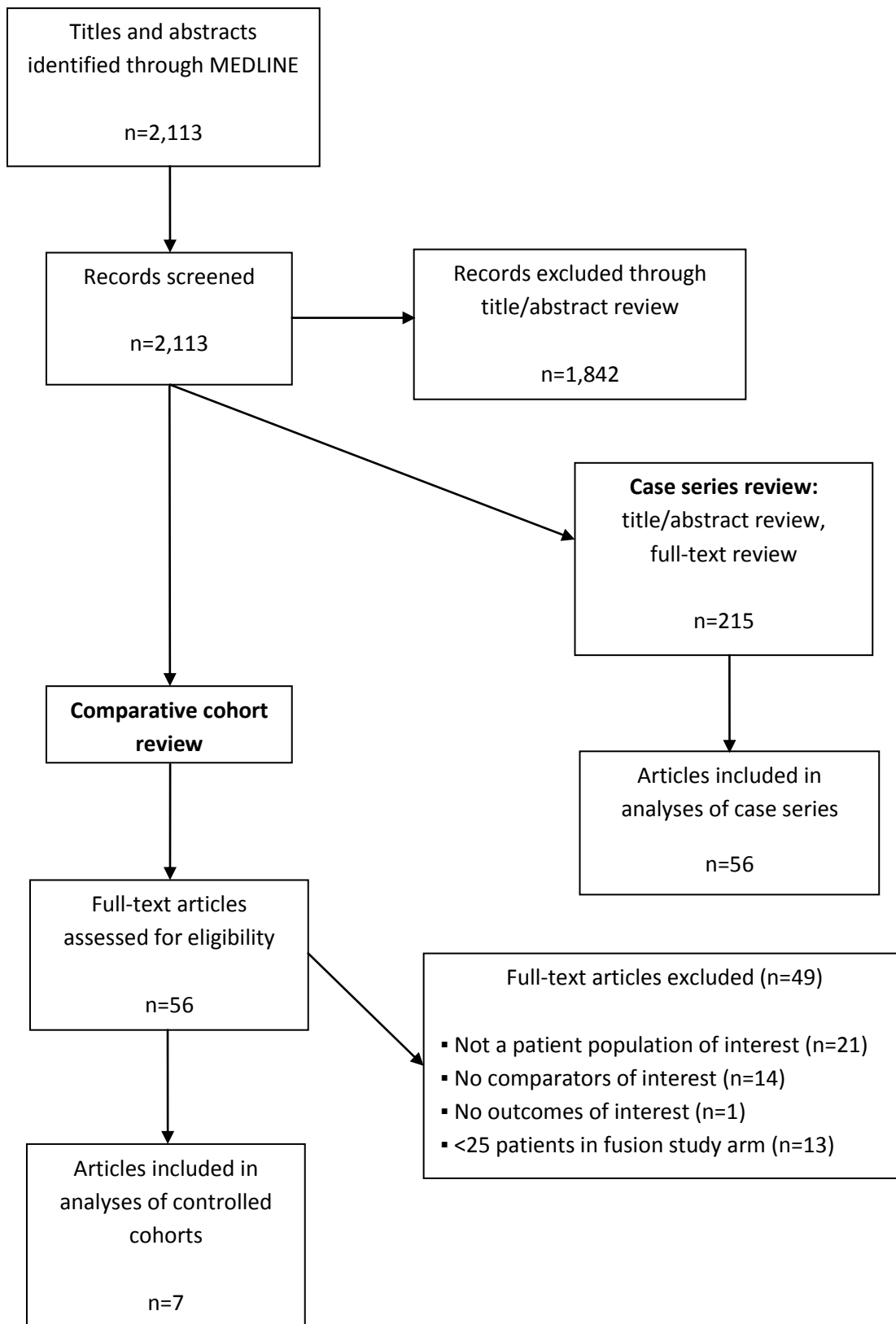
Figure 1. PRISMA flow chart showing results of literature search (RCTs).

Figure 2. PRISMA flow chart showing results of literature search (observational studies).



Study Quality

We used standardized criteria specific to previous systematic reviews in back pain to rate the quality of each included RCT; these criteria have also been widely adopted for use in studies of neck pain (Nikolaidis, 2010). The criteria, which related to issues of study design, reporting, and minimization of bias, are presented in Appendix A. RCTs meeting a majority of criteria (i.e., 5 of 9) were deemed to be “higher quality”. We used general criteria to assess the quality of comparative cohort studies, using the categories “good”, “fair”, or “poor”. Our methods were based on the criteria employed by the U.S. Preventive Services Task Force (AHRQ, 2008), as described below:

- **Good:** Comparable groups (for comparative studies) are assembled initially and maintained throughout the study (follow-up of at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.
- **Fair:** Generally comparable groups are assembled initially but some question remains whether minor/moderate differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.
- **Poor:** Any of the following problems exist: (1) groups assembled initially are not close to being comparable or maintained throughout the study; (2) unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and (3) key confounders are given little or no attention.

Data from all retrieved studies were included in evidence tables regardless of study quality. However, the focus of attention in presentation of results was on higher-quality studies alone where available.

Study quality was not assessed for case series, as the focus of quality ratings was on the level of bias in assessing the *comparative* impact of fusion vs. alternative treatments on measures of effectiveness and harm.

Data Synthesis

Where feasible, estimates of treatment effect were synthesized using meta-analysis. Random-effects models were generated based on head-to-head data from available RCTs. Data were deemed to be sufficient if (a) the number of eligible higher-quality RCTs was 2 or more; (b) the measure of interest was reported using uniform methods; and (c) judgment of the clinical heterogeneity of the patient populations in candidate studies was judged to be low enough to attempt meta-analysis. For continuous variables such as pain or function ratings, the measure of choice for generating pooled estimates of effect was the standardized mean difference (SMD) at the latest reported timepoint. For dichotomous variables (e.g., likelihood of treatment success or return to work), the rate ratio (RR) was

used. Primary meta-analyses focused on comparisons of fusion to a uniform comparator (e.g., discectomy); sensitivity analyses also were conducted comparing fusion to any available control population. Additional, sensitivity analyses were conducted comparing fusion to any available control in all available RCTs, regardless of study quality. Finally, while cohort and case series studies were not candidates for meta-analyses of treatment effect, qualitative findings from these studies are described for each measure of interest. Detailed evidence tables are presented in Appendix C for all key outcomes and study designs evaluated in this review.

7.8 Results

Overview of Evidence and Quality Assessment

Of the 14 RCTs identified (total N=1,209), nearly all (13) focused on patients with radiculopathic symptoms and radiographic evidence of nerve root compression; 1 included patients with evidence of disc herniation. Most available RCTs limited patients to those with single- or 2-level disease (see Appendix C, Tables C1 & C2). ***Importantly, we found no RCT evidence for spinal fusion procedures in patients with only generalized neck pain.*** Of the RCTs conducted in patients with radiculopathy, 2 also required evidence of cervical spondylosis, and 4 were conducted in patients with a recorded attempt at prior conservative treatment. Sample sizes were generally small, ranging from 10-50 patients per treatment arm. In the majority of RCTs, the comparator was discectomy, endoscopic discectomy, or microdiscectomy. Foraminotomy alone or in combination with discectomy was evaluated in 3 RCTs. Fusion was also compared alternatively to physical therapy or cervical collar in 1 RCT.

The 7 comparative cohorts included 929 patients evaluated in single- and multicenter studies, as well as nearly 100,000 patients assessed in a retrospective evaluation of the Nationwide Inpatient Sample database maintained by the U.S. Agency for Healthcare Research and Quality (AHRQ) (Shamji, 2008). Of the 7 studies, 1 was prospective. Comparators were varied, and included discectomy or microdiscectomy, laminoplasty, foraminotomy, and interdisciplinary rehabilitation. One of these studies explicitly compared anterior and posterior fusion techniques, and 3 compared fusion conducted in inpatient vs. outpatient settings.

Study quality is presented in Table 1 on the following page by study type and fusion comparator. A total of 10 of the 14 RCTs were identified as higher quality, including 1 comparing fusion to conservative management, 3 with minimally-invasive surgery as a comparator, and 6 comparing fusion to alternative open surgical approaches. Among the 7 comparative cohort studies, none were identified as “good” quality. Four studies were deemed to be of “fair” quality, including 1 comparing fusion to conservative management, 1 comparing fusion to foraminotomy, 1 comparing fusion procedures performed in inpatient vs. outpatient settings, and 1 comparing anterior to posterior fusion techniques.

Table 1. Studies of cervical fusion: study quality, by type of study and patient population.

<i>Study Type</i>	<i>Comparator</i>	<i>Higher</i>	<i>Lower</i>
RCT	Physical Therapy/ Cervical Collar	1	0
	Discectomy	5	2
	Discectomy/Foraminotomy	1	1
	Microdiscectomy	2	0
	Endoscopic discectomy	1	0
	Endoscopic foraminotomy	0	1
Comparative Cohort	Interdisciplinary Rehabilitation	1	0
	Laminoplasty	0	1
	Foraminotomy	1	0
	Fusion (in- vs. outpatient)	1	2
	Fusion (anterior vs. posterior)	1	0

While it might appear that the evidence base for cervical fusion in patients with radiculopathic symptoms is relatively robust, further investigation revealed several concerns with study design, entry criteria, and protocol. For one, the relatively small sample sizes in most RCTs were evaluated in single institutions, limiting the generalizability that might come from multicenter evaluations of treatment effect. In addition, studies were inconsistent with respect to whether the same or different groups of surgeons performed the surgical procedures being compared in the study. Studies also differed with respect to post-surgery protocol. For example, in some, patients wore a cervical collar for varying periods of time. In others, patients received advice on immobilization, and in still others, no restrictions were placed on mobilization after surgery.

It should be further noted that, despite our intent to focus on studies evaluating patients presenting for treatment after attempts at short-term (4-6 weeks) conservative management, symptom duration was much longer at baseline in most RCTs. Of the 14 RCTs identified, only 3 reported a mean duration of symptoms less than 3 months. Several RCTs randomized patients only if they had a minimum of 2-4 years of symptoms.

Finally, all of the RCTs and comparative cohorts identified compared fusion to other forms of surgery or some form of conservative treatment; as a result, we found no comparative studies of fusion and minimally-invasive therapies such as spinal injections, radiofrequency denervation, or coblation nucleoplasty. As such, any conclusions drawn regarding the comparative benefits and risks of these procedures would be indirect only. Even indirect comparisons might in fact be problematic, as patients evaluated in studies of minimally-invasive procedures may have less severe pain and radicular symptoms than those assessed in surgical studies.

Due to the concerns described above, and because none of these studies stand apart from others based on a distinctive combination of size, duration, quality, and/or generalizability, we have not labeled any comparative study as “key” for the purposes of this appraisal. Important elements of specific studies are highlighted in the report where relevant, however.

Training Standards and Relationship to Outcomes

The benefits and harms associated with all procedures vary to some extent according to the skills of the operator. This is certainly true for spinal fusion procedures in patients with chronic neck pain. Unfortunately, the relative importance of training and experience on patient outcomes has been little studied. Moreover, whatever impact training and skill differences has on the outcomes reported in the published literature, it is likely that even broader variations are seen in general clinical practice. Despite this, there are few widely-accepted training standards for preoperative, operative, and postoperative management of patients undergoing cervical fusion procedures.

Studies examining the relation of procedure volume to outcome in patients with cervical disorders are relatively few in number. In an examination of Medicare inpatient data, Taylor and colleagues observed lower mortality rates at hospitals performing a high volume of back and neck procedures (Taylor, 1997). An examination of cervical fusion procedures performed in California in 2008 suggests a high degree of variation in hospital volume (2-169 procedures), rates of complications (0-12.5%), and implant cost (\$2,053-\$14,382), but made no attempt to evaluate the degree to which these factors were correlated (Berkeley Center for Health Technology, 2009). Other studies focusing specifically on factors associated with outcomes in patient cohorts undergoing cervical spinal procedures were conducted only in high-volume centers (Fehlings, 2012) or using databases that did not include data on procedure volume by setting (Wang, 2007).

8. Clinical Benefits (KQ 1)

Findings are organized by type of comparator to fusion in the sections that follow. As mentioned previously, no comparative data were available comparing fusion to minimally-invasive *nonsurgical* management options such as spinal injections, radiofrequency denervation, or coblation nucleoplasty.

1. Spinal Fusion vs. Conservative Treatment

A total of 2 studies, an RCT (Persson, 2001) and a cohort study (Mayer, 2002) compared cervical spinal fusion to conservative management approaches. These studies are summarized by outcome and population in the sections that follow.

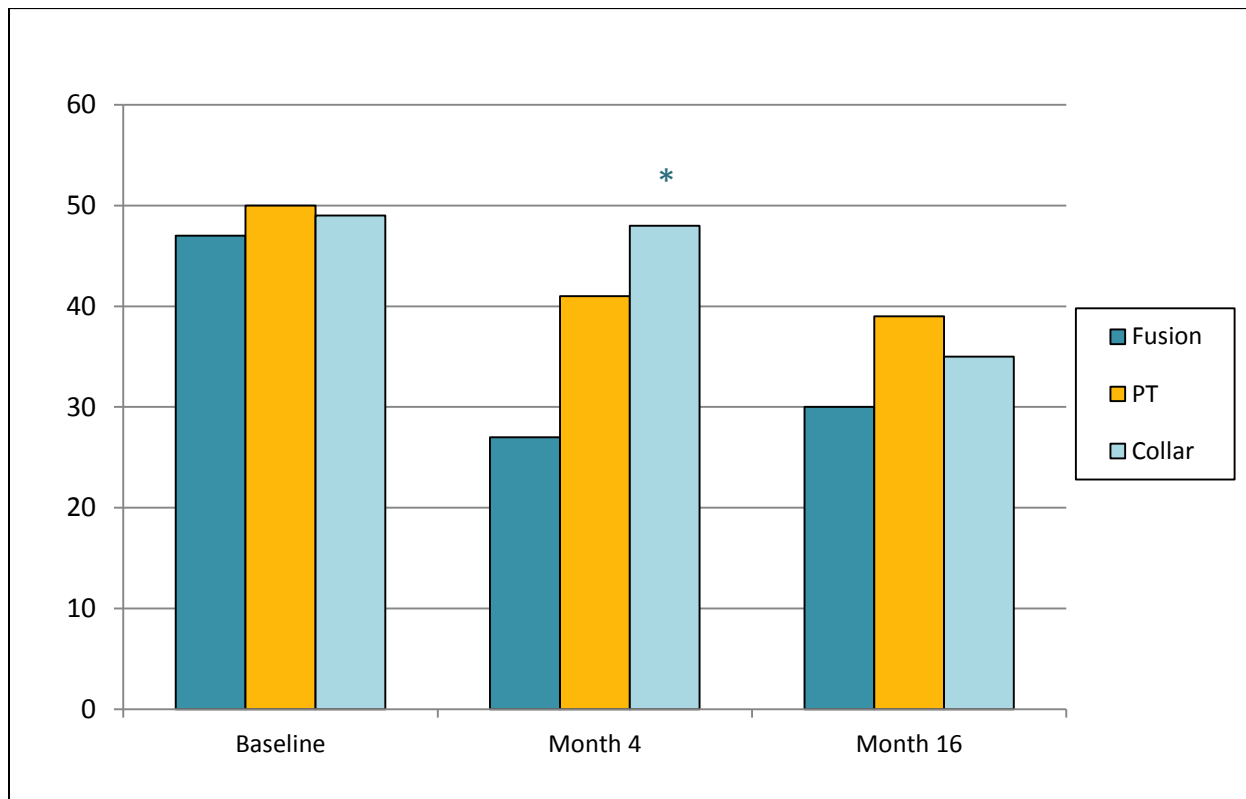
“Treatment Success”

Neither of the studies comparing fusion to conservative treatment included measures of treatment success.

Pain and Function

A higher-quality RCT comparing outcomes for patients with cervicobrachial pain of > 3 months' duration and nerve root compression due to spondylitic spurs randomized 81 patients into equal groups receiving anterior discectomy with fusion, physical therapy, or cervical collar immobilization; patients were followed for 16 months (Persson, 2001) (Appendix C, Tables C4 and C5). Pain was evaluated on a 100 mm VAS scale and measured at baseline, 4 months, and 16 months. As noted in Figure 3 on the following page, pain was reduced at 4 months among fusion patients vs. those receiving either form of conservative management; in the case of cervical collar immobilization, this difference was statistically significant. By month 16, however, the gap in pain scores between conservative management and fusion groups had narrowed, and VAS scores did not differ statistically at this timepoint. (NOTE: as a reminder, 5-10 point changes on VAS scores represent the minimum change that would be considered “clinically important”, and changes $\geq 30\%$ from baseline represent those that would involve significant improvements for patients.)

Figure 3. Self-rated current pain on visual analogue scale, fusion vs. physical therapy vs. cervical collar.



*: $p < .01$, fusion vs. collar; all other comparisons not statistically significant

Source: Persson et al., *Disability & Rehabilitation*;2001;23:325-35

Data on pain and function were also available from the comparative cohort study (Appendix C, Tables C13 and C14) prospectively evaluating the effects of anterior fusion in combination with an interdisciplinary rehabilitation program compared to interdisciplinary rehabilitation alone in 202 patients filing worker's compensation claims for cervical spinal disorders (Mayer, 2002). Rehabilitation consisted of medically-supervised exercise, psychological counseling, workplace and vocational services, and case management. Patients were followed for 12 months. No statistically-significant differences between groups were noted during follow-up in measures of pain, including a 10 cm VAS scale and a questionnaire-based VAS scale known as the Million VAS (Anagnostis, 2003). In addition, no statistically-significant differences were observed in either mean cumulative scores for physical function or the percentage of patients with total cumulative functional scores demonstrating a "significant degree of pathology" (Mayer, 2002).

Quality of Life

In the Persson RCT, no statistically-significant differences between fusion and physical therapy were observed in Sickness Impact Profile or Mood Adjective Check List scores at any point during follow-up (Persson, 2001) (Appendix C, Table C6). Quality of life was also evaluated in the cohort study comparing fusion and interdisciplinary rehabilitation to rehabilitation alone (Mayer, 2002) (Appendix C, Table C15); however, such evaluation focused only on mean Beck Depression Inventory scores at 12 months without controlling for baseline levels or change from baseline.

Return to Work

Work-related outcomes were not evaluated in the Persson RCT (Appendix C, Table C7). In the Mayer comparative cohort study of fusion vs. interdisciplinary rehabilitation (Appendix C, Table C16), no statistically-significant differences were observed between treatment arms in the percentages of patients returning to full or modified work, returning to work at the same employer, or filing additional claims for recurrent injury at 12 months (Mayer, 2002).

2. *Spinal Fusion vs. Discectomy and Foraminotomy*

A total of 13 RCTs (9 higher-quality) examined the effects of fusion compared to discectomy or foraminotomy for cervical DDD. In 10 of these, the comparator was discectomy, microdiscectomy, or endoscopic discectomy alone. In one RCT, separate treatment arms receiving discectomy or foraminotomy were included (Wirth, 2000), and in another, comparator patients received a combination of discectomy and foraminotomy (Martins, 1976). Patients in a third RCT received endoscopic foraminotomy (Ruetten, 2008). Characteristics of all RCTs comparing fusion to these alternative surgical approaches are summarized in Table 2 on the following page as well as in Appendix C, Table C1.

Fusion was compared to foraminotomy in a single fair-quality comparative cohort study of 292 patients who were treated for radicular symptoms and followed for 6 years (Korin, 2006).

“Treatment Success”

Treatment success was evaluated in 6 of the 9 higher-quality RCTs (Appendix C, Table C3). In one, 3 types of discectomy with fusion (autograft, polymethylmethacrylate [PMMA] graft, and titanium cage) were compared to microdiscectomy alone in 125 patients with single-level cervical disc disease and radiculopathy who were treated at a single institution in Switzerland and followed for 12 months (Barlöcher, 2002). Based on Odom’s criteria, a greater percentage of patients undergoing fusion with titanium cage had “excellent” or “good” results vs. microdiscectomy alone at 12 months (94.4% vs. 75.5%, $p < .02$); differences were not statistically-significant for the other fusion groups compared to microdiscectomy.

No statistically-significant differences were observed for measures of treatment success in the other higher-quality RCTs. In one, 91 patients with single-level radicular symptoms were randomized to receive fusion with bone graft, fusion with plating, or discectomy alone and followed for 4 years (Savolainen, 1998). Clinical outcome was based on patient self-report of symptoms, with “good” classified as absence of symptoms, “fair” described as improved but still with some complaints, and “poor” defined as no better or worse than the preoperative state. The distribution of clinical outcome was not statistically different between the 3 groups at any timepoint including after 4 years of follow-up.

Table 2. Characteristics of RCTs comparing fusion to discectomy or foraminotomy.

Author	Year	Comparator(s)	Sample Size	Study Duration (months)	Quality
Abd-Alrahman	1999	Discectomy	90	15	Lower
Barlöcher	2002	a--Microdiscectomy b--PMMA Fusion c--Fusion w/Cage	125	12	Higher
Dowd	1999	Discectomy	84	54	Lower
Hauerberg	2008	Discectomy	86	24	Higher
Martins	1976	Discectomy and foraminotomy	51	12	Higher
Oktenoglu	2007	Microdiscectomy	20	18	Higher
Rosenørn	1983	Discectomy	63	12	Higher
Ruetten	2009	Endoscopic discectomy	120	24	Higher
Ruetten	2008	Endoscopic foraminotomy	200	24	Lower
Savolainen	1998	a--Discectomy b--Fusion w/Plating	91	36	Higher
van den Bent	1996	Discectomy	81	24	Higher
Wirth	2000	a--Discectomy b--Foraminotomy	72	60	Lower
Xie	2007	a--Discectomy b--Instrumented Fusion	45	24	Higher

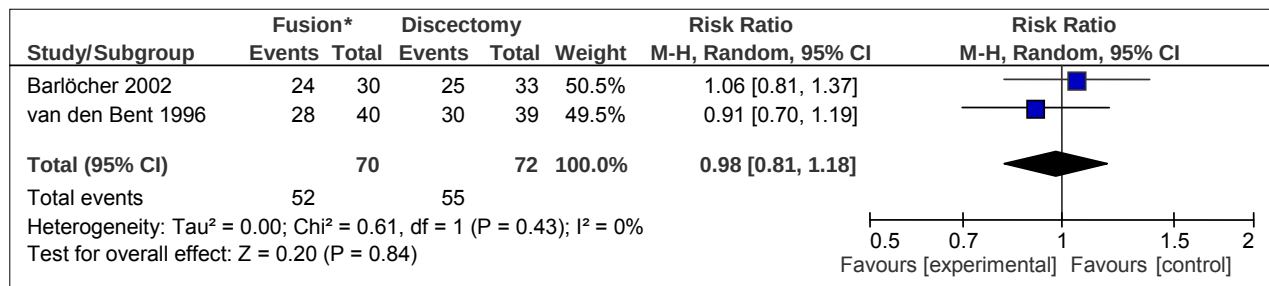
Another RCT evaluated 86 patients with symptoms of nerve root compression, who were randomized to fusion with titanium cage or discectomy alone and followed for 24 months (Hauerberg, 2008). Treatment outcome was defined dichotomously, based on full recovery or improved symptoms ("good") or no change or worse symptoms ("poor"). The percentage of patients with good outcome did not differ statistically between groups at months 3, 12, and 24. A third RCT assessed clinical outcome using Odom's criteria in 81 patients randomized to discectomy with PMMA fusion or discectomy alone who were followed for 24 months (van den Bent, 1996). The percentage of patients with an excellent or good result at 24 months was over 70% in both groups and did not differ statistically.

Hilibrand's criteria were used to assess treatment outcome in an RCT comparing anterior discectomy with fusion to endoscopic anterior discectomy alone in 120 patients with radiculopathy secondary to disc herniation who were treated at a spine center in Germany and followed for 24 months (Ruetten, 2009). Approximately 90% of patients in both arms were categorized as having "excellent" or "good" outcome on this scale at 24 months. No statistically-significant differences were noted at any earlier timepoint as well. A final, shorter-term RCT evaluated anterior fusion with bone graft vs. discectomy and foraminotomy in 51 patients who were followed for 6 months (Martins, 1976). A study-

defined outcome scale rated treatment results as fair, good, or excellent based on the number of preoperative symptoms that were improved, or poor if signs and symptoms were unchanged. At 6 months, two-thirds of patients in each treatment group reported excellent or good results; differences were not statistically significant.

While 6 higher-quality RCTs were available, only 2 of these used the same instrument to measure treatment success (Odom's criteria). We conducted a random-effects meta-analysis examining the likelihood of treatment success for fusion vs. discectomy based on data from these 2 studies. No statistically-significant difference was observed, as noted in Figure 4 below (Rate ratio [RR]: 0.98, 95% CI: 0.81, 1.18; $p=.84$).

Figure 4. Meta-analysis of treatment success, based on Odom's criteria.



*Anterior discectomy and fusion

A sensitivity analysis also was conducted including data from a lower-quality RCT (Abd Al-Rahman, 1999). Findings were also not statistically-significant in this analysis (RR: 0.90; 95% CI: 0.79, 1.03; $p=.11$)(Appendix C, Figure C2).

The retrospective comparative cohort study also evaluated outcome based on Odom's criteria (Appendix C, Table C12). In this study, an assessment of 292 patients receiving either PMMA fusion or posterior foraminotomy (Korinth, 2006), long-term outcome was assessed after a mean of 6 years. The number of patients reporting excellent or good outcome was statistically-significantly greater in the fusion group (93.6% vs. 85.1%, $p<.05$).

Pain and Function

Information on pain was available from 6 of the 9 higher-quality RCTs comparing fusion to alternative surgical procedures (Appendix C, Tables C4 and C5). In the van den Bent RCT comparing discectomy with PMMA fusion to discectomy alone (van den Bent, 1996), the percentage of patients reporting relief of neck pain was statistically-significantly greater in the fusion group at 6 weeks (78% vs. 43% for discectomy, $p=.04$). Pain relief improved in the discectomy group thereafter, however, and differences were no longer statistically-significant for the remainder of the 24-month follow-up. In the Hauerberg RCT of discectomy with titanium cage fusion vs. discectomy alone (Hauerberg, 2008), subjective assessments of arm and neck pain on a 0-11 scale did not differ statistically between treatment groups at 3, 12, and 24 months of follow-up. Pain was also evaluated in the 3 lower-quality RCTs; differences between treatment groups were either not statistically-significant or not measured statistically. In a smaller RCT ($n=45$) comparing discectomy

with fusion, discectomy with instrumented fusion, and discectomy alone (Xie, 2007), no statistically-significant differences were observed in the percentage of patients reporting arm or neck pain at 12 months or in 3 distinct scales of the McGill Pain Questionnaire (pain rating index, number of words chosen, and present pain intensity).

The percentage of patients with any improvement in VAS neck or radicular pain was assessed at 2, 6, and 12 months in the RCT comparing 3 types of fusion to microdiscectomy alone (Barlöcher, 2002). At month 12, a statistically-significant difference in favor of fusion with titanium cage (97.3% vs. 81.9% for microdiscectomy alone, $p < .05$) was seen for radicular pain; no other measures differed statistically at any timepoint. In the previously-described RCT comparing anterior discectomy with fusion to endoscopic anterior discectomy alone (Ruetten, 2009), no statistical differences were observed between groups on VAS measures of neck or arm pain as well as on the German version of the North American Spine Society (NASS) pain score. Finally, change in VAS arm and neck pain on a 10-point scale was also assessed in a small RCT comparing 20 Turkish patients receiving anterior cervical microdiscectomy with or without fusion (Oktenoglu, 2007); patients were followed for 12 months. Statistically-significant improvement in arm pain was seen for both groups, while improvement in neck pain was only statistically-significant for the fusion group. When groups were compared, however, no statistical differences were noted for either arm or neck pain at 12 months.

While VAS-based measures of arm and neck pain were available in several surgical studies, sufficient information on data variance (i.e., standard deviations or standard errors) was not. Meta-analyses of VAS pain were therefore not possible. We did, however, conduct “sensitivity” meta-analyses in which we assumed VAS data were normally distributed and standard deviations could therefore be derived. In these analyses, we transformed VAS scores to a 10-point scale where necessary. No statistically-significant treatment effects were observed in these analyses, which are presented in Appendix C, Figures C3-C8.

Quality of Life

Data on quality of life were found in the Xie RCT comparing fusion with or without instrumentation to discectomy (Xie, 2007) (Appendix C, Table C6). Quality of life was assessed via the SF-36 instrument; in repeated-measures analyses, no statistically-significant differences were noted between groups in SF-36 total scores as well as scores for individual domains at 12 months of follow-up.

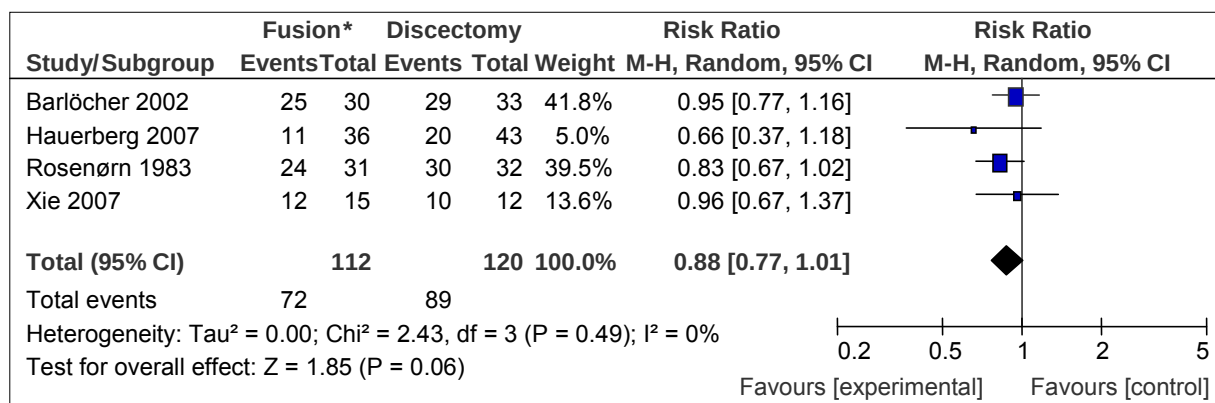
Return to Work

Data on return to work were available from 4 higher-quality RCTs (Appendix C, Table C7). The proportion of patients returning to work did not statistically differ at any timepoint between treatment groups in the previously-described Hauerberg and Xie RCTs. In a third RCT examining 63 patients undergoing anterior cervical discectomy with and without fusion who were followed for 12 months (Rosenørn, 1983), a statistically-significantly greater percentage of fusion patients had returned to work at 2, 3, 4, 6, and 9 weeks postoperatively; differences were no longer significant when measured at weeks 12, 26, and 52, however. Finally, the percentage of working individuals not yet able to return to work was assessed in the Barlöcher RCT (Barlöcher, 2002). At 6 months, a statistically-

significantly lower percentage of patients undergoing fusion with titanium cage were not yet able to work as compared to microdiscectomy alone (5.5% vs. 18.1%, $p < .05$). However, differences were nonsignificant when evaluated at 12 months.

We also assessed return to work in a random-effects meta-analysis comparing fusion to discectomy in 4 higher-quality RCTs; for the Barlöcher RCT, we used the inverse of the data on “not yet able to work”. As shown in Figure 5 below and in Appendix C, Figure C9, the pooled estimate directionally favored discectomy in terms of return to work at 12-24 months, but this difference was not statistically significant.

Figure 5. Meta-analysis of likelihood of return to work at 12-24 months, fusion vs. discectomy.



* Anterior discectomy and fusion

A second analysis of return to work was conducted to examine the possible differential impact of these procedures on short-term recovery. The Xie and Barlöcher RCTs provided data on return to work at 6 months following surgery. No statistically-significant differences between fusion and discectomy were noted (RR: 0.77; 95% CI: 0.28, 2.11; $p = .62$) (Appendix C, Figure C10).

Publication Bias

We also assessed the possibility of publication bias in analyses of return-to-work data (the number of studies was too small to generate statistics for measures of treatment success). Statistical analyses using Egger's regression suggested no significant asymmetry in findings. Results of testing can be found in Appendix C, Figure C11.

9. Potential Harms (KQ 2)

Cervical spinal fusion is associated with a number of different harms, some of which are common to both fusion and other surgical alternatives, and others of which are unique to the fusion procedure itself (e.g., pseudarthrosis). Relevant harms are presented on Table 3 on page 76, described in the sections that follow, and categorized according to their timing. Complications occurring during the “perioperative” period (i.e., during the operative episode through the 30 days following) are categorized separately from longer-term harms and adverse events tallied through the remainder of follow-up.

Note that repeat surgery, while not technically a patient harm, is also presented, as it represents the potential for additional clinical risk and inconvenience and plays an important role in patient and clinician decision-making. For the perioperative period, data were collected on procedure revisions and returns to the operating room. For longer-term follow-up, data on reoperation and/or need for subsequent treatment were tallied.

Information on other procedure-related measures, such as procedure duration, perioperative blood loss, and hospital length of stay, while not a point of focus in this section, is nevertheless available for review in Appendix C (Tables C8 and C17 for RCTs and comparative cohort studies respectively).

Data on harms are presented for cervical fusion and its relevant comparators, including non-invasive interventions. While reported complications were rare in these populations, data do exist on requirements for subsequent treatment. Among all interventions for cervical DDD, however, good evidence on the true rates of serious harms is not available from published RCTs. Individual studies are too small to capture reliable data on complications that occur infrequently, and the relatively low rate of serious complications has led to standards for research reporting that often do not include formal reports on all complications. Other contributing factors to the dearth of data on complications include the general exclusion from many RCTs of patients with significant disability or otherwise at high risk, possible publication bias that disfavors reports of unsuccessful outcomes, and the relative short-term nature of most studies, which can fail to detect adverse outcomes associated with surgical interventions that do not manifest until later years. *Because of these factors, as well as the often variable level of detail on complications available in study reports, no attempt was made to meta-analyze data on harms.*

Information from the observational studies examined in this review suggests that risks of surgical interventions may be higher than reported in RCTs. For example, in the 14 RCTs examined for this appraisal, only 1 provided any data on perioperative mortality (Xie, 2007; rates were 0% in both treatment groups). In contrast, rates of in-hospital and 30-day mortality from large database studies, while <1%, are certainly nonzero (Shamji, 2008; Wang, 2007). Other harms that may not be apparent until after hospital discharge, such as pneumonia or venous thrombosis, appear relatively rarely in observational studies but are not reported at all in available RCTs.

1. *Data from RCTs and Comparative Cohorts*

Information on harms is presented on the following page in Table 3 for RCTs and comparative cohort studies evaluating fusion and its major comparators. As mentioned previously, certain types of complications and adverse outcomes were not reported in any available RCT or comparative cohort study. For example, data on perioperative paralysis or hemorrhage were not available in any RCT or comparative cohort study, and information on thrombosis was only reported in comparative cohort studies of fusion. In addition, there was a significant degree of overlap between treatment alternatives in reported rates of complications, with no clear or discernible pattern of differential rates for most complication types.

As described previously, perioperative mortality was rarely identified or reported in any RCT or comparative cohort study. Among perioperative complications, the most frequently reported for fusion included dysphagia, hoarseness, and infection. Not surprisingly, generally higher rates of dysphagia and hoarseness were reported for fusion, given the increasing use of anterior surgical approaches to this procedure (Shamji, 2008); rates were similar to those reported for discectomy in available RCTs, however. The upper end of the range of infection rates was higher with fusion relative to other procedures, which was related to 2 cases of donor site infection in a small RCT (Xie, 2007). Leakage of cerebrospinal fluid was rarely reported for any type of procedure.

Rates of longer-term events were annualized to account for differential follow-up across studies. Mortality was again rarely reported in RCTs or comparative cohort studies, with a significant degree of overlap by intervention. In some fusion studies, relatively high rates of adjacent segment disease and pseudarthrosis were reported. High rates of neurological decline were also reported in 1 RCT comparing fusion to discectomy, but these included measures of unchanged or worsened sensory loss in 1 RCT (Persson, 2001). Rates of repeat surgery or subsequent therapy were more commonly reported across study types. Again, ranges of reported rates overlapped significantly between them. The highest rate of reoperation was reported in the Persson RCT, where 8 of 30 patients underwent a second surgery by 16 months of follow-up (Persson, 1997); 6 of these had surgery adjacent to the initial surgical site.

Table 3. Reported ranges of rates of potential harms from RCTs and comparative cohort studies, by type of study and comparator.

Type of Harm	Fusion		Conservative Rx		Surgical Approaches				No. of studies reporting harms		
% of Patients with Event											
	RCT	CC	RCT [¥]	CC [¥]		RCT		CC		RCT	CC
<i>Perioperative Events</i>					Discectomy	Foraminotomy	Laminoplasty	Foraminotomy			
Mortality	0	0-0.05	NR	NR	0	NR	0	NR		1	2
<i>Complications</i>											
○ Hemorrhage	NR	NR	NA	NA	NR	NR	NR	NR		0	0
○ Hematoma	1-6.6	0-0.8	NA	NA	0	NR	NR	0		4	2
○ Nerve Damage*	2.5-8	0.8-6	NA	NA	0-8	9-14	6	0.6		3	3
○ Paralysis	NR	NR	NA	NA	NR	NR	NR	NR		0	0
○ Infection	0-13	0-0.02	NA	NA	0	4	6	0.6		2	4
○ Hoarseness	5-20	1.6	NA	NA	0-8	NR	NR	0		3	1
○ Dysphagia	3-17.5	0-10	NA	NA	15.2-25	3.3	NR	0		4	3
○ Thrombosis	NR	0.02	NA	NA	NR	NR	NR	NR		0	1
○ CSF Leak	NR	0	NA	NA	NR	NR	NR	NR		0	1
Return to OR	NR	0	NA	NR	NR	NR	10	0.6		0	2
<i>Long term Events†</i>											
<i>Complications</i>											
○ Chronic pain	4.8	NR	NR	NR	2.6	NR	NR	NR		2	0
○ ASD	6.9-16.6	NR	NR	NR	2.4-8.3	NR	NR	NR		2	0
○ Pseudarthrosis	8	3.2	NA	NR	0	NR	NR	NR		1	1
○ Neurological Decline*	3-23.3	0	14.2	NR	27.2	NR	NR	0		2	1
○ Myelopathy	NR	NR	NR	NR	NR	NR	NR	NR		0	0
○ Muscle weakness	NR	NR	NR	NR	NR	NR	NR	NR		0	0
○ Paresthesia	14.2	3	8.2	NR	NR	NR	0	NR		1	1
Subsequent Rx	0.5-21.7	0-3.2	13.8	3.7	1.1-9.8	5.1	NR	1		10	4

NR: Not reported; NA: Not Applicable; ASD: Adjacent segment disease

¥: Conservative treatment = Physiotherapy; ¥: Conservative treatment = Interdisciplinary treatment; *: Nerve damage includes numbness, weakness and nerve palsy. **: Neurological decline includes sensory loss and neurological deficit; † Rates are annualized.

2. Data from Fusion Case Series

Long-term data on harms were reported in 46 reports of case series, describing events in nearly 6,000 patients. Follow-up ranged from 1 to 21 years in these studies. The most frequently-documented events included reoperation (n=23), pseudarthrosis (n=19), and adjacent segment disease (n=13), with ranges similar to those reported in RCTs and comparative cohorts. Mortality data were reported in 9 studies; rates ranged from 0-2.6% on an annualized basis.

In an effort to create an exhaustive list of long-term adverse events reported in patients undergoing cervical fusion, all reported harms from these studies are listed in Table 4 below.

Table 4. Reported ranges of annualized rates of potential harms from fusion case series.

<i>Type of Harm</i>	<i>Number of Studies</i>	<i>% of Patients With Event (Range)</i>
Mortality	9	0-2.6
Complications		
Adjacent segment disease	13	0-27
Arm pain	1	0.1
Donor site pain	1	8.7
Dysphagia	2	3.6-33
Dysphonia	1	2.0
Hepatitis C infection	1	0.08
Hoarseness	1	0.08
Laryngeal paresis	2	0.5-1.4
Neck pain	3	0.3-2.5
New-onset radiculopathy	2	0.8-5.0
Paresis	1	1.3
Pseudarthrosis	19	0-8.5
Ptosis	1	0.5
Tetraparesis	1	0.08
Upper limb numbness	2	0.3-2.2
Upper limb weakness	1	0.4
Worsening headache pain	1	25.5
Worsening lower extremity function	1	1.7
Worsening sensory function/strength	2	0.7-2.7
Worsening upper extremity function	1	0.4
Re-operation	23	0-6.8
Inability to return to work	2	0.5-4.3

Data on General Surgical Risks

As previously mentioned, we also sought current information on the general risks associated with any surgical procedure. These should be considered to be broad-based estimates only, and not indicative of what might be expected for cervical spinal fusion specifically.

Recent data on complication risks associated with all surgical procedures are available from a retrospective review of the records of 1,442 surgical patients at Emory University Hospital from 2009-2011 (Kassin, 2012). Complications occurring during the surgical hospitalization or the 30-day period following were identified in 455 of these patients (31.6%); hospital readmission during this period occurred in 163 patients (11.3%). Data on the frequency of complications by type can be found in Table 5 below. The most frequent complications included need for transfusion (16.6%) and wound complications (superficial or deep wound infection, wound disruption; 12.4%).

Table 5. Frequency of perioperative surgical complications in a cohort of 1,442 patients, by type of complication.

Complication Type	n	%
Transfusion	239	16.6
Wound (superficial/deep wound infection, wound disruption)	179	12.4
Bacteremia/sepsis/shock	105	7.3
Pulmonary (ventilation >48h, pneumonia, unplanned intubation)	85	5.9
Urinary tract infection	40	2.8
Renal (acute renal failure, progressive renal insufficiency)	28	1.9
Vascular (DVT, PE, graft/prosthesis failure)	25	1.7
Cardiac (MI, cardiac arrest)	13	0.9
Neurologic (Stroke, Coma >24h, peripheral nerve injury)	12	0.8

DVT: Deep vein thrombosis; PE: Pulmonary embolism; MI: Myocardial infarction

Source: Kassin et. al, J Am Coll Surg 2012;215:322-30

Because one of the intentions of the study described above was to examine readmission rates, patients who died during the index hospitalization were excluded from analysis. Perioperative mortality nevertheless remains a significant concern with surgery. Findings from a recent study examining in-hospital mortality among nearly 47,000 adults undergoing non-cardiac surgery at 498 hospitals in 28 European countries during a 1-week period in 2011 indicated a 4% mortality rate (Pearse, 2012). While the rate ranged widely by country (i.e., from 1.2% in Iceland to 21.5% in Latvia), mortality in nations with developed health systems such as France, Germany, and the UK was higher than anticipated, ranging from 2.5-3.6%.

10. Differential Effectiveness & Safety of Cervical Fusion in Key Patient Subgroups (KQ 3)

Data examining the differential effects of cervical fusion in key patient subpopulations were obtained from RCTs, comparative cohort studies and case series where available. Findings are reported below by type of study and subgroup; detailed information is also available in Appendix C, Tables C19, C20, and C23.

1. *Randomized Controlled Trials*

A total of 3 higher-quality RCTs included data on specific patient subgroups, as described below (see Appendix C, Table C19).

Single- vs. 2-level Surgery

In an RCT comparing anterior cervical discectomy with fusion to discectomy alone in 51 patients (Martins, 1976), the percentage of patients with excellent or good results (complete relief or minimal persistence of preoperative symptoms and abnormal signs improved or unchanged) was compared by level of surgery. Among patients undergoing single-level procedures, the percentage of those with excellent or good results was higher in the fusion group (82% vs. 66% for discectomy), while the rate for 2-level surgery was lower for fusion (26% vs. 63%). Rates were not tested statistically.

Smoking Status

In the RCT comparing fusion to physical therapy and cervical collar immobilization (Persson, 2001), the improvement in VAS pain among those undergoing surgery was found to be better among nonsmokers vs. smokers ($p < .05$), although the actual data on VAS changes among these subgroups are not provided.

Gender

In an RCT comparing anterior discectomy with and without fusion in 63 patients (40 men and 23 women) (Rosenørn, 1983), a higher percentage of males ($n=16$) undergoing fusion had excellent or good results (defined as return to previous occupation with no or minimal symptoms) at 12 months (15 [94%] vs. 19 [86%] for discectomy), while a lower percentage of females ($n=13$) had excellent or good results (5 [38%] vs. 8 [89%] for discectomy). While

statistical testing was not performed for the stratified analysis across treatment groups, the percentage of patients with treatment success in the fusion group was greater ($p < .005$) among males vs. females.

2. *Comparative Cohort Studies*

Data were available from 4 comparative cohort studies; while all studies are presented in detail in Appendix C, Table C20), the focus of attention in the descriptions below is on the 2 studies that were fair-quality. In these studies, the subgroups of interest defined the study comparators (i.e., inpatient vs. outpatient fusion, posterior vs. anterior fusion).

Inpatient vs. Outpatient Fusion

The effects of fusion performed in inpatient vs. ambulatory care settings were assessed in a single fair-quality comparative cohort study. In this study, a comparison of 50 consecutive day-surgery patients to 53 retrospectively-analyzed inpatient controls (Silvers, 1996), no statistically-significant differences by setting were noted for functional outcomes, VAS pain, performance of activities of daily living, or return to work or normal activities. The rate of reoperation was numerically higher in the inpatient group (9.4% vs. 4.0% for outpatient), but this difference was not statistically tested.

Anterior vs. Posterior Fusion

Comparisons of anterior vs. posterior fusion techniques were performed in 1 fair-quality retrospective cohort study. This study examined differences between anterior and posterior fusion techniques using the U.S. Nationwide Inpatient Sample (NIS) database (AHRQ, 2012), and assessed hospital outcomes among nearly 100,000 patients undergoing anterior or posterior fusion for cervical DDD between 1988 and 2003 (Shamji, 2008). Patients were further stratified by whether their record included a diagnosis of myelopathy (approximately 75% of patients did *not* have such a diagnosis). On an unadjusted basis, patients undergoing posterior fusion experienced higher rates of death and major complications ($p \leq .001$), regardless of the presence of myelopathy on the record. Length of stay and inflation-adjusted cost was also significantly increased, as shown in Table 6 below (data on myelopathy patients are displayed for context). After adjustment for differences in patient characteristics between groups, patients undergoing posterior fusion had significantly higher rates of all complications except for thrombophlebitis when compared to anterior fusion.

Table 6. Outcomes of anterior vs. posterior fusion surgery, stratified by neurological status (n=96,773).

<i>Outcome</i>	<i>Anterior</i>		<i>Posterior</i>		<i>p-value</i>
	No Myelo	Myelo	No Myelo	Myelo	
<i>Death (%)</i>	0.05	0.52	0.36	0.67	<.001
<i>Pulmonary embolism (%)</i>	0.02	0.06	0.14	0.12	<.001
<i>Pneumonia (%)</i>	0.14	0.62	1.04	1.10	<.001
<i>Transfusion (%)</i>	0.34	1.02	3.33	5.64	<.001
<i>Thrombophlebitis (%)</i>	0.02	0.07	0.04	0.16	.001
<i>Infection %</i>	0.02	0.10	0.36	0.55	<.001
<i>Length of stay (mean days)</i>	1.95	3.42	4.37	5.76	<.001
<i>Inflation-adjusted cost (\$)</i>	20,639	28,581	34,963	40,313	<.001

Source: Shamji et al., J Neurosurg: Spine, 2008;9:10-16

Myelo: Myelopathy diagnosis on inpatient record

While the results of this study suggest higher rates of complications with posterior fusion, it is often the case that contemporary posterior techniques are reserved for patients with greater disability and/or spinal instability who require multi-level intervention (Caridi, 2011). Information from administrative databases is understandably limited in controlling for differences in clinical presentation.

While not considered a “comparative cohort” study per se, an earlier study analyzing data from the NIS also showed higher rates of complications and mortality for posterior vs. anterior fusion (Wang, 2007); in multiple logistic regression analyses, posterior fusion was significantly associated with a higher risk of in-hospital complications (but not mortality).

3. *Fusion Case Series*

A total of 28 fusion case series stratified data according to key patient subgroups of interest; findings are presented in Appendix C, Table C23 and described in further detail below.

Single- vs. Multi-Level Surgery

Subgroup analyses of patients undergoing single- and multi-level fusion procedures were analyzed in 17 case series. In most of these studies, increases in the number of levels involved were associated with increased rates of pseudarthrosis, although the statistical significance of any observed differences was often not tested. Reoperation rates and development of adjacent segment disease were assessed in 3 studies (Matsumoto, 2009; Heidecke, 2000; Bishop, 1996); no statistically-significant differences in these rates according to number of levels involved were observed. In one series, rates of dysphagia were reported for patients undergoing 1-, 2-, and 3+ level anterior fusion; these rates increased according to the number of levels involved (11% vs. 24% vs. 43%, significance not tested)

(Riley, 2005). Findings from a later systematic review by the same author were similar in nature (Riley, 2010).

Smoking Status

Six case series examined the impact of pre-operative smoking status on adverse events and clinical outcomes. While 1 study described statistically-significantly fewer cases of pseudarthrosis among non-smokers (20% vs. 50% for smokers, $p=.001$) (Goldberg, 2002), 2 found no correlation between smoking status and development of pseudarthrosis or adjacent segment disease (Matsumoto, 2009; Bindal, 2007). In terms of clinical outcomes, 3 series evaluated the effect of smoking status on treatment success using Odom's criteria. In one, data from a series of 144 patients indicated that smokers had a significantly ($p=.008$) higher rate of fair or poor outcomes (Jensen, 2009), although actual percentages were not reported. Another study ($n=190$) found non-smokers to have a significantly higher rate of excellent outcomes (43.0% vs. 27.3%, $p<.03$) (Hilibrand, 2001). A third smaller series ($n=66$) found no statistically-significant differences in this measure (Samartzis, 2005).

Gender

Clinical outcomes and adverse events did not statistically differ according to patient gender in 4 case series (Chen, 2009; Matsumoto, 2009; Bindal, 2007; Javid, 2001). Data from an additional series did find statistically-significantly greater rates of dysphagia (41.2% vs. 22.9% for women vs. men, $p<.05$) and dysphonia (28.2% vs. 8.6%, $p<.05$) among women (Yue, 2005b).

Anterior vs. Posterior Fusion

Fusion approach was evaluated in a single case series of 120 patients undergoing revision procedures for pseudarthrosis (Carreon, 2006). Over 3-4 years of follow-up, the rate of subsequent reoperation was lower among patients undergoing posterior revision (2.2% vs. 44.4%), although this difference was not tested statistically.

Duration of Symptoms

Four case series analyzed the impact of symptom duration on clinical prognosis and long-term outcomes. While 1 study found no correlation (Chen, 2009), 3 case series demonstrated significantly better outcomes in patients with shorter duration of symptoms (Kadoya, 2003; Hamburger, 2001; Heidecke, 2000). In one study, patients with a symptom duration of less than 3 months had a statistically-significantly higher rate of excellent outcomes based on Odom's criteria as compared to those with symptoms > 12 months (48.9% vs. 33.3%, $p<.03$) (Hamburger, 2001). In a study of anterior microdiscectomy with fusion, no significant difference in the percentage of patients with a self-reported "good" outcome was seen in patients with radiculopathy symptoms; however, patients with myeloradiculopathy symptoms for < 1 year had a significantly higher rate of good outcome (78.9% vs. 50.0%, $p<.01$) (Heidecke, 2000). Finally, a significant ($p=.01$) correlation was observed between outcome scores derived from the Neurological Cervical Spine Scale and duration of symptoms. Those with symptom duration of 6 months or less had the highest mean score (3.3); scores declined with increasing symptom duration, culminating with score of 1.2 among patients with symptom duration > 4 years (Kadoya, 2003).

Age

Seven case series provided data on patient subgroups based on age. While 3 studies described no correlation between age and clinical outcomes such as the Neck Disability Index and the Hirabayashi recovery rate (Chen, 2009; Matsumoto, 2009; Bindal, 2007), 3 other case series demonstrated statistically-significant differences based on patient age in rates of adverse events and neurologic outcomes (Cabraja, 2011; Kadoya, 2003; Heidecke, 2000). For example, the rate of neurologic improvement significantly declined with increasing age, from 71.0% among those age < 40 years to 11.1% among patients age 70 years or older ($p=.014$) (Kadoya, 2003). An additional case series found a greater incidence of dysphagia in younger (mean age 48 years) vs. older (mean age 55 years) patients (Yue, 2005b); differences were not tested statistically, however.

Workers' Compensation

Goldberg et al. evaluated outcomes in 80 patients with and without worker's compensation (Goldberg, 2002). Patients underwent anterior discectomy and fusion with a mean follow-up of 4 years. There were no statistically-significant differences in outcome based on Odom's criteria; incidence of donor site pain and the development of pseudarthrosis also did not differ. Seventy percent of patients with workers' compensation returned to work without restriction vs. 80% of patients without workers' compensation, although this difference was not tested.

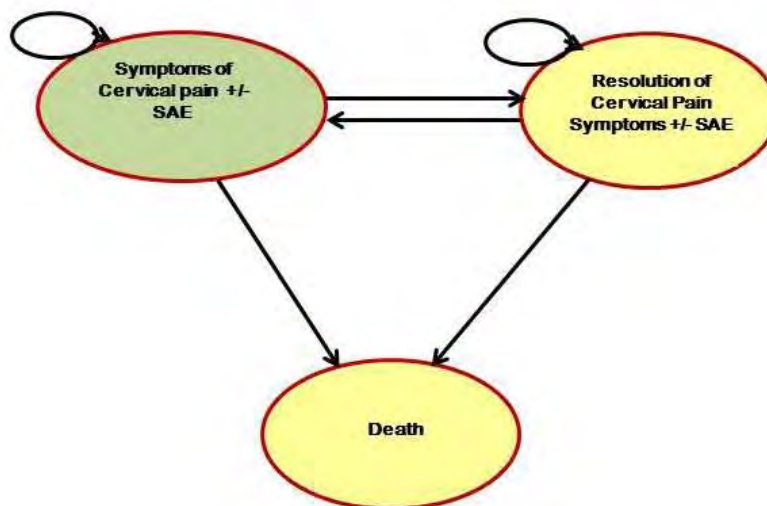
In a case series involving 66 patients undergoing ACDF, a subgroup analysis of work- and non-work-related injuries demonstrated no significant differences in outcome based on Odom's criteria at 22 months of follow-up (Samartzis, 2005).

11. Decision Analytic Model (KQ 4)**8.1 Objectives**

The primary objective of this decision analytic model was to assess the relative cost and cost-effectiveness of treatment pathways involving spinal fusion versus alternative treatments for the management of cervical degenerative disc disease.

8.2 Methods**Analytic Approach**

The decision model designed for this evaluation was a Markov state transition model, as shown in Figure 6 below. The clinical status of patients is represented by one of the three mutually exclusive states in the model. The model states were chosen to be reflective of available clinical data and key clinical states that patients may experience in terms of treatment success (with or without complications or other adverse events). The model was designed to shift patients between the different model states at three-month intervals over a 1-3 year time horizon.

Figure 6. Markov Disease State Diagram for Cervical Degenerative Disc Disease

SAE = Serious adverse event.

Perspective

We adopted a public payer perspective for the reference case (i.e., primary analysis), thus following the majority of recommendations for health care economic evaluation (Drummond, 2005). However, an analysis taking an employer perspective was also considered as a sensitivity analysis that incorporated consideration of work productivity gains or losses from treatment.

Type of Economic Evaluation

A cost-utility analysis was conducted that reported results as an incremental cost per quality adjusted life-year (QALY) gained. This form of analysis enables comparison of cost-effectiveness estimates for spinal fusion with other treatments funded by payers. It also facilitates the identification of subpopulations where use of spinal fusion appears to be more (or less) cost-effective. In the interest of transparency, however, major model outcomes are also presented in disaggregated form (e.g., outcomes, costs). In addition, the cost per additional “treatment responder” (i.e., percentage of patients with resolution of symptoms) was calculated to provide additional context to disaggregated findings.

Target Patient Population

The target population of the decision model was the same as the population assessed in the corresponding systematic review, namely adults with cervical DDD who continue to have severe cervical pain after an initial course of conservative therapy of 6 to 12 weeks. It was further assumed that patients’ neck pain was not a consequence of systemic disease or other excluded medical diagnosis/condition (e.g., trauma, malignancy). Consistent with the findings of the systematic review, the model focused attention on patients with radiculopathic symptoms in addition to axial neck pain. The analysis therefore did not include patients having only generalized neck pain, as there was no evidence to support use of surgery in this patient population.

Intervention and Comparators

Anterior cervical discectomy and fusion (ACDF) was chosen as the primary approach of spinal fusion for the analysis. The reference case analysis compared spinal fusion with conservative management with physical therapy. Transition probabilities for spinal fusion were derived using data from an RCT which compared fusion with cervical arthroplasty (Sasso, 2011). The Sasso et al. study provided transition probabilities at three, six, twelve, twenty-four, and forty-eight months after fusion – equivalent data were not available in the Persson et al. study. Clinical effects for physical therapy versus fusion were, however, estimated from Persson, 2001, where it was assumed that fusion would initially have more pronounced effects versus conservative management but these effects would diminish over time (40% better at 6 months; 20% better at 12 months, 10% better at 24 months; equal at 48 months). Comparisons of spinal fusion with other potential treatment alternatives of interest are also reported:

- Manual therapy with spinal manipulation
- Epidural steroid injections
- Posterior laminoforaminotomy
- Anterior discectomy without fusion

Outcome Measures

This evaluation assessed key clinical outcomes related to the diagnosis of cervical DDD including the proportion of patients who resolved cervical pain symptoms, the proportion of patients who had cervical pain symptoms, and the occurrence of rare but important adverse events such as perioperative complications (e.g., nerve damage, cerebrospinal fluid leak, new-onset radiating pain, and stroke or other thrombotic events), longer-term complications such as adjacent segment disease, and death. Costs related to treatments, total costs to the payer, and the impact of different treatment pathways on quality of life (as reflected by QALYs) were also calculated.

The model was also designed to allow “break-even” analyses of cost and effect size parameters to be conducted to investigate the values that would potentially make cervical fusion cost-neutral or cost-effective across different thresholds relative to nonsurgical management.

Time Horizon

For the reference case analysis, multiple time horizons ranging from 1 to 3 years were considered (a) to match the typical duration of follow-up in relevant clinical trials; and (b) to capture the heterogeneity of treatment effect over time.

Decision Modeling & Assumptions

The decision model designed for this evaluation is shown in Figure 6 on page 83. The use of decision modelling to assess the comparative value of healthcare interventions is widespread (Briggs, 1998; Beck, 1993). Models facilitate the synthesis of data from various sources and permit the evaluation of both costs and outcomes simultaneously (Briggs, 1998; Beck, 1993). Typically, models divide the disease in question into distinct states and

transition probabilities are assigned for movement between these states over a discrete time period. As noted above, the decision analysis was based on a cohort level Markov model consisting of three states. The clinical outcomes of interest, the costs over the 1- to 3-year time horizons, and the impacts of the different treatments on QALYs were incorporated into the design of the model to compare different treatment pathways for cervical DDD. The probability of transitioning between states in the model was affected by treatment. A cycle length of 3 months was selected to allow modeling of changes in the therapeutic approach to management of patients in the model and to best align model design with outcomes reported in the most relevant clinical literature. To enhance transparency and use a more parsimonious model, the impact of adverse events for each treatment within a pathway were applied by incorporating cost and QALY decrements to relevant health states rather than developing a separate health state for adverse events.

The clinical outcomes that were used in the model to evaluate each treatment pathway included the proportion of patients who resolve cervical pain symptoms, the proportion of patients who continue to have cervical pain symptoms, and the number of deaths observed. Baseline transition probabilities for clinical outcomes were based on the Sasso trial. Resolution of cervical pain symptoms was based on the definition applied in Sasso et al.; patients had to achieve all of the following: an improvement of 15 points in the NDI, neurological improvement, no serious (WHO grade-3 or 4) adverse events related to the implant or surgical implantation procedure, and no subsequent surgery or intervention that would be classified as a treatment failure.

Listed in Table 7 below are assumptions made in designing the model for this evaluation. Our model was based to some degree on past decision models associated with the management of cervical DDD (Carreon, 2012; Van der Velde, 2008) as well as on clinical studies comparing spinal fusion with conservative treatment or cervical arthroplasty (Persson, 2001; Sasso, 2011).

Table 7. Key Model Assumptions

Prior to entering the model patients have had an initial trial of conservative management lasting between 6-12 weeks which did not resolve symptoms.

The gap in clinical benefit between spinal fusion and conservative treatment narrows over time as patients with conservative treatment reach similar pain and function levels, consistent with observations from clinical studies.

All forms of conservative management (e.g., physical therapy, spinal manipulation) have approximately equal clinical effectiveness.

Patients who do not resolve symptoms of cervical pain will have a reduction in health related quality of life and will incur costs equivalent to approximately \$1,983 per cycle (~ equal to cost of ongoing physical therapy).

Clinical Efficacy, Effectiveness and Safety

The probabilities associated with the different clinical outcomes included in the decision model are described in Table 8 on the following page. For the comparison treatment pathways evaluated, the probabilities of transitioning between states in the model were based on the Sasso and Persson studies. Importantly, because data were limited comparing conservative treatment with fusion, we assumed that fusion was more effective than conservative therapy, although the relative benefits diminished over time, consistent with observations from clinical studies (Persson, 2001). We assumed that fusion was 40% better at 6 months (i.e., relative risk=0.60), 20% better at 12 months, 10% better at 24 months and equal at 48 months (see Table 8). We conservatively assumed that fusion was not associated with an increased risk of mortality in the reference case. However, a sensitivity analysis was conducted where we assumed a 30% risk reduction (RR=0.70) for conservative therapy (Kadaňka, 2011).

Table 8. Transition Probabilities Over 36 Months, by Type of Treatment

Month	Fusion			Conservative Treatment		
	Symptoms of Cervical Pain	Resolution of Cervical Pain Symptoms	Death	Symptoms of Cervical Pain	Resolution of Cervical Pain Symptoms	Death
6	28.5%	71.4%	0.1%	57.0%	42.8%	0.1%
12	25.8%	74.0%	0.2%	40.6%	59.2%	0.2%
24	26.3%	73.2%	0.5%	33.7%	65.9%	0.5%
36	26.5%	72.9%	0.7%	30.1%	69.2%	0.7%

Risk multipliers for sub-group analysis were applied to the natural history data. Table 9 below provides a summary of the important relative risk measures used to evaluate each treatment comparison and an overview of the relevant probabilities included in the economic model for both deterministic and probabilistic analyses.

Table 9. Clinical Parameters and Probabilities for the Decision Model

Parameters	Base Estimate	Probability Distribution	Reference
EVENT RATE ADJUSTMENTS			
<i>Risk of neck pain resolution or improvement vs. spinal fusion</i>			
Physical therapy	See Table 1	Fixed	Sasso, 2011 ; Persson, 2001
Manual therapy/Spinal manipulation	See Table 1	Fixed	Sasso, 2011 ; Persson, 2001
Epidural spinal injections	0.39	Lognormal (-0.94, 0.42)	Clinical expert input
Laminoforaminotomy	0.98	Lognormal (0.02, 0.095)	Systematic Review
Anterior discectomy without fusion	0.98	Lognormal (0.02, 0.095)	Systematic Review

Beta distributions parameterized by alpha and beta, lognormal distributions parameterized by log means and log standard errors

The adverse events considered in the model are reported in Table 10 on the following page. As mentioned previously, to enhance transparency and use a more parsimonious model, the impact of adverse events for each treatment within a pathway were applied by incorporating cost and QALY effects (versus developing a separate state). To enhance transparency, these are applied via a separate analysis to ensure that such inclusion does not alter findings. We applied a “disutility” (i.e., an estimate of the decrement in quality of

life) for radiating pain of 0.02264 to 80% of patients and applied the costs and utility decrements associated with a very small risk of stroke to the conservative management treatment options. We also applied an incremental cost of \$29,721, associated with adjacent segment disease and \$1070 for perioperative complications for spinal fusion to 4.1% and 2% of patients, respectively (Sasso, 2011), as well as a disutility estimate of 0.20 (due to the need for subsequent surgery in these patients).

Table 10. Adverse Events Incorporated in the Decision Model

Treatment	Adverse Event	Probability of Adverse Event	Reference
Physical Therapy	radiating pain	80%	Gouveia, 2009
	stroke	0.01%	Multiple
ACDF	adjacent segment disease	4.1%	Sasso, 2011
	perioperative complications	2%	Sasso, 2011; FDA report

Valuing Outcomes

Utility values for the model were derived from Richardson, 2012 (see Table 11 below) using their methods for predicting SF-36 scored based on Neck Disability Index (NDI) scores with the standard gamble method. Patients with cervical neck pain were assigned a mean utility score of 0.542 (based on an NDI score of 50.2 [Sasso, 2011]). A utility gain of 0.185 (equivalent to gaining 67.5 days of perfect health) was applied for resolution of symptoms of cervical neck pain. Because this utility gain exceeds values for resolving severe complications such as a myocardial infarction or stroke (Sullivan, 2006), we also conducted a sensitivity analysis using a smaller utility gain of 0.0737 (based on ICD-9 722 [Sullivan, 2006]). There are limitations to this estimate since the ICD-9 code does not consist entirely of surgical candidates with a diagnosis of cervical radiculopathy.

Table 11. Utility Values Incorporated in the Decision Model

Variable Description	Base Estimate	Probability Distribution	Source
Utility value for patients experiencing cervical pain	0.5428	Beta (18.55,15.63)	Richardson, 2012; Sasso, 2011
Utility value for resolution of cervical pain symptoms	0.7279	Beta (19.7, 7.37)	Richardson, 2012; Sasso, 2011
Utility for death	0	Fixed	

Costs and Resource Use

The cost and resource use variables used in the decision model are provided in Table 12 below. Costs of direct medical services were estimated using the 2012 Medicare fee schedule and data from the Washington State Health Care Authority.

Table 12. Cost Information for Treatments Considered			
Treatment	Cost	# of Units per Cycle	Source
ACDF	\$29,722	1	Washington HCA
Laminoforaminotomy	\$29,556	1	Washington HCA
Discectomy	\$22,284	1	Washington HCA
Physical therapy			
Evaluation	\$76	1	Washington HCA
Therapy	\$53	36	Washington HCA
Manual therapy			
Evaluation	\$72	1	CMS Medicare, 2012B
Spinal X-ray	\$98	1	CMS Medicare, 2012B
Therapy	\$27	12	Washington HCA
Epidural Steroid Injections	\$433	2	Washington HCA

Each cycle has a duration of three months.

To account for lost productivity, we assumed that patients receiving spinal fusion would return to work after 61 days, and a mean wage of \$23.73 per hour was applied (Bureau of Labor Statistics, 2012; Heller 2009). We conservatively assumed that patients receiving conservative therapy miss approximately 10 more days of work at the same hourly rate.

Discount Rate

Future costs (i.e., beyond 1 year) and QALYs were discounted at an annual rate of 3% in the reference case analysis. Discount rates of 1% and 5% were explored in sensitivity analyses.

Sensitivity & Variability Analyses

Deterministic Sensitivity & Variability Analyses

Several univariate sensitivity and variability analyses were also conducted to explore the impact of varying parameter values and assumptions within the model. These included the following factors of interest: severity of cervical pain (mild, moderate, and severe); treatment effect (assume fusion is consistently 10% better; 50% better); perspective (payer, employer); time horizon (1 years, 2 years); and discount rates (1% and 5%).

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses were performed using Monte Carlo simulation and adopted standard methods for defining uncertainty around parameters. Where possible, transition probabilities were characterized by beta distributions, relative risks by log normal distributions, utilities by beta distributions, and utility decrements by normal distributions. The costs of the different treatment strategies and cost-consequences associated with clinical outcomes were assumed to be fixed unless otherwise stated. Costs and effectiveness for each treatment pathway, as derived from 1,000 Monte Carlo iterations, were plotted as cost-effectiveness acceptability curves to convey the uncertainty in the results.

Subsequent Treatments

To enhance transparency, the reference case assumes that patients in the symptoms of cervical pain health state in years 2+ all receive the same treatment at the same cost and benefits. However, because this may not be reflective of clinical practice, additional analyses were performed in which additional costs were applied assuming that that 10% of patients who initially received conservative treatment and remain symptomatic after years 2 and beyond are treated with ACDF. In patients who initially received ACDF, we assumed that 4.5% over 48 months (or 1.15% per year) had a subsequent surgery (Sasso, 2011). We also conducted another sensitivity analysis in which we assumed that 100% of patients who were initially managed using conservative treatment and did not have resolution of symptoms would receive ACDF. A cost of \$29,722 was applied for ACDF for sensitivity analyses.

Analyses

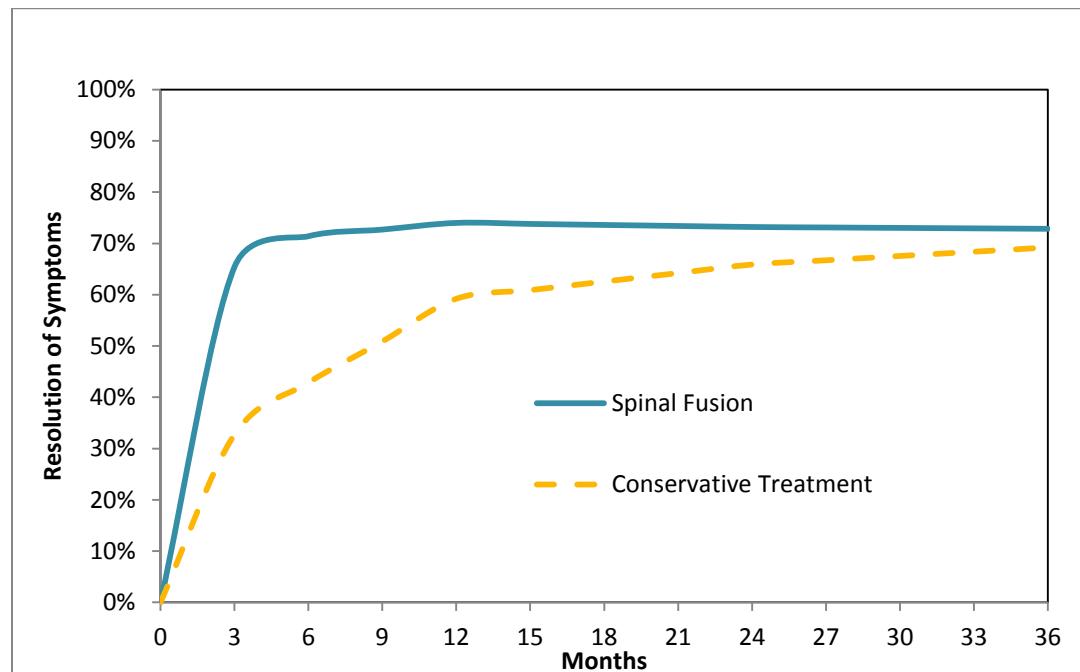
All analyses were conducted using Microsoft Excel 2010 (Microsoft Corporation, Seattle, Washington).

8.3 Results**Spinal Fusion vs. Conservative Treatment**

Table 13 below provides the results for adult patients with severe cervical pain who have failed an initial conservative therapy course of 6-12 weeks' duration. A greater percentage of patients using spinal fusion improved their cervical pain symptoms in the short-intermediate term than patients treated with conservative therapy, although the benefits diminished over time; the absolute difference in the percentage of patients with complete resolution of symptoms was >15% after 1 year, but only 3.6% after 3 years. The results from Table 13 are also presented graphically in Figure 7 on the following page.

Table 13. Clinical Results from Reference Case Analyses

Time Horizon	Symptoms of Cervical Pain	Resolution of Symptoms of Cervical Pain	Death
Spinal Fusion			
1 year	25.8%	74.0%	0.2%
2 year	26.3%	73.2%	0.5%
3 year	26.5%	72.9%	0.7%
Conservative Treatment			
1 year	40.6%	59.2%	0.2%
2 year	33.7%	65.9%	0.5%
3 year	30.1%	69.2%	0.7%
Absolute Difference			
1 year	-14.8%	14.8%	0.0%
2 year	-7.3%	7.3%	0.0%
3 year	-3.6%	3.6%	0.0%
Number Needed to Treat to Obtain 1 Additional Patient with Resolved Symptoms			
1 year	7	7	NA
2 year	14	14	NA
3 year	27	27	NA

Figure 7: Resolution of Cervical Pain Symptoms of Spinal Fusion versus Conservative Treatment in Reference Case Analysis

Following the pattern of clinical benefit, the incremental cost to achieve 1 additional treatment response (i.e., a patient with resolution of cervical pain symptoms) increased from \$174,515 in year 1 to \$677,917 in year 3 (see Table 14 below).

Table 14. Results of Reference Case Cost-Effectiveness Analysis

	Spinal Fusion		Conservative Therapy		Difference		Cost per Additional Responder
	Cost	% With Resolution of Symptoms	Cost	% With Resolution of Symptoms	Cost	% With Resolution of Symptoms	
1 year	\$31,981	74.0%	\$6,153	59.2%	\$25,828	14.8%	\$174,515
2 year	\$33,957	73.2%	\$8,895	65.9%	\$25,062	7.3%	\$342,380
3 year	\$35,897	72.9%	\$11,204	69.2%	\$24,693	3.6%	\$677,917

From a cost-utility perspective, spinal fusion produced more QALYs than conservative therapy, albeit at an increased cost (Table 15 below). The incremental cost per QALY gained for spinal fusion versus conservative therapy ranged from \$347,473 to \$579,428 depending on the time horizon considered.

Table 15. Results of Reference Case Cost-Utility Analysis

	Spinal Fusion		Conservative Therapy		Difference		Cost per QALY, Spinal Fusion versus Conservative Treatment
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
1 year	\$31,981	0.6609	\$6,153	0.6163	\$25,828	0.0446	\$579,428
2 year	\$33,957	1.3060	\$8,895	1.2435	\$25,062	0.0625	\$401,306
3 year	\$35,897	1.9303	\$11,204	1.8592	\$24,693	0.0711	\$347,473

The expected values of costs, effects and ICERs for probabilistic sensitivity analysis did not vary significantly from the reference case analysis. The cost-effectiveness acceptability curve for spinal fusion versus conservative therapy for the 3 year time horizon indicated that there is a 0% chance that spinal fusion is the more cost-effective treatment strategy at a willingness-to-pay threshold of \$100,000 per QALY, and a 1% chance at a willingness-to-pay threshold of \$150,000 per QALY.

Results of Sensitivity & Variability Analyses (3-Year Time Horizon)

Table 16 below provides the results of deterministic sensitivity analyses for the 3-year time horizon. The incremental cost-effectiveness of spinal fusion versus conservative therapy varied across sensitivity and variability analyses, ranging from \$101,796 when we assumed a 50% benefit of cervical fusion is maintained over time, to \$1.9 million when more conservative benefits were assumed.

Included in Table 16 below are the results when the employer perspective is taken and estimated productivity losses/gains are included for the 3-year time horizon. The incremental cost-effectiveness of spinal fusion versus conservative therapy was \$322,429 when this perspective was taken, indicating that considering productivity has relatively small impact on estimates of the incremental cost-effectiveness of surgery vs. conservative management.

Table 16. Results of Sensitivity & Variability Analyses (3-Year Time Horizon)

Scenario	Incremental Cost for Spinal Fusion	Incremental QALYs for Spinal Fusion	Incremental Cost per QALY Gained (ICER), Spinal Fusion versus Conservative Treatment
Reference Case	\$24,693	0.0711	\$347,473
a.) Treatment effects			
Assume 10% benefit of fusion is maintained over time horizon	\$26,095	0.0384	\$680,376
Assume 25% benefit of fusion is maintained over time horizon	\$23,630	0.0959	\$246,441
Assume 50% benefit of fusion is maintained over time horizon	\$19,521	0.1918	\$101,796
b.) Severity of cervical pain (Reference case, NDI score=50.2)			
Moderate (NDI score = 40; utility gain of 0.12)	\$24,693	0.0459	\$537,914
Mild (NDI score = 25; utility gain of 0.033)	\$24,693	0.0128	\$1,929,072
c.) Discount rate (Reference case, 3% for both costs and QALYs)			
0%	\$24,597	0.0733	\$335,482
5%	\$24,754	0.0697	\$355,369
d.) Perspective			
Employer perspective with productivity included	\$22,913	0.0711	\$322,429
e.) Inclusion of severe adverse events			
Inclusion of side effects in conservative & spinal fusion	\$25,932	0.0857	\$302,468

Table 16. Results of Sensitivity & Variability Analyses (3-Year Time Horizon)

Scenario	Incremental Cost for Spinal Fusion	Incremental QALYs for Spinal Fusion	Incremental Cost per QALY Gained (ICER), Spinal Fusion versus Conservative Treatment
Reference Case	\$24,693	0.0711	\$347,473
f.) Subsequent treatments			
Assume 10% of patients receiving conservative therapy who have symptoms after treatment receive ACDF and 3.4% of patients receiving surgery have re-peat surgery	\$23,027	0.0711	\$324,030
Assume 100% of patients receiving conservative therapy who have symptoms after treatment receive ACDF; and 3.4% of patients receiving surgery have re-peat surgery	\$14,972	0.0711	\$210,675
g.) Utilities from Sullivan et al., 2006			
Utility gain of 0.0737 for resolving cervical pain symptoms (baseline utility of 0.778)	\$24,693	0.0283	\$872,925

Spinal Fusion vs. Other Treatments

Table 17 below provides a summary of comparisons of spinal fusion with the other treatment pathways of interest. Spinal fusion was slightly more effective and slightly less expensive than laminoforaminotomy (based on Washington HCA reimbursement amounts), but was more expensive than discectomy, leading to an incremental cost-effectiveness ratio of \$603,558. Fusion was most cost-effective when compared to initial therapy with epidural steroid injections, as we assumed that such injections would only be one-third as effective as fusion at a constant rate over time.

Table 17. Comparisons of Spinal Fusion to Other Treatments					
Comparator	Incremental Cost for Fusion	Incremental QALYs for Fusion	Incremental Response (% Improvement) for Fusion versus Comparator	Incremental Cost per QALY Gained (ICER)	Incremental Cost per Responder for Fusion
Manual therapy with spinal manipulation	\$28,465	0.0711	3.6%	\$400,544	\$781,460
Laminoforaminotomy (relative risk (RR) of cervical pain resolution, 0.98 vs. spinal fusion, mean cost, \$29,556)	-\$328	0.0115	2.2%	Less expensive and more effective	Less expensive and more effective
Discectomy (RR of cervical pain resolution, 0.98 vs. spinal fusion, mean cost, \$22,284)	\$6,945	0.0115	2.2%	\$603,558	\$317,757
Epidural steroid Injection (RR of cervical pain resolution, 0.39 vs. spinal fusion, mean cost, \$443 and 2 per cycle)	\$18,831	0.2340	44.4%	\$80,488	\$42,375

8.4 Discussion

Summary of Main Findings from the Decision Analytic Model

To the best of our knowledge, this is the first economic analysis that has compared the use of spinal fusion with alternative treatments in the management of patients with cervical degenerative disc disease. We found that spinal fusion is more effective than conservative therapy initially but the difference in clinical benefits diminishes over time as the proportion of patients treated conservatively whose symptoms resolve “catches up” to that of patients treated surgically. The use of spinal fusion was associated with an increased cost relative to conservative therapies. Results showed that the incremental cost per QALY gained for spinal fusion ranged from \$347,473 to \$579,428 in the reference case analysis over a 1-3 year time horizon.

The cost of ACDF is approximately \$30,000 per surgery. This exceeds the cost of managing patients with conservative treatments such as physical therapy, manual therapy, and steroid injections where costs are typically less than \$2,000 per year, although patients may incur costs for the aforementioned treatments continuously over time unless they proceed to a state where they resolve their symptoms. The cost-effectiveness of spinal fusion therefore depends on the relative efficacy of spinal fusion in comparison to other treatments.

Our analysis also suggests that the cost-effectiveness of fusion is lower when surgery is performed on patients who have milder symptoms from cervical degenerative disc disease. Patients with more severe cervical DDD will start with lower quality of life, and if treatment is successful, they will achieve relatively large QALY gains. However, when patients have a milder form of disease, they will have a quality of life closer to that of the general population, and therefore will have lower potential to achieve substantial improvements in quality of life, which will increase the cost-effectiveness ratio of fusion relative to alternative treatments.

Our results also suggest that the cost-effectiveness of ACDF will vary depending on the comparator. There were sharp differences in cost-effectiveness estimates depending on the comparator treatment. The cost differential between spinal fusion and laminoforaminotomy or discectomy is much smaller than the cost differential between spinal fusion and physical therapy or manual therapy. As a result, the cost-effectiveness estimates will vary considerably depending on the treatment comparator chosen.

Strengths and Limitations

There are a number of strengths of this study. First, this is the first independent economic analysis to assess the value of spinal fusion in patients with cervical DDD. Second, clinical inputs were derived from a systematic review of available clinical evidence. Third, our analysis followed a transparent and accepted methodology and adheres to the guidelines for the economic evaluation of health technologies. Fourth, wherever possible, the model used cost data for 2012 reflective of the Washington State Health Care Authority experience. Finally, detailed sensitivity and variability analyses were performed to examine the robustness of results to variation in model parameters and assumptions.

Despite its strengths, this analysis has certain limitations that warrant discussion. First, there were considerable gaps in available clinical evidence. As a result, findings from the economic evaluation should be interpreted with caution. There was a limited body of clinical evidence comparing spinal fusion with alternative treatments other than surgery. Further, there was considerable variation in patient populations, study design, and outcome definitions across studies, which limits the comparability of evidence. As a result, we were forced to make assumptions around the clinical effects of conservative treatment versus spinal fusion, using data derived from the Persson study. Because of the underlying uncertainty around clinical effects of fusion versus conservative treatment, we conducted numerous sensitivity analyses where efficacy for surgery versus conservative treatments was varied. Nonetheless, to obtain more robust comparative clinical and cost-effectiveness estimates, more clinical studies are needed comparing fusion with alternative conservative therapies after patients have had a trial of conservative therapy.

Comparison to Other Economic Studies of ACDF

Carreon conducted a cost-effectiveness analysis of single level ACDF in the United States (Carreon, 2012). Carreon reported cost per QALY estimates of \$106,256 at year 1, \$54,622 at year 2, \$38,836 at year 3, \$29,454 at year 4 and \$24,479 at year 5, and concluded that single-level instrumented ACDF is both effective and durable resulting in QALY gained as compared to other widely accepted healthcare interventions. The results from Carreon differ from those reported in our study largely because the Carreon study *did not compare fusion's costs and effects to any alternative treatment strategy*. Standard guidelines for economic evaluation recommend that a comparator be used when conducting economic evaluations when they are available. Further, Carreon *applied a cost of \$15,714 which is almost half the cost of fusion in the Washington State Health Care Authority*. If the cost of surgery (~\$30,000) in Washington State Health Care Authority was applied in the Carreon analysis, the cost per QALY estimates in the Carreon study would approximately double.

Although the Carreon study applied similar utility gains for resolving cervical pain to those applied in this report (0.18), it is important to note that assumed utility gains are equivalent to gaining 67.5 days of perfect health each year. These estimates exceed those reported for severe complications such as stroke or myocardial infarction (Sullivan, 2006).

Consequently, the utility gains in the Carreon analysis (and our reference case analysis) may not be generalizable to patients with less severe forms of cervical DDD, where utility gains may be less pronounced. These aforementioned issues (no comparator, assumed cost of fusion of \$15,714, and assumed utility gain of 0.18) limit the generalizability of findings from the Carreon analysis to patient populations with more severe forms of cervical DDD in which conservative treatments are not an option. Indeed, we were able to produce findings similar to those reported in the Carreon analysis (~\$40,000 per QALY gained at year 3) when we: 1) did not use a comparator (i.e., assumed conservative treatment costs \$0 and fusion is 100% more effective), 2) assumed fusion costs \$15,714, and 3) applied utility gains of 0.185 for resolution of cervical pain symptoms.

Our analysis is more generalizable to the Washington State Health Care Authority – we consider alternative treatment strategies; use Washington State Health Care Authority specific costs; and our analysis considers multiple sources of utilities, some of which may be

more generalizable to broader patient populations such as those less severe forms of disease where an alternative conservative treatment remains an option despite a previous trial of conservative treatment. Nonetheless, further research is needed exploring how gains in health related quality of life vary by disease severity.

The only other study identified compared the cost-effectiveness of various types of fusion (i.e., plating and allograft vs. autograft) (Angevine, 2005). Because this type of comparison was outside the scope of our systematic review, it is not discussed in detail here.

11. Recommendations for Future Research

As documented in this appraisal report, despite the relatively high prevalence, clinical significance, and economic impact of chronic neck pain, syntheses of all the available medical literature continue to highlight many notable areas of uncertainty that hinder comparisons of the clinical effectiveness and value of major management options. In part the uncertainty is driven by the natural history of the condition itself, in that many patients may see improvement in their symptoms over time regardless of the intervention used. However, the current body of evidence also suffers from a lack of rigor and applicability, as nearly all randomized studies have been small, conducted in single, specialized centers, and have not employed standard techniques for measuring or evaluating outcomes.

Informed by the evidence gaps highlighted by our systematic review, we present below high-level recommendations for all research on spinal fusion for cervical neck pain and related symptoms arising from degenerative disc disease.

1. To date, very few RCTs have been conducted in a population of patients who have attempted conservative management for 4-6 weeks; most studies have involved individuals suffering from neck pain for months to years. Given that case series suggest that fusion's benefits relative to conservative management decline the longer patients have been experiencing symptoms, trials should be developed to determine if "early" fusion provides a benefit relative to treatment alternatives. These trials should include a focus on functional outcomes, particularly return to work/work productivity. Although limited data suggest possible earlier pain relief with fusion, it is unknown whether this translates into earlier return to work and/or higher work productivity.
2. All clinical trials of management options for cervical pain and radiculopathy should use a common set of outcome measures, measured at the same time points so that results across trials can be more easily pooled and evaluated. For example, pain could be measured on a VAS that uses a uniform 100 mm measurement scale across trials, or through standardized and scored instruments such as the Million VAS or McGill Pain Questionnaire. In addition, despite recommendations from clinical

societies to use validated functional instruments such as the Neck Disability Index, function has only been minimally-assessed in RCTs comparing fusion to treatment alternatives. Future RCTs should always include functional outcomes.

3. Health-related quality of life has not been adequately studied in RCTs of cervical spinal fusion. All future trials should directly assess quality of life by validated instruments such as the EQ-5D or SF-36.
4. Whenever possible, studies should capture healthcare utilization and cost outcomes. Information on indirect costs should also be collected, including detailed data on work loss, disability leave, and return to normal activities.
5. More trials are needed of treatment “pathways” or “algorithms” that would characterize care for patients who need more than an initial form of treatment. In particular, trials are needed of minimally-invasive nonsurgical interventions such as radiofrequency denervation and spinal injections to assess their potential for delaying or eliminating the need for surgery.
6. More trials are needed of patient preferences for different types of treatment options and how these preferences correlate with treatment outcomes.
7. More trials are needed in more broadly representative patient populations, including among clinical providers in the community, not just the elite practitioners at top academic sites.
8. Long-term observational studies are necessary to gain a better understanding of treatment-related harms, requirements for retreatment and additional treatment, and real-world healthcare utilization. In particular, clinical registries with careful notation of clinical and psychosocial patient characteristics prior to spinal fusion could be useful in understanding those factors associated with better overall outcomes.

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APPENDIX A

Measures of Treatment Success

1. Hilibrand Criteria

Outcome	Pain	Medication	Activity	Work Status
Excellent	None	None	Normal	Normal
Good	Mild	Occasional use of non-steroidal anti-inflammatory drugs	Normal	Normal
Fair	Moderate	Frequent use of non-steroidal anti-inflammatory drugs	Restricted	Limited
Poor	Severe	Oral use of narcotics	Incapacitated	Disabled

Source: Hilibrand AS et al. *J Bone Joint Surg.* 1999;81:A(4).

2. Odom's Criteria

Outcome	Patient Characteristics
Excellent	No complaints referable to cervical disease. Patients able to carry on daily occupations without impairment.
Good	Intermittent discomfort related to cervical disease which did not significantly interfere with work.
Satisfactory	Subjective improvement with limited physical activity.
Poor	No improvement/ worse compared to pre-operative condition.

Source: Odom GL et al. *JAMA.*1958;166(1):23-28.

3. Japanese Orthopaedic Association (JOA) Cervical Myelopathy Evaluation Questionnaire

With regard to your health condition during the last week, please circle the number of the *one* answer that best applies for each of the following questions. If your condition varies depending on the day or the time, circle the number of the answer that applies when your condition was at its *worst*.

Q1-1 While in the sitting position, can you look up at the ceiling by tilting your head upward?

- 1) Impossible
- 2) Possible to some degree (with some effort)
- 3) Possible without difficulty

Q1-2 Can you drink a glass of water without stopping despite the neck symptoms?

- 1) Impossible
- 2) Possible to some degree
- 3) Possible without difficulty

Q1-3 While in the sitting position, can you turn your head toward the person who is seated to the side but behind you and speak to that person while looking at his/her face?

- 1) Impossible
- 2) Possible to some degree
- 3) Possible without difficulty

Q1-4 Can you look at your feet when you go down the stairs?

- 1) Impossible
- 2) Possible to some degree
- 3) Possible without difficulty

Q2-1 Can you fasten the front buttons of your blouse or shirt with both hands?

- 1) Impossible
- 2) Possible if I spend time
- 3) Possible without difficulty

Q2-2 Can you eat a meal with your dominant hand using a spoon or a fork?

- 1) Impossible
- 2) Possible if I spend time
- 3) Possible without difficulty

Q2-3 Can you raise your arm? (answer for the weaker side)

- 1) Impossible
- 2) Possible up to shoulder level
- 3) Possible although the elbow and/or wrist is a little flexed
- 4) I can raise it straight upward

Q3-1 Can you walk on a flat surface?

- 1) Impossible
- 2) Possible but slowly even with support
- 3) Possible only with the support of a handrail, a cane, or a walker
- 4) Possible but slowly without any support
- 5) Possible without difficulty

Q3-2 Can you stand on either leg without the support of your hand?

(Do you need to support yourself?)

- 1) Impossible with either leg
- 2) Possible on either leg for more than 10 seconds
- 3) Possible on both legs individually for more than 10 seconds

Q3-3 Do you have difficulty going up stairs?

- 1) I have great difficulty
- 2) I have some difficulty
- 3) I have no difficulty

Q3-4 Do you have difficulty with one of the following motions: bending forward, kneeling, or stooping?

- 1) I have great difficulty.
- 2) I have some difficulty
- 3) I have no difficulty

Q3-5 Do you have difficulty walking more than 15 minutes?

- 1) I have great difficulty
- 2) I have some difficulty
- 3) I have no difficulty

Q4-1 Do you have urinary incontinence?

- 1) Always
- 2) Frequently
- 3) When retaining urine over a period of more than 2 hours
- 4) When sneezing or straining
- 5) No

Q4-2 How often do you go to the bathroom at night?

- 1) Three times or more
- 2) Once or twice
- 3) Rarely

Q4-3 Do you have a feeling of residual urine in your bladder after voiding?

- 1) Most of the time
- 2) Sometimes
- 3) Rarely

Q4-4 Can you initiate (start) your urine stream immediately when you want to void?

- 1) Usually not
- 2) Sometimes
- 3) Most of the time

Q5-1 How is your present health condition?

- 1) Poor
- 2) Fair
- 3) Good
- 4) Very good
- 5) Excellent

Q5-2 Have you been unable to do your work or ordinary activities as well as you would like?

- 1) I have not been able to do them at all.
- 2) I have been unable to do them most of the time.
- 3) I have sometimes been unable to do them.
- 4) I have been able to do them most of the time.
- 5) I have always been able to do them.

Q5-3 Has your work routine been hindered because of the pain?

- 1) Greatly
- 2) Moderately
- 3) Slightly (somewhat)
- 4) Little (minimally)
- 5) Not at all

Q5-4 Have you been discouraged and depressed?

- 1) Always
- 2) Frequently
- 3) Sometimes
- 4) Rarely
- 5) Never

Q5-5 Do you feel exhausted?

- 1) Always
- 2) Frequently
- 3) Sometimes
- 4) Rarely
- 5) Never

Q5-6 Have you felt happy?

- 1) Never
- 2) Rarely
- 3) Sometimes
- 4) Almost always
- 5) Always

Q5-7 Do you think you are in decent health?

- 1) Not at all (my health is very poor)
- 2) Barely (my health is poor)
- 3) Not very much (my health is average)

- 4) Fairly (my health is better than average)
- 5) Yes (I am healthy)

Q5-8 Do you feel your health will get worse?

- 1) Very much so
- 2) A little bit at a time
- 3) Sometimes yes and sometimes no
- 4) Not very much
- 5) Not at all

On a scale of 0 to 10, regarding 0 as “no pain (numbness) at all” and 10 as “the most intense pain (numbness) imaginable,” mark a point between 0 and 10 on the lines below to show the degree of your pain or numbness when your symptom was at its worst during the last week.

If you feel pain or stiffness in your neck or shoulders, mark the degree.
0 _____ 10

If you feel tightness in your chest, mark the degree.
0 _____ 10

If you feel pain or numbness in your arms or hands, mark the degree.
(If there is pain in both limbs, judge the worse of the two.)
0 _____ 10

If you feel pain or numbness from chest to toe, mark the degree
0 _____ 10

Source: Fukui et al. *J Orthop Sci.* 2009;14:348–365.

4. Hirabayashi Recovery Rate

$$\text{Hirabayashi Recovery rate} = \frac{\text{Post operative condition} - \text{Preoperative condition}}{\text{Normal condition} - \text{Preoperative condition}} * 100$$

Source: Hirabayashi et al. *Spine.* 1981;6(4):354-363.

Study Quality Rating Criteria

Study Quality Rating System for Randomized Controlled Trials

A) Was the method of randomization adequate?

The randomization sequence should be random and unpredictable, using methods such as a computer-generated random-number sequence or use of sealed envelopes. Allocation methodology based on date of birth or hospital numbers is not adequate.

B) Was the treatment allocation concealed?

Treatment assignment is conducted by an independent party without information about patient eligibility or any patient-specific data.

C) Were groups similar at baseline regarding the most important prognostic factors?

For assignment of a “yes” score, patient demographics including age, sex, duration of symptoms, should be similar at baseline.

D) Was the patient blinded to the intervention?

Sufficient information regarding patient blinding should be provided.

E) Was the care provider blinded to the intervention?

Sufficient information regarding caregiver blinding should be provided.

F) Was the outcome assessor blinded to the intervention?

Sufficient information regarding blinding of the outcome assessment should be provided.

G) Were co-interventions avoided or similar?

Co-interventions should be avoided, or be similar, in the trial design.

H) Was adherence acceptable in all groups?

Based on factors such as intensity and duration of interventions, frequency of sessions, the reviewer will assess if adherence is acceptable.

I) Was the dropout rate described and acceptable ($\leq 15\%$)?

All patient dropouts should be described or accounted for without exceeding 15% per treatment arm.

J) Was the timing of the outcome assessment in all groups similar?

Outcome assessment should occur at similar time points for all intervention arms, with evaluation of all important outcomes.

K) Did the analysis include an intention-to-treat analysis?

All randomized patients are evaluated according to the original allocation, regardless of adherence, and < 5% of randomized patients are excluded.

Each question is scored as Yes/No/Don't Know with every "Yes" score assigned one point. If more than 50% of all possible points are awarded, the study is rated as "high" quality, e.g. a study is scored as 6/11 points and is a "high" quality study.

Source: Chou R et al. *Ann Intern Med.* 2007;147(7):492-504.

Study Quality of Comparative Cohort Studies

The quality of all included comparative cohorts was assessed using the framework employed by the U.S. Preventive Services Task Force (USPSTF Procedure Manual, 2008). Studies were rated “good,” “fair,” or “poor,” using the criteria described below:

- **Good:** Comparable group are assembled initially and maintained throughout the study (follow-up of at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis. Intention to treat analysis is used.
- **Fair:** Generally comparable groups are assembled initially but some question remains whether moderate differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done.
- **Poor:** Any of the following problems exist: (1) groups assembled initially are not close to being comparable or maintained throughout the study; (2) unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); (3) key confounders are given little or no attention; and (4) intention to treat analysis is *not* conducted.

APPENDIX B

Search Strategy for OVID

Databases searched:

- Medline 1996 to Present with Daily Update
- EBM Reviews – Cochrane Central Register of Controlled Trials 4th Quarter 2012

1. Randomized controlled trial.pt
2. Controlled clinical trial.pt
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. single blind method/
7. 1 or 2 or 3 or 4 or 5 or 6
8. Animal /not human.mp
9. 7 not 8
10. Clinical trial.pt
11. Exp Clinical trial/
12. (clin\$ adj25 trial\$).tw
13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).tw
14. Placebos/
15. Placebo\$.tw
16. Random\$.tw
17. Research design/
18. (latin adj square).tw
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 19 not 8
21. 20 not 9
22. Comparative study/
23. Exp Evaluation Studies/
24. Follow-up studies/
25. Prospective studies/
26. (control\$ or prospective\$ or volunteer\$).tw
27. Cross-over studies/
28. 22 or 23 or 24 or 25 or 26 or 27
29. 28 not 8
30. 29 not (9 or 21)
31. 9 or 21 or 30
32. Exp cervical vertebrae/
33. Cervical.mp

34. Degenerative.mp
35. 32 or 33 or 34
36. Fusion.mp
37. Exp spinal fusion/
38. Interbody.mp
39. Spondylodes*.mp
40. 36 or 37 or 38 or 39
41. 31 and 35 and 40

Search limited to studies published from 2000 to present, English language only and filtered by randomized controlled trials.

Cohort search limited to Medline with focused elimination of animal and cadaver studies.

Search Strategy for EMBASE

1. 'clinical article'/exp AND [embase]/lim AND [1996-2013]/py
2. 'clinical study'/exp AND [embase]/lim AND [1996-2013]/py
3. 'clinical trial'/exp AND [embase]/lim AND [1996-2013]/py
4. 'controlled study'/exp AND [embase]/lim AND [1996-2013]/py
5. 'multicenter study'/exp AND [embase]/lim AND [1996-2013]/py
6. 'randomized controlled trial'/exp AND [embase]/lim AND [1996-2013]/py
7. 'major clinical study'/exp AND [embase]/lim AND [1996-2013]/py
8. 'phase 3 clinical trial'/exp AND [embase]/lim AND [1996-2013]/py
9. 'phase 4 clinical trial'/exp AND [embase]/lim AND [1996-2013]/py
10. 'crossover procedure'/exp AND [embase]/lim AND [1996-2013]/py
11. 'double blind procedure'/exp AND [embase]/lim AND [1996-2013]/py
12. 'single blind procedure'/exp AND [embase]/lim AND [1996-2013]/py
13. 'placebo'/exp AND [embase]/lim AND [1996-2013]/py
14. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15. 'human'/exp AND [embase]/lim AND [1996-2013]/py
16. 'nonhuman'/exp AND [embase]/lim AND [1996-2013]/py
17. 'animal'/exp AND [embase]/lim AND [1996-2013]/py
18. 'animal experiment'/exp AND [embase]/lim AND [1996-2013]/py
19. #16 OR #17 OR #18
20. #15 AND #19
21. #14 NOT #19
22. #14 AND #20
23. #21 OR #22

24. 'cervical spine'/exp AND [embase]/lim AND [1996-2013]/py
25. cervical:de,ab,ti AND [embase]/lim AND [1996-2013]/py
26. degenerative:de,ab,ti AND [embase]/lim AND [1996-2013]/py
27. #24 OR #25 OR #26
28. fusion:de,ab,ti AND [embase]/lim AND [1996-2013]/py
29. 'spine fusion'/exp AND [embase]/lim AND [1996-2013]/py
30. interbody:de,ab,ti AND [embase]/lim AND [1996-2013]/py
31. spondylodes*:de,ab,ti AND [embase]/lim AND [1996-2013]/py
32. #28 OR #29 OR #30 OR #31
33. #23 AND #27 AND #32
34. #27 AND #32
35. #34 AND 'randomized controlled trial'/de

Additional databases searched

- OT Seeker: Occupational Therapy Systematic Evaluation of Evidence
- PEDro: Physiotherapy Evidence Database

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

Question: How can we best modify the existing tonsillectomy and sleep apnea guidelines for children?

Question Source: HOSC/HSC; HERC staff; OHP Medical Directors; DMAP; Drs. Holger Link and Kyle Johnson, OHSU Sleep Medicine

Issues:

A revised sleep apnea guideline was reviewed at the May, 2013 VBBS meeting. There was a lively discussion around the requirements in the guideline. HERC staff was directed to arrange a meeting with pediatric sleep specialists, OHP plan medical directors, and HERC staff to further discuss the guideline and refine the wording. This meeting occurred on June 25th, between Dr. Holger Link (pulmonologist and sleep specialist, OHSU), Dr. Derek Lam (sleep medicine specialist, OHSU), Dr. Henry Milcuk (ENT and sleep medicine, OHSU), Dr. Tracy Muday (OHP medical director), Dr. John Sattenspiel (OHP medical director) and HERC staff.

The group discussion determined that some type of validated test should be required to make the diagnosis of OSA in children. The plans are finding the validated questionnaires to be useful, while polysomnography (PSG) remains the gold standard of diagnosis. Daytime symptoms should not be required, because such symptoms are taken into consideration with the validated test requirement. Previously, the guideline had differentiated mild, moderate, and severe sleep apnea. The group members did not feel that this distinction was helpful except for hospital management after surgery, and would require a sleep study to determine. There was discussion about whether to require PSG prior to surgery for high risk children, including young children (under age 3). It was thought that a high risk child with history and exam consistent with OSA may not benefit from a PSG and that it was not a good use of OHP resources to require it. The decision was to encourage PSGs in this group, but not require them. However, the specialists felt that children with a history inconsistent with physical exam should have a sleep study to more fully determine the diagnosis. The group did not comment on what constituted a positive PSG.

One question posed to the experts by the VBBS was how “child” should be defined. The group felt that a person younger than age 16 would generally have the physiology of a child rather than an adult. Adolescents 16 and older are generally diagnosed and treated for OSA as adults.

A second meeting was scheduled, but did not occur. Outstanding questions exist, and further input from experts and PCPs/medical directors/etc. is still being solicited.

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

Current guidelines:

GUIDELINE NOTE 27, SLEEP APNEA

Line 211

Surgery for sleep apnea for adults is only covered after documented failure of both CPAP and an oral appliance.

GUIDELINE NOTE 36, TONSILLECTOMY

Lines 49, 84, 210, 395, 574

Tonsillectomy is an appropriate treatment in a case with:

1. Five documented attacks of strep tonsillitis in a year or 3 documented attacks of strep tonsillitis in each of two consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed;
2. Peritonsillar abscess requiring surgical drainage;
3. Moderate or severe obstructive sleep apnea (OSA) in children 18 and younger, or mild OSA in children with daytime symptoms and/or other indications for surgery. For children 3 and younger or for children with significant co-morbidities, OSA must be diagnosed by nocturnal polysomnography. For children older than 3 who are otherwise healthy, OSA must be diagnosed by either nocturnal polysomnography, use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), or consultation with a sleep medicine specialist; or,
4. Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

Recommendations:

- 1) Adopt a new guideline for pediatric sleep apnea diagnosis and treatment as shown below
 - a. Issues:
 - i. Age to define “child”
 - ii. Methods of diagnosing OSA, definition of positive sleep study
 - iii. Requirements for continued CPAP use
- 2) Modify the existing Tonsillectomy Guideline and Sleep Apnea Guideline as shown below

GUIDELINE NOTE XXX, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN

Line 210

Obstructive sleep apnea (OSA) in children (younger than 16) must be diagnosed by

- 1) nocturnal polysomnography with an AHI >5 episodes/h, OR
- 2) nocturnal pulse oximetry with 3 or more SpO₂ drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR
- 3) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
- 4) consultation with a sleep medicine specialist.

Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

- 1) high risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
- 2) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),
- 3) children younger than three years of age

Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese. Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

CPAP is covered for a 3 month trial for children through age 18 who have

- 1) undergone surgery or are not candidates for surgery, AND
- 2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

CPAP will be covered for children through age 18 on an ongoing basis if:

- 1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

- 2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA

Lines 49, 84, ~~210~~, 395, 574

Tonsillectomy/adenotonsillectomy is an appropriate treatment for patients with:

1. Five documented attacks of strep tonsillitis in a year or 3 documented attacks of strep tonsillitis in each of two consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed;
2. Peritonsillar abscess requiring surgical drainage;
- ~~3. Moderate or severe obstructive sleep apnea (OSA) in children 18 and younger, or mild OSA in children with daytime symptoms and/or other indications for surgery. For children 3 and younger or for children with significant co-morbidities, OSA must be diagnosed by nocturnal polysomnography. For children older than 3 who are otherwise healthy, OSA must be diagnosed by either nocturnal polysomnography, use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), or consultation with a sleep medicine specialist; or,~~
4. ~~3.~~ Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

See Guideline Note XXX for diagnosis and treatment of obstructive sleep apnea in children

GUIDELINE NOTE 27, SLEEP APNEA

Line 210

Surgery for sleep apnea for adults (16 and older) is only covered after documented failure of both CPAP and an oral appliance.

Contents lists available at [SciVerse ScienceDirect](#)

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Algorithm for the diagnosis and treatment of pediatric OSA: A proposal of two pediatric sleep centers

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ABSTRACT

There is currently no consensus on the best method of managing of obstructive sleep apnea (OSA) in childhood. In the present paper, an algorithm for the diagnosis and treatment of the disorder is proposed. Sleep apnea is suspected when parents report relevant symptoms or when there are abnormalities that predispose to OSA such as adenotonsillar hypertrophy, obesity, craniofacial anomalies, or neuromuscular disorders. OSA-associated morbidity including elevated blood pressure, daytime sleepiness or learning problems, growth failure, and enuresis should be recognized. Severity of intermittent upper airway obstruction during sleep can be determined objectively by polysomnography or, if polysomnography is not available, by nocturnal pulse oximetry. Risk factors predicting persistence of OSA in adolescence (male gender, development of obesity) need to be identified. Children with moderate-to-severe OSA, or with mild OSA, but accompanied by morbidity, or by risk factors predicting persistence of the disorder should have priority for treatment. An individualized and multifaceted therapeutic approach which addresses in a step-by-step fashion all abnormalities that contribute to upper airway obstruction during sleep is necessary.

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1. Introduction

Obstructive sleep-disordered breathing describes a spectrum of abnormal breathing patterns during sleep characterized by snoring and increased respiratory effort [1]. Depending on the severity of upper airway obstruction, these breathing patterns may range from primary snoring to upper airway resistance syndrome, obstructive hypoventilation, and obstructive sleep apnea (OSA) [1]. The American Thoracic Society has defined OSA as a disorder of breathing during sleep characterized by prolonged partial or intermittent complete upper airway obstruction (hypopnea or obstructive apnea) which impairs normal ventilation and sleep pattern [2]. Polysomnography (nocturnal sleep recordings) is the main tool for the diagnosis of sleep-disordered breathing and the apnea–hypopnea index (mean number of central + mixed + obstructive apneas and hypopneas per hour of total sleep) (AHI) is the most frequently used polysomnography index for characterizing the severity of upper airway obstruction [3].

OSA is not a distinct disease, but rather a syndrome of functional impairment of the upper airway in a sleeping individual resulting from multiple disorders. Each of these multiple OSA

etiologies is a disease entity by itself with its own genetic background and influences from the environment (Table 1). Dysfunction of the upper airway activates a number of pathogenetic mechanisms that may lead to overt morbidity in the long term, depending on the degree of functional impairment of the airway, the individual's genetic background, and, possibly, environmental and lifestyle factors.

More specifically, patency of the upper airway during sleep is controlled by complex interactions between upper airway resistance, pharyngeal collapsibility, tone of pharyngeal dilator muscles, and negative intraluminal pressure generated by the muscles of inspiration [4]. In some children this fine balance of mechanical forces is disrupted. For example, enlarged adenotonsillar tissue and obesity may increase resistance to airflow and pharyngeal collapsibility [5]. The tendency of the airway walls to collapse under the influence of negative intraluminal pressure is counterbalanced by increased neuromuscular activation of the pharyngeal dilator muscles. Nevertheless, abrupt, intermittent reductions in activation of the pharyngeal dilator muscles during sleep in susceptible individuals lead to episodic airway collapse and hypopneic or apneic events [6].

Response to adenotonsillectomy, the standard treatment for pediatric OSA, is relatively unpredictable in regards to normalization of the breathing patterns during sleep [7–9]. In a recent multicenter study, 21.6% of children with OSA had an AHI >5 episodes/h, postoperatively [9]. This finding is consistent with

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Guideline Note 37 Disorders of Spine with Neurologic Impairment

Question: should GN37 be clarified?

Question source: DMAP

Issue: GN37 specifies that certain diagnoses are included on line 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT only when neurologic impairment is present; otherwise they are included on line 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT. However, some diagnoses on line 400 are not included on line 562 and it is unclear if the guideline applies to these diagnoses.

From DMAP:

The Medical Section would like some additional clarification for the diagnosis codes on line 400 and the application of Guideline Note 37. It is my understanding that the Guideline Note 37 applies to those codes that fall both on lines 400 and 562. It has been more broadly interpreted to apply to all diagnoses on line 400 "for the purpose of treatment" and was challenged in hearings recently. Is the Guideline intended to apply to all diagnoses on line 400 or only those that are also included on line 562? Please let me know if my understanding of the intent of Guideline Note 37 is inaccurate. If my interpretation is correct, is it possible to further clarify the application of Guideline Note 37 with the next List revisions? Suggestion—"For the purpose of treatment coverage of diagnoses that are included on both Lines 400 and 562, neurologic impairment or radiculopathy is defined as: [current wording]. Conditions not meeting these criteria (e.g. pain alone) fall on Line 562."

On review of this question, HERC staff found that some diagnoses on line 400 do not appear on line 562. In some cases, this is because the diagnosis always includes neurologic impairment. In other cases, there are milder subdiagnoses that would be appropriate for line 562 yet that ICD9 code does not appear on that line.

Current guideline note:

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Line 400

For the purpose of treatment coverage on Line 400, neurologic impairment or radioculopathy is defined as:

- A) Markedly abnormal reflexes
- B) Segmental muscle weakness
- C) Segmental sensory loss
- D) EMG or NCV evidence of nerve root impingement
- E) Cauda equina syndrome,
- F) Neurogenic bowel or bladder
- G) Long tract abnormalities

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 562.

Diagnoses on line 400 not found on line 562

ICD9 code	Code description	Other lines with code	Comments
336.0	Syringomyelia and syringobulbia	Dysfunction lines (78,318,375,407)	May be asymptomatic
344.61	Cauda equina syndrome with neurogenic bladder	Dysfunction lines	Meets GN37 criteria by definition
742.59	Other specified congenital anomalies of spinal cord	Dysfunction lines	Many subdiagnoses of various severity
349.2	Disorders of meninges, not elsewhere classified	359 BENIGN CEREBRAL CYSTS 607 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT	Several subdiagnoses of various severity
722.70-722.73	Intervertebral disc disorder with myelopathy		Myelopathy and radiculopathy may involve only pain
723.4	Brachial neuritis or radiculitis NOS		See above
724.4	Thoracic or lumbosacral neuritis or radiculitis, unspecified		See above

HERC staff recommendations:

- 1) Add ICD-9 336.0, 349.2, 722.70-722.73, 723.4, 724.4 and 742.59 to line 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT and keep on line 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT
 - a. Defines when a neurologic disorder should be included on the higher priority line
 - b. Makes all diagnoses on line 400 that do not automatically meet GN37 criteria present on both lines
- 2) Modify GN37 to read as below:

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Line 40, 562

Diagnoses are included ~~For the purpose of treatment coverage~~ on Line 400 when neurologic impairment or radiculopathy is present, as ~~, neurologic impairment or radioculopathy is~~ defined as:

- A) Markedly abnormal reflexes
- B) Segmental muscle weakness
- C) Segmental sensory loss
- D) EMG or NCV evidence of nerve root impingement
- E) Cauda equina syndrome,
- F) Neurogenic bowel or bladder
- G) Long tract abnormalities

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 562.

Section 6

ICD-10-CM Conversion

Perinatal gastrointestinal conditions - new line

Question: Perinatal gastrointestinal conditions - new line

Question source: Pediatric Surgery ICD-10 Review Group

Issue: At the March 2012 VBBS meeting, the ICD-10 Group for Pediatric Surgery proposed a new line to include non-congenital neonatal gastrointestinal conditions. This line was approved in concept. A suggestion was made to ask the ICD-10 Neonatology consultants for assistance.

However, this line has not yet been ranked/created and would need to wait until the biennial review to go into effect January 1, 2016 (or possibly October 15, 2015).

Here is the proposed line:

Line XXX

Condition: PERINATAL GASTROINTESTINAL CONDITIONS

Treatment: Medical therapy

ICD-10: P78.2, P78.3, P78.82, P78.83, P78.89, P78.9

CPT: TBD

Ranking: TBD

Code	CodeDescription	Current Mapping Placement
P78.2	Neonatal hematemesis and melena due to swallowed maternal blood	16, 105
P78.3	Noninfective neonatal diarrhea	16, 105, 312
P78.82	Peptic ulcer of newborn	16, 105,312
P78.83	Newborn esophageal reflux	16, 105,312
P78.89	Other specified perinatal digestive system disorders	16, 105,312
P78.9	Perinatal digestive system disorder, unspecified	16, 105

These codes are currently inappropriately mapping to other lines:

Line	Condition	Treatment
16	CONGENITAL SYPHILIS	MEDICAL THERAPY
105	CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION	MEDICAL AND SURGICAL TREATMENT

Perinatal gastrointestinal conditions - new line

Line	Condition	Treatment
312	CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE	LIVER TRANSPLANT, LIVER-KIDNEY TRANSPLANT

HERC Staff Recommendations:

- 1) Temporarily place the benign newborn gastrointestinal codes on Line 551, DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS removing them from other lines they are on.
- 2) For the next biennial review, scheduled to go into effect January 1, 2016, adopt a new line PERINATAL GASTROINTESTINAL CONDITIONS with the following scoring: **Score 120, approximately line 544.**

Criteria	Score	Comments (from Dr. Craft)
Category	Maternity & Newborn Care (100)	
Impact on Healthy Life Years	2	Note a modest impact on health due to potential for dehydration with diarrhea.
Impact on Pain and Suffering	1	Some suffering for concerned parents but no long term issues
Population Effects	0	
Impact on Vulnerable Populations	0	
Tertiary Prevention	0	No need for treatment and no true extension of disease
Effectiveness	2	Typically no treatment required
Need for Treatment	0.2	Almost none...unless diarrhea associated with dehydration or reflux associated with failure to thrive
Net Cost	4	Again, no significant treatment needed so no real net cost

Frenotomy for Tongue-tie

Question: Should frenotomy for ankyloglossia pair higher on the Prioritized List?

Question Source: Community pediatrician

Issue: Frenulotomy (also frenectomy/frenotomy) is currently on line 626 TONGUE TIE AND OTHER ANOMALIES OF TONGUE below the funding line because of previous reviews demonstrating conflicting evidence on the efficacy of frenulotomy for ankyloglossia.

Per Carrie Phillipi, MD, PhD, of OHSU, frenulotomy is indicated with ankyloglossia, breastfeeding difficulty with persistent nipple pain, and no improvement after lactation consultation.

Current Prioritized List Status

Code	Code Description	Line Placement
41010	Incision of lingual frenum (frenotomy)	171 LEUKOPLAKIA AND CARCINOMA IN SITU OF ORAL MUCOSA, INCLUDING TONGUE 626 TONGUE TIE AND OTHER ANOMALIES OF TONGUE

Line: 626
 Condition: TONGUE TIE AND OTHER ANOMALIES OF TONGUE
 Treatment: FRENOTOMY, TONGUE TIE
 ICD-9: 529.5,750.0,750.10-750.19
 CPT: 40806,40819,41010,41115

October 1, 2014 Prioritized List Status

Line: 19
 Condition: FEEDING PROBLEMS IN NEWBORNS (See Guideline Notes 64,65)
 Treatment: MEDICAL THERAPY
 ICD-10: P92.1-P92.9
 CPT: 98966-98969,99051,99060,99070,99078,99201-99239,99281-99285,99291-99404,99408-99412,99429-99444,99460-99463,99468-99477,99480,99487-99496,99605-99607
 HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,S0270-S0274

Line: 604
 Condition: TONGUE TIE AND OTHER ANOMALIES OF TONGUE
 Treatment: FRENOTOMY, TONGUE TIE
 ICD-10: Q38.1-Q38.3
 CPT: 40806,40819,41010,41115,98966-98969,99051,99060,99070,99078,99201-99239,99281-99285,99291-99404,99408-99412,99429-99444,99468-99477,99480,99487-99496,99605-99607
 HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,S0270-S0274

Frenotomy for Tongue-tie

Evidence Summary:

- 1) *Segal et al, 2007*, review in Canadian Family Practice. This review analyzed prevalence of ankyloglossia, diagnosis of ankyloglossia and effectiveness of frenotomy for treatment of ankyloglossia.
 - a. N=7 studies on effectiveness, all showed benefit and no harms.
 - b. Most were graded as poor quality by authors.
 - c. 1 RCT (Hogan et al) comparing frenotomy to 48 hours of intensive intervention by a lactation consultation. 27 of 28 in frenotomy group had reduced nipple pain and improved breastfeeding at 1 week compared to 1 of 29 in the comparison group. All the remaining mothers in the control group 28 or 29 then chose for their infants to have frenotomy.
 - d. Ankyloglossia prevalence estimated to be 4.2% to 10.7%
 - e. 80% of breastfeeding women with infants with ankyloglossia have persistent nipple pain, 25% have intractable pain or difficulty latching at 6 weeks.
 - f. Overall, recommended frenotomy due to positive benefit without serious complications.
- 2) *National Institute for Health and Clinical Excellence (NICE), 2005*, Interventional Procedure Guidance
 - a. N= 5
 - b. 3 case-series, 1 RCT, and 1 cross-over study
 - c. RCT included is Hogan et al as above
 - d. Overall, recognized that evidence in support is limited, but without major safety concerns, recommended for the procedure.
- 3) *Buryk, Bloom, and Shope, 2011*, provided by Dr. Phillipi
 - a. Single-blinded RCT comparing frenotomy in 30 infants to a sham procedure in 28.
 - b. Mothers rated their nipple pain using the Short-Form McGill Pain Questionnaire (SF-MPQ). SF-MPQ scores decreased from 16.77 to 4.9 in the intervention group and from 19.25 to 13.5 in the sham group ($p<0.01$). This yielded an effect size of 0.38.
 - c. The Infant Breastfeeding Assessment Tool (IBFAT) was used to assess latch. IBFAT scores improved from 9.3 to 11.6 in the frenotomy group and were virtually unchanged in the sham group (8.48 to 8.07). ($p=0.29$) This yielded an effect size of 0.31.
- 4) *Finigan and Long, 2013*, Royal College of Midwives Review
 - a. 9 case series, inter-rater reliability study, 3 RCTs, 1 case-control study, 1 literature review
 - b. Dollberg et al 2006, 25 infants (14 frenectomy, 11 control), significant improvement in nipple pain in intervention group ($p=0.001$), improvement in latch not significant ($p=0.06$)
 - c. Also included Buryk and Hogan as above

Frenotomy for Tongue-tie

- d. Berry *et al* 2012, double-blind RCT, 57 breastfed infants (27 frenectomy, 30 control). 78% in maternal report of breastfeeding success in intervention and 47% in control, $p < 0.02$
- e. Ricke *et al* , Case-control, 49 babies with tongue tie and 98 controls, (RR 3.11 of bottle feeding without frenectomy, 95% CI 1.21-8.03)
- f. Author's conclusions "Tongue-tie division is important in supporting both the initiation and continuation of breastfeeding"
- 5) Webb, Hao, and Hong, 2013
 - a. 5 RCTs, 1 case control and 14 case series
 - b. Included Berry, Buryk, Dollberg, Hogan as above
 - c. Other RCT (Heller) and case control (Dollburg) measure speech outcomes, and did not study breastfeeding.
 - d. Author's Conclusion: "the procedure should only be performed by a trained healthcare professional, in newborns with significant ankyloglossia and associated breastfeeding problems who have failed conservative management".

Society Guidelines:

- 1) *American Academy of Pediatric Dentistry, 2010*
 - a. Guideline on pediatric oral surgery
 - b. "The significance and management of ankyloglossia are very controversial due to the lack of evidence-based studies". "Frenectomy for functional limitations due to severe ankyloglossia should be considered on an individual basis".
- 2) *Canadian Pediatric Society, 2011*
 - a. Position Statement on Ankyloglossia and breastfeeding
 - b. Conclusion: "Based on available evidence, frenotomy cannot be recommended. If, however, the association between significant tongue-tie and major breastfeeding problems is clearly identified and surgical intervention is deemed necessary, frenotomy should be performed by a clinician experienced with the procedure and with appropriate analgesia."

Commerical Payers

- 1) *Aetna, 2013*
 - a. Aetna considers inferior lingual frenectomy or lingual frenotomy for ankyloglossia medically necessary when newborn feeding difficulties or childhood articulation problems exist.

Summary

There is limited evidence to suggest that frenotomy/frenulotomy for tongue tie may be beneficial when the ankyloglossia interferes with breastfeeding. It is a relatively safe procedure with continuation of breastfeeding being a desired outcome.

Frenotomy for Tongue-tie

HERC Staff Recommendations

- 1) Add CPT code 41010 *Incision of lingual frenum (frenotomy)* to ICD10 Prioritized List Line 19 FEEDING PROBLEMS IN NEWBORNS.
- 2) Add ICD-10 Q38.1 (Ankyloglossia) to line 19 and keep on line 610
- 3) Add a guideline to lines 19 FEEDING PROBLEMS IN NEWBORNS and 604 TONGUE TIE AND OTHER ANOMALIES OF TONGUE

GUIDELINE NOTE XX: FRENOTOMY FOR TONGUE-TIE IN NEWBORNS

Lines 19, 604

ICD-10 Q38.1 (Ankyloglossia) is included on line 19 for pairing with CPT 41010 (Frenotomy) only when the ankyloglossia interferes with breastfeeding. Otherwise, ICD-10 Q38.1 and CPT 41010 are included on Line 604.

Prevalence, diagnosis, and treatment of ankyloglossia

Methodologic review

Lauren M. Segal MD Randolph Stephenson PhD Martin Dawes MBBS MD FRCGP Perle Feldman MD FCFP

ABSTRACT

OBJECTIVE To review the diagnostic criteria for, the prevalence of, and the effectiveness of frenotomy for treatment of ankyloglossia.

DATA SOURCES MEDLINE and CINAHL databases were searched for articles suitable for a methodologic review of studies on various aspects of ankyloglossia.

STUDY SELECTION Studies that presented data on patients and addressed ankyloglossia in relation to breastfeeding were selected. Case reports, case series, retrospective studies, prospective controlled studies, and randomized controlled trials were included in the analysis. Opinion pieces, literature reviews, studies without data on patients, studies that did not focus on breastfeeding, position statements, and surveys were excluded.

SYNTHESIS There is no well-validated clinical method for establishing a diagnosis of ankyloglossia. Five studies using different diagnostic criteria found a prevalence of ankyloglossia of between 4% and 10%. The results of 6 non-randomized studies and 1 randomized study assessing the effectiveness of frenotomy for improving nipple pain, sucking, latch, and continuation of breastfeeding all suggested frenotomy was beneficial. No serious adverse events were reported.

CONCLUSION Diagnostic criteria for ankyloglossia are needed to allow for comparative studies of treatment. Frenotomy is likely an effective treatment, but further randomized controlled trials are needed to confirm this. A reliable frenotomy decision rule is also needed.

RÉSUMÉ

OBJECTIF Faire le point sur les critères diagnostiques, la prévalence et l'efficacité de la frénotomie pour traiter l'ankyloglosse.

SOURCES DES DONNÉES On a repéré dans MEDLINE et CINAHL les articles pouvant servir à une revue méthodologique de divers aspects de l'ankyloglosse.

CHOIX DES ÉTUDES On a retenu les articles contenant des données sur les patients et qui portaient sur la relation entre l'ankyloglosse et l'allaitement. L'analyse incluait des rapports de cas, séries de cas, études rétrospectives, essais prospectifs avec témoins et essais contrôlés randomisés. On a exclu de l'analyse les articles d'opinion, les critiques des ouvrages spécialisés, les études ne comportant pas de données sur les patientes et celles qui ne portaient pas sur l'allaitement, les exposés de position et les sondages.

SYNTHÈSE Il n'existe pas de méthode clinique reconnue pour établir un diagnostic d'ankyloglosse. Cinq études qui utilisaient différents critères diagnostiques ont estimé que la prévalence de l'ankyloglosse se situait entre 4% et 10%. Les résultats de 6 études non randomisées et d'une étude randomisée ont tous démontré que la frénotomie a des effets favorables sur la douleur mamelonnaire, la succion, le verrouillage et la poursuite de l'allaitement. Aucun effet indésirable sérieux n'a été rapporté.

CONCLUSION Il faudra établir des critères diagnostiques pour l'ankyloglosse si on veut mener des études comparatives sur le traitement. La frénotomie est probablement un traitement efficace, mais il faut d'autres études contrôlées randomisées pour le confirmer. Il faut aussi élaborer des règles fiables pour prendre la décision de procéder à une frénotomie.

This article has been peer reviewed.

Cet article a fait l'objet d'une révision par des pairs.

Can Fam Physician 2007;53:1027-1033

Issue date: **December 2005**

National Institute for Health and Clinical Excellence

Division of ankyloglossia (tongue-tie) for breastfeeding

1 Guidance

- 1.1 Current evidence suggests that there are no major safety concerns about division of ankyloglossia (tongue-tie) and limited evidence suggests that this procedure can improve breastfeeding. This evidence is adequate to support the use of the procedure provided that normal arrangements are in place for consent, audit and clinical governance.
- 1.2 Division of ankyloglossia (tongue-tie) for breastfeeding should only be performed by registered healthcare professionals who are properly trained.
- 1.3 Publication of further controlled trials on the effect of the procedure on successful long-term breastfeeding will be useful.

2 The procedure

2.1 Indications

- 2.1.1 Ankyloglossia, also known as tongue-tie, is a congenital anomaly characterised by an abnormally short lingual frenulum, which may restrict mobility of the tongue. It varies from a mild form in which the tongue is bound only by a thin mucous membrane, to a severe form in which the tongue is completely fused to the floor of the mouth. Breastfeeding difficulties may arise, such as problems with latching (getting the mother and baby appropriately positioned to breastfeed successfully), sore nipples and poor infant weight gain.

- 2.1.2 Many tongue-ties are asymptomatic and cause no problems. Some babies with tongue-tie have breastfeeding difficulties. Conservative management includes breastfeeding advice, and careful assessment is important to determine whether the frenulum is interfering with feeding and whether its division is appropriate. Some practitioners believe that if division is required, this should be undertaken as early as possible. This may enable the mother to continue to breastfeed, rather than having to feed artificially.

2.2 Outline of the procedure

- 2.2.1 In early infancy, division of the tongue-tie is usually performed without anaesthesia, although local anaesthetic is sometimes used. The baby's head is stabilised, and sharp, blunt-ended scissors are used to divide the lingual frenulum. There should be little or no blood loss and feeding may be resumed immediately. After the early months of life, general anaesthesia is usually required.

2.3 Efficacy

- 2.3.1 One randomised controlled trial compared division of tongue-tie with 48 hours of intensive support from a lactation consultant. Mothers reported that 95% (19/20) of babies had improved breastfeeding 48 hours after tongue-tie division, compared with 5% (1/20) of babies in the control group ($p < 0.001$).

Interventional Procedure Guidance 149

This guidance is written in the following context

This guidance represents the view of the Institute which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. Interventional procedures guidance is for health professionals and people using the NHS in England, Wales and Scotland.

This guidance is endorsed by NHS QIS for implementation by NHSScotland.



- 2.3.2 In one case series of 215 babies, 80% (173/215) of mothers reported improved breastfeeding 24 hours after the procedure. In another case series of 123 babies, 100% (70/70) of mothers reported improved latch after the procedure, and the 53 mothers with nipple pain noted significant improvement immediately after the procedure. In a third case series, 100% (36/36) of babies were reported to have normal tongue motion at 3 months. For more details, refer to the Sources of evidence.
- 2.3.3 There were conflicting opinions among the Specialist Advisors and some stated that it is difficult to be certain whether any perceived improvement in breastfeeding is due to division of the tongue-tie.

2.4 Safety

- 2.4.1 Few adverse effects were reported. One case series reported that, after the procedure, 2% (4/215) of babies had an ulcer under the tongue for more than 48 hours. Two studies, including a total of 159 babies, stated that there were no complications.
- 2.4.2 Two studies reported that 8% (3/36) and 18% (39/215) of babies slept through the procedure. For more details, refer to the Sources of evidence.
- 2.4.3 The Specialist Advisors stated that adverse effects were likely to be rare. Potential adverse events include bleeding, infection, ulceration, pain, damage to the tongue and submandibular ducts, and recurrence of the tongue-tie.

2.5 Other comments

- 2.5.1 It was recognised that breastfeeding is a complex interaction between mother and child, and that many factors can affect the ability to feed. Skilled breastfeeding support is an integral part of the management of breastfeeding difficulties.

- 2.5.2 Public consultation highlighted that this procedure may also be relevant for bottle feeding, but it was noted that this was not included in the scope or in the literature search for this guidance.

3 Further information

- 3.1 The Institute is developing a clinical guideline on postnatal care, which is expected to be published in July 2006 (for details see www.nice.org.uk). The Health Development Agency has also published a systematic review on breastfeeding (www.publichealth.nice.org.uk/page.aspx?o=502749).

Andrew Dillon
Chief Executive
December 2005

Information for the public

NICE has produced information describing its guidance on this procedure for patients, carers and those with a wider interest in healthcare. It explains the nature of the procedure and the decision made, and has been written with patient consent in mind. This information is available from www.nice.org.uk/IPG149publicinfo

Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the following document.

'Interventional procedure overview of division of ankyloglossia (tongue-tie) for breastfeeding', February 2005
Available from www.nice.org.uk/ip279overview

Ordering information

Copies of this guidance can be obtained from the NHS Response Line by telephoning 0870 1555 455 and quoting reference number N0951. *Information for the public* can be obtained by quoting reference number N0952.

The distribution list for this guidance is available at www.nice.org.uk/IPG149distributionlist

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Efficacy of Neonatal Release of Ankyloglossia: A Randomized Trial

Melissa Buryk, David Bloom and Timothy Shope
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Efficacy of Neonatal Release of Ankyloglossia: A Randomized Trial



WHAT'S KNOWN ON THIS SUBJECT: Ankyloglossia affects 1.7% to 4.8% of all infants. There is evidence that poor latch and maternal nipple pain are more common in infants with ankyloglossia. Some studies have shown that frenotomy benefits these infants; however, significant controversy regarding frenotomy still exists.



WHAT THIS STUDY ADDS: When frenotomy is performed for clinically significant ankyloglossia, there is a clear and immediate improvement in reported maternal nipple pain and infant breastfeeding scores. This study also provides compelling evidence to seek frenotomy when indicated.

AUTHORS: Melissa Buryk, MD, David Bloom, MD, and Timothy Shope, MD, MPH

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KEY WORDS

ankyloglossia, frenotomy, breastfeeding, Hazelbaker, tongue-tie

ABBREVIATIONS

NMCP—Naval Medical Center Portsmouth

HATLFF—Hazelbaker Assessment Tool for Lingual Frenulum Function

ENT—ear, nose, and throat

SF-MPQ—Short-Form McGill Pain Questionnaire

IBFAT—Infant Breastfeeding Assessment Tool

Dr Buryk contributed to the study design, data analysis, and drafting of the manuscript; Dr Bloom contributed to the study design and data collection and also performed the frenotomies; and Dr Shope contributed to the study design, data analysis, and drafting of the manuscript.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00967915).

Dr Buryk is a military service member; this work was prepared as part of her official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person's official duties.

Research data were derived from an approved Naval Medical Center Portsmouth institutional review board protocol.

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abstract

FREE

BACKGROUND: Ankyloglossia has been associated with a variety of infant-feeding problems. Frenotomy commonly is performed for relief of ankyloglossia, but there has been a lack of convincing data to support this practice.

OBJECTIVES: Our primary objective was to determine whether frenotomy for infants with ankyloglossia improved maternal nipple pain and ability to breastfeed. A secondary objective was to determine whether frenotomy improved the length of breastfeeding.

METHODS: Over a 12-month period, neonates who had difficulty breastfeeding and significant ankyloglossia were enrolled in this randomized, single-blinded, controlled trial and assigned to either a frenotomy (30 infants) or a sham procedure (28 infants). Breastfeeding was assessed by a preintervention and postintervention nipple-pain scale and the Infant Breastfeeding Assessment Tool. The same tools were used at the 2-week follow-up and regularly scheduled follow-ups over a 1-year period. The infants in the sham group were given a frenotomy before or at the 2-week follow-up if it was desired.

RESULTS: Both groups demonstrated statistically significantly decreased pain scores after the intervention. The frenotomy group improved significantly more than the sham group ($P < .001$). Breastfeeding scores significantly improved in the frenotomy group ($P = .029$) without a significant change in the control group. All but 1 parent in the sham group elected to have the procedure performed when their infant reached 2 weeks of age, which prevented additional comparisons between the 2 groups.

CONCLUSIONS: We demonstrated immediate improvement in nipple-pain and breastfeeding scores, despite a placebo effect on nipple pain. This should provide convincing evidence for those seeking a frenotomy for infants with significant ankyloglossia. *Pediatrics* 2011;128:280–288

The effectiveness of frenulotomy on infant-feeding outcomes: a systematic literature review

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Abstract

Background. Tongue-tie is a congenital anomaly in which the short lingual frenulum or highly attached genioglossus muscle restricts tongue movement. NICE (2005) called for robust clinical trials to be conducted on frenulotomy, the surgical procedure in which the lingual frenulum of infants is separated. The available evidence showed that the procedure posed very little, if any, risk for infants, yet NICE also noted that there was little evidence to underpin the conclusions being drawn by experts that frenulotomy improved infant-feeding.

Aim. To assess the effectiveness of frenulotomy on breastfeeding outcomes and maternal satisfaction with infant-feeding.

Method. The search was undertaken through Cochrane Library, Medline, CINAHL and UpToDate. Inclusion and exclusion criteria were set, and the search was restricted to evidence following the release of the 2005 NICE review. MESH search terms were applied: tongue-tie, ankyloglossia, frenotomy, frenulotomy, and breastfeeding. Two independent reviewers appraised all items, referring to the Cochrane Risk of Bias methodology. The Cochrane Library Critical Appraisal Skills Programme (CASP) tools and guidelines were used.

Results. A total of 53 papers were identified, of which 16 met the criteria: nine case studies, five randomised controlled trials, one prospective inter-rater reliability study and one systematic literature review. Frenulotomy appears to offer long-term breastfeeding benefits for more than 50% of cases. No evidence was available relating to the impact of tongue-tie on bottle-feeding infants.

Implications. Development of a robust, objective manual to assess the degree of tongue-tie and impact on feeding is vital. Research is needed to establish the impact on early parent-infant relationships of feeding a tongue-tied infant.

Key words: Tongue-tie, ankyloglossia, frenulotomy, breastfeeding, bottle-feeding, evidence-based midwifery

Introduction

Partial ankyloglossia (tongue-tie) is defined as a short lingual frenulum that results in restricted movement of the tongue (Hazelbaker, 2010). The restriction appears to be in the forwards protrusion of the tongue (extension); lateral mobility (lateralisation) and tongue lift (Geddes et al, 2008). The reported incidence ranges from 3.2% to 10.7%, depending on the diagnostic criteria used at assessment (Messner et al, 2000; Ballard et al, 2002). There is a greater incidence in boys, with a male to female ratio of 1.5-2.6:1 (Renfrew, 2012). Anterior ankyloglossia is most common, being easily seen near the tip of the tongue and lending a classic heart-shaped appearance to the tongue. It often restricts extension, lift and lateralisation. The less common posterior ankyloglossia is often missed on examination, lying at the base of the tongue. Nevertheless, its functional effect also causes problems with feeding, particularly causing nipple pain and trauma (Hazelbaker, 2010). The findings of recent studies suggest that this condition is associated with feeding problems in early infancy and also with mastication, swallowing, dental and speech problems later in infancy (Geddes et al, 2008).

Historically, division of the lingual frenulum was performed routinely and early in infancy in order to prevent challenges with breastfeeding. The procedure was performed swiftly by the midwife (Notestine, 1990). There is convincing evidence that breastfeeding prevents infection, allergies and obesity in infants (Horta et al, 2007;

UNICEF, 2012). It also impacts on maternal health and wellbeing, reducing the risks of breast and ovarian cancer (UK National Case Control Study Group, 1993; Furberg et al, 1999; Marmot et al, 2007), uterine inertia (Riordan, 2005) and osteoporosis (Chantry et al, 2004).

The purpose of this systematic review was to assess the effectiveness of frenulotomy on breastfeeding outcomes and maternal satisfaction with feeding infants.

Rationale

In order to feed from the breast, a baby must be able to extend its tongue across its lower gum margin, cup the areola with its tongue, and elongate its mother’s nipple to extend to the junction of its hard and soft palate (Geddes et al, 2008). The position of the tongue protects the delicate maternal nipple from trauma and enables the baby to move its tongue and jaw freely to extract milk from the ducts within the breast (Geddes et al, 2008).

The symptoms reported by mothers of tongue-tied babies are clearly similar to the symptoms reported in the infant-feeding surveys (Bolling et al, 2007; Renfrew, 2012) that caused mothers to stop breastfeeding prematurely. These were detailed as:

- Sore, cracked and bleeding nipples
- Engorgement
- Recurrent blocked ducts
- Mastitis
- Breast abscesses

- Poor milk supply
- Unsettled baby
- Frequent feeding
- Faltering infantile growth.

With the resurgence of breastfeeding in the UK, ankyloglossia has again become an important issue in breastfeeding success or failure. However, across the UK, services to divide a tight frenulum in infants are sparse. The lack of objectivity in available studies to support assessment, treatment and evaluation of ankyloglossia results in inadequately robust foundations to underpin future service development.

Breastfeeding is pivotal to infant and maternal health and wellbeing; a key component in enabling mothers to build reciprocal and meaningful relationships with their infants (UNICEF, 2012). Advances in neuroscience have shown that the close and intimate contact during breastfeeding episodes enhances infant brain development and thus impacts on later life outcomes (Gerhardt, 2004; UNICEF, 2013).

Method

A systematic review of the literature ‘is a well planned review to answer a specific research question using a systematic and explicit methodology to identify, select and critically evaluate the results of the studies included’ (Brettle and Grant, 2004; Aveyard, 2007). The Cochrane Critical Appraisal Skills Programme (CASP, 2004) tool was used to ensure consistency in review of the evidence, and the *Cochrane handbook for systematic reviews of interventions* (Higgins and Green, 2011) guided efforts in risk of bias assessment.

Search strategy

The search strategy involved interrogation of electronic databases: Cochrane Library, Medline, CINAHL, and UpToDate. Limits were applied to restrict the search to publications from 2005 (the year of the NICE review) to 2013, relating only to humans, in English, and with full text available. MESH terms relevant to tongue-tie division in infants were applied: ‘tongue-tie’, ‘ankyloglossia’, ‘frenotomy’, ‘frenulotomy’, ‘breastfeeding’ and ‘bottle-feeding’. A further search of Google Scholar and bibliographies sought papers that might have originally been overlooked. A total of 53 papers were identified.

Study selection

Two reviewers independently reviewed the initial selection, applying inclusion and exclusion criteria. Items in which either reviewer was uncertain, or on which the reviewers differed were discussed and reviewed jointly until agreement was reached. The inclusion criteria for studies were:

- Included infants aged from birth up to six months of age
- Addressed challenges with breastfeeding or bottle-feeding
- Reported means of measuring the frenulum
- Employed randomised controlled trial (RCT), systematic literature review (after 2005), or case controlled study.

Exclusion criteria were:

- Sample focused on children older than six months
- No focus on feeding problems
- Reporting only on non-measured and non-notable frenulum
- Case series of less than five infants
- Surveys or opinion-based papers
- Duplicate studies.

A total of 16 reports met the criteria and formed the final selection: nine case studies, five RCTs, one prospective inter-rater reliability study, and one systematic literature review. No papers were found that examined the impact of ankyloglossia on bottle-feeding, most likely because the mechanics of feeding from the bottle differ and it is less common to find bottle-feeding problems in tongue-tied infants.

Data extraction and synthesis

Data were extracted from the studies according to study design, nature and size of sample, intervention, outcomes, and significance and confidence intervals (see Table 1). The quality of the studies was assessed using the CASP tool. Risk of bias was evaluated with consideration of sample, data collection, clarity of inclusion and exclusion criteria, outcome measures and reliability. The review also appraised outcome level for randomisation, blinding and withdrawals. Quality assessment of RCTs was based on the classification of ‘risk of bias’ (Higgins and Green, 2011). The domains included low risk for bias, high risk for bias, and unclear categories.

Results

All studies, except for Dollberg et al (2011), employed consecutive sampling. The RCTs employed double-blinding (Amir et al, 2006; Dollberg et al, 2006; Berry et al, 2012), or single-blinding of mothers (Buryk et al, 2011) or researchers (Hogan et al, 2005). Blinding with this procedure relies on comparable periods of time for removal of the baby from the mother, insertion of a swab under the tongue for both intervention and control group babies, and feeding after the procedure without examination of the mouth by mother or observer. Even in a well-planned and competently conducted trial, such as that by Berry et al (2012), blinding can fail when a small blood stain appears on the swab. Clearly, blinding can be maintained for only a short period.

Details of blinding were not always clear, resulting in a greater risk of bias. Of the five RCTs, only one study presented effect size calculation (Buryk et al, 2011). Confidence intervals varied as would be expected in case series of different sizes, with smaller samples leading to wider confidence limits. However, the results indicated that the effect would still be likely to be demonstrated in larger studies.

Assessment of degree of tongue-tie

Assessment of the degree of tongue-tie and impact on tongue function was mainly subjective, with the construction of questionnaires as a common approach to assessment in case studies. Three studies employed the Hazelbaker Assessment Tool for Lingual Frenulum Function (HATLFF)



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Review article

The effect of tongue-tie division on breastfeeding and speech articulation: A systematic review

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ABSTRACT

Objective: To systematically review the outcomes of tongue-tie division procedures in patients with ankyloglossia with the goal of (1) deriving clinically oriented insights into the effect of tongue-tie division procedures and (2) identifying needs in knowledge to stimulate further research.

Data sources: Medline, EMBASE, and Cochrane databases were searched without any limitations, for studies published between 1966 and June 2012.

Review methods: Studies were included (level 4 evidence or above) if subjects of any age had ankyloglossia and underwent tongue-tie release. Outcome measures of interest were any subjective or objective measures of breastfeeding and speech outcomes, or reports of adverse events.

Results: In all, 378 abstracts were generated from the literature searches; 20 studies met the criteria for data extraction and analysis. Of those, 15 studies were observational and 5 were randomized controlled trials. Tongue-tie division provided objective improvements in the following: LATCH scores (3 studies); SF-MPQ index (2 studies); IBFAT (1 study); milk production and feeding characteristics (3 studies); and infant weight gain (1 study). Subjective improvements were also noted in maternal perception of breastfeeding (14 studies) and maternal pain scores (4 studies). No definitive improvements in speech function were reported. The only significant adverse events were recurrent tongue-ties that required repeat procedures.

Conclusion: Ankyloglossia is a well-tolerated procedure that provides objective and subjective benefits in breastfeeding; however, there was a limited number of studies available with quality evidence. There are no significant data to suggest a causative association between ankyloglossia and speech articulation problems. Aspects of ankyloglossia that would benefit from further research are described, and recommendations for tongue-tie release candidacy criteria are provided.

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Abbreviations: HATLFF, Hazelbaker assessment tool for lingual frenulum function; IBFAT, infant breastfeeding assessment tool; LATCH, latch, audible swallowing, type of nipple, comfort, and hold; RCT, randomized controlled trial; SF-MPQ, short-form McGill pain questionnaire.

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Guideline Summary NGC-8083

Guideline Title

Guideline on pediatric oral surgery.

Bibliographic Source(s)

American Academy of Pediatric Dentistry (AAPD). Guideline on pediatric oral surgery. Chicago (IL): American Academy of Pediatric Dentistry (AAPD); 2010. 8 p. [77 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: American Academy of Pediatric Dentistry (AAPD). Guideline on pediatric oral surgery. Chicago (IL): American Academy of Pediatric Dentistry (AAPD); 2005. 9 p. [61 references]

Scope

Disease/Condition(s)

Diseases and disorders that require oral surgery, including:

- Odontogenic infections
- Erupted teeth needing extraction
- Fractured teeth
- Unerupted and impacted teeth
- Supernumerary teeth and mesiodens
- Oral lesions in the newborn such as Epstein's pearls, dental lamina cysts, Bohn's nodules, and congenital epulis (Neumann's tumor)
- Eruption cysts
- Mucocele
- Oral structural anomalies such as maxillary frenum, mandibular labial frenum, mandibular lingual frenum/ankyloglossia, and natal and neonatal teeth

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Dentistry

Pediatrics

Surgery

Intended Users

Dentists

Guideline Objective(s)

To define, describe clinical presentation, and set forth general criteria and therapeutic goals for common pediatric oral surgery procedures

Target Population

Infants, children, and adolescents

Interventions and Practices Considered

Assessment

1. Physical exam
2. Differential diagnosis
3. Radiographic evaluation

Treatment

1. Treatment of odontogenic infections and associated complications
 - Pulp therapy
 - Extraction, or incision and drainage
 - Antibiotic therapy
 - Hospitalization and referral/consultation with an oral and maxillofacial surgeon
2. Extraction of erupted and unerupted teeth
3. Management of fractured primary tooth roots
4. Management of unerupted, impacted, and supernumerary teeth
5. Evaluation and management of oral pathologies occurring in the newborn
6. Surgical opening of eruption cyst
7. Surgical excision of mucocele and adjacent minor salivary glands
8. Frenectomy (for maxillary frenum and mandibular labial and lingual frenum) and frenectomy techniques
9. Frenuloplasty and frenectomy (for ankyloglossia)
10. Assessment and treatment of Riga-Fede disease

Major Outcomes Considered

- Risk of complications from surgical procedures
- Spontaneous eruption and alignment of teeth

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline is an update of the previous document adopted in 2005. It is based on a review of the current dental and medical literature related to pediatric oral surgery, including a systematic literature search of the MEDLINE/PubMed electronic database with the following parameters: Terms: "pediatric," "oral surgery," "extraction," "odontogenic infections," "impacted canines," "third molars," "supernumerary teeth," "mesiodens," "mucocele," "eruption cyst," "eruption hematoma," "attached frenum," "ankyloglossia," "gingival keratin cysts," "Epstein pearls," "Bohn's nodules," "congenital epulis of newborn," "dental lamina cysts," "natal teeth," and "neonatal teeth"; Fields: all fields; Limits: within the last 10 years; humans; English; clinical trials. There were 7761 articles that matched these criteria. Papers for review were chosen from this list and from references with selected articles.

Number of Source Documents

Seventy-seven electronic and hand-searched articles met the defined criteria and were included.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The oral health policies and clinical guidelines of the American Academy of Pediatric Dentistry (AAPD) are developed under the direction of the Board of Trustees, utilizing the resources and expertise of its membership operating through the Council on Clinical Affairs (CCA).

Proposals to develop or modify policies and guidelines may originate from 4 sources:

1. The officers or trustees acting at any meeting of the Board of Trustees
2. A council, committee, or task force in its report to the Board of Trustees
3. Any member of the AAPD acting through the Reference Committee hearing of the General Assembly at the Annual Session
4. Officers, trustees, council and committee chairs, or other participants at the AAPD's Annual Strategic Planning Session

Regardless of the source, proposals are considered carefully, and those deemed sufficiently meritorious by a majority vote of the Board of Trustees are referred to the CCA for development or review/revision.

Once a charge (directive from the Board of Trustees) for development or review/revision of an oral health policy or clinical guideline is sent to the CCA, it is assigned to 1 or more members of the CCA for completion. CCA members are instructed to follow the specified format for a policy or guideline. All oral health policies and clinical guidelines are based on 2 sources of evidence: (1) the scientific literature; and (2) experts in the field. Members may call upon any expert as a consultant to the council to provide expert opinion. The Council on Scientific Affairs provides input as to the scientific validity of a policy or guideline.

The CCA meets on an interim basis (midwinter) to discuss proposed oral health policies and clinical guidelines. Each new or reviewed/revised policy and guideline is reviewed, discussed, and confirmed by the entire council.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A published cost analysis was reviewed.

Method of Guideline Validation

Comparison with Guidelines from Other Groups

Peer Review

Description of Method of Guideline Validation

Once developed by the Council on Clinical Affairs (CCA), the proposed policy or guideline is submitted for the consideration of the Board of Trustees. While the board may request revision, in which case it is returned to the council for modification, once accepted by majority vote of the board, it is referred for Reference Committee hearing at the upcoming Annual Session. At the Reference Committee hearing, the membership may provide comment or suggestion for alteration of the document before presentation to the General Assembly. The final document then is presented for ratification by a majority vote of the membership present and voting at the General Assembly. If accepted by the General Assembly, either as proposed or as amended by that body, the document then becomes the official American Academy of Pediatric Dentistry (AAPD) oral health policy or clinical guideline for publication in the AAPD's Reference Manual and on the AAPD's Web site.

Recommendations

Major Recommendations

Odontogenic Infections

In children, odontogenic infections may involve more than 1 tooth and usually are due to carious lesions, periodontal problems, or a history of trauma. Untreated odontogenic infections can lead to pain, abscess, and cellulitis. As a consequence of this, children are prone to dehydration—especially if they are not eating well due to pain and malaise. Prompt treatment of the source of infection is important in order to control pain and prevent the spread of infection.

With infections of the upper portion of the face, patients usually complain of facial pain, fever, and inability to eat or drink. Care must be taken to rule out sinusitis, as symptoms may mimic an odontogenic infection. Occasionally in upper face infections, it may be difficult to find the true cause. Infections of the lower face usually involve pain, swelling, and trismus. They frequently are associated with teeth, skin, local lymph nodes, and salivary glands. Swelling of the lower face more commonly has been associated with dental infection.

Most odontogenic infections can be managed with pulp therapy, extraction, or incision and drainage. Infections of odontogenic origin with systemic manifestations (e.g., elevated temperature of 102° to 104°F, facial cellulitis, difficulty in breathing or swallowing, fatigue, nausea) require antibiotic therapy. Severe but rare complications of odontogenic infections include cavernous sinus thrombosis and Ludwig's angina. These conditions can be life threatening and may require immediate hospitalization with intravenous antibiotics, incision and drainage, and referral/consultation with an oral and maxillofacial surgeon.

Extraction of Erupted Teeth

Maxillary and Mandibular Anterior Teeth

Most primary and permanent maxillary and mandibular central incisors, lateral incisors, and canines have conical single roots. In most cases, extraction of anterior teeth is accomplished with a rotational movement, due to their single root anatomies. However, there have been reported cases of accessory roots observed in primary canines. Radiographic examination is helpful to identify differences in root anatomy prior to extraction. Care should be taken to avoid placing any force on adjacent teeth that could become luxated or dislodged easily due to their root anatomy.

Maxillary and Mandibular Molars

Primary molars have roots that are smaller in diameter and more divergent than permanent molars. Root fracture in primary molars is not uncommon due to these characteristics as well as the potential weakening of the roots caused by the eruption of their permanent successors. To avoid inadvertent extraction or dislocation of or trauma to the permanent successor, careful evaluation of the relationship of the primary roots to the developing succedaneous tooth should be completed. Primary molars with roots encircling the successor's crown may need to be sectioned to protect the permanent tooth's location.

Molar extractions are accomplished by using slow continuous palatal/lingual and buccal force allowing for the expansion of the alveolar bone to accommodate the divergent roots and reduce the risk of root fracture. When extracting mandibular molars, care should be taken to support the mandible to protect the temporomandibular joints from injury.

Fractured Primary Tooth Roots

The dilemma to consider when treating a fractured primary tooth root is that removing the root tip may cause damage to the succedaneous tooth, while leaving the root tip may increase the chance for postoperative infection and delay eruption of the permanent successor. Radiographs can assist in the decision process. The literature suggests that if the fractured root tip can be removed easily, it should be removed. If the root tip is very small, located deep in the socket, situated in close proximity to the permanent successor, or unable to be retrieved after several attempts, it is best left to be resorbed.

Unerupted and Impacted Teeth

Impacted Canines

Permanent maxillary canines are second to third molars in frequency of impaction. Early detection of an ectopically erupting canine through visual inspection, palpation, and radiographic examination is important to minimize such an occurrence. Panoramic and periapical films are useful in locating potentially ectopic canines. Routine evaluation of patients in mid-mixed dentition should involve identifying signs such as lack of canine bulges and asymmetry in pattern of exfoliation. Eruption of canines and abnormal angulation or ectopic eruption of developing permanent cuspids can be detected with a radiograph. When the cusp tip of the permanent canine is just mesial to or overlaying the distal half of the long axis of the root of the permanent lateral incisor, canine palatal impaction usually occurs. Extraction of the primary canines is the treatment of choice when malformation or ankylosis is present, when the risk of resorption of the adjacent tooth is evident, or when trying to correct palatally impacted canines, provided there are normal space conditions and no incisor resorption. One study showed that 78% of ectopically erupting permanent canines normalized within 12 months after removal of the primary canines; 64% normalized when the starting canine position overlapped the lateral incisor by more than half of the root and 91% normalized when the starting canine position overlapped the lateral incisor by less than half of the root. If no improvement in canine position occurs in a year, surgical and/or orthodontic treatment were suggested. Although a Cochrane review yielded a lack of randomized controlled clinical studies to support extraction of primary canines to facilitate eruption of ectopic permanent maxillary canines, the literature suggests that this can be considered to minimize complications resulting from impacted canines. Consultation between the practitioner and an orthodontist may be useful in the final treatment decision.

Third Molars

Panoramic or periapical radiographic examination is indicated in late adolescence to assess the presence, position, and development of third molars. The American Association of Oral and Maxillofacial Surgeons (AAOMS) recommends that a decision to remove or retain third molars should be made before the middle of the third decade. Little controversy surrounds their removal when pathology (e.g., cysts or tumors, caries, infection, pericoronitis, periodontal disease, detrimental changes of adjacent teeth or bone) is associated and/or the tooth is malpositioned or nonfunctional (i.e., an unopposed tooth). A systematic review of research literature from 1984 to 1999 concluded there is no reliable evidence to support the prophylactic removal of disease-free impacted third molars. Although prophylactic removal of all impacted or unerupted disease-free third molars is not indicated, consideration should be given to removal by the third decade when there is a high probability of disease or pathology and/or the risks associated with early removal are less than the risks of later removal. Removing the third molars prior to complete root formation may be surgically prudent. AAOMS performed an age-related third molar study among board-certified oral and maxillofacial surgeons in 2001 and concluded that third molar removal in adults is safe with minimal complications and negative effects on the patient's quality of life. The report showed that mandibular third molars exhibited more pathology or abnormalities. All intraoperative complications (e.g., nerve injury, unexpected hemorrhage, unplanned transfusion or parenteral drugs, compromised airway, fracture, other injuries to adjacent teeth/structures) occurred at a frequency less than 1%. Excluding alveolar osteitis, postoperative complications (e.g., paresthesia, infection, trismus, hemorrhage) were similarly low. Factors that increase the risk for complications (e.g., coexisting systemic conditions, location of peripheral nerves, history of temporomandibular joint disease, presence of cysts or tumors) and position and inclination of the molar in question should be assessed. The age of the patient is only a secondary consideration. Referral to an oral and maxillofacial surgeon for consultation and subsequent treatment may be indicated. When a decision is made to retain impacted third molars, they should be monitored for change in position and/or development of pathology, which may necessitate later removal.

Supernumerary Teeth

Supernumerary teeth and hyperdontia are terms to describe an excess in tooth number. Supernumerary teeth are thought to be related to disturbances in the initiation and proliferation stages of dental development. Although some supernumerary teeth may be syndrome associated (e.g., cleidocranial dysplasia) or of familial inheritance pattern, most supernumerary teeth occur as isolated events.

Supernumerary teeth can occur in either the primary or permanent dentition. In 33% of the cases, a supernumerary tooth in the primary dentition is followed by the supernumerary tooth complement in the permanent dentition. Reports in incidence of supernumerary teeth can be as high as 3%, with the permanent dentition being affected 5 times more frequently than the primary dentition and males being affected twice as frequently as females.

frequency than the primary dentition and males being affected three as frequently as females.

Supernumerary teeth will occur 10 times more often in the maxillary arch versus the mandibular arch. Approximately 90% of all single tooth supernumerary teeth are found in the maxillary arch, with a strong predilection to the anterior region. The maxillary anterior midline is the most common site, in which case the supernumerary tooth is known as a mesiodens; the second most common site is the maxillary molar area, with the tooth known as a paramolar. A mesiodens can be suspected if there is an asymmetric eruption pattern of the maxillary incisors, delayed eruption of the maxillary incisors with or without any over-retained primary incisors, or ectopic eruption of a maxillary incisor. The diagnosis of a mesiodens can be confirmed with radiographs, including occlusal, periapical, or panoramic films, or computed tomography. Three-dimensional information needed to determine the location of the mesiodens or impacted tooth can be obtained by taking 2 periapical radiographs using either 2 projections taken at right angles to one another or the tube shift technique (buccal object rule or Clark's rule) or by cone beam computed tomography.

Complications of supernumerary teeth can include delayed and/or lack of eruption of the permanent tooth, crowding, resorption of adjacent teeth, dentigerous cyst formation, pericoronal space ossification, and crown resorption. Early diagnosis and appropriately timed treatment are important in the prevention and avoidance of these complications.

Because only 25% of all mesiodens erupt spontaneously, surgical management often is necessary. A mesiodens that is conical in shape and is not inverted has a better chance for eruption than a mesiodens that is tubercular in shape and is inverted. The treatment objective for a nonerupting permanent mesiodens is to minimize eruption problems for the permanent incisors. Surgical management will vary depending on the size, shape, and number of supernumeraries and the patient's dental development. The treatment objective for a nonerupting primary mesiodens differs in that the removal of these teeth usually is not recommended, as the surgical intervention may disrupt or damage the underlying developing permanent teeth. Erupted primary tooth mesiodens typically are left to shed normally upon the eruption of the permanent dentition.

Extraction of an unerupted primary or permanent mesiodens is recommended during the mixed dentition to allow the normal eruptive force of the permanent incisor to bring itself into the oral cavity. Waiting until the adjacent incisors have at least two-thirds root development will present less risk to the developing teeth but still allow spontaneous eruption of the incisors. In 75% of the cases, extraction of the mesiodens during the mixed dentition results in spontaneous eruption and alignment of the adjacent teeth. If the adjacent teeth do not erupt within 6 to 12 months, surgical exposure and orthodontic treatment may be necessary to aid their eruption. The diagnosing dentist may consider a multidisciplinary approach when treating difficult or complex cases.

Pediatric Oral Pathology

Lesions of the Newborn

Oral pathologies occurring in newborn children include Epstein's pearls, dental lamina cysts, Bohn's nodules, and congenital epulis. Epstein's pearls are common and found in about 75% to 80% of newborns. They occur in the median palatal raphe area, as a result of trapped epithelial remnants along the line of fusion of the palatal halves. Dental lamina cysts, found on the crests of the dental ridges, most commonly are seen bilaterally in the region of the first primary molars. They result from remnants of the dental lamina. Bohn's nodules are remnants of salivary gland epithelium and usually are found on the buccal and lingual aspects of the ridge, away from the midline. Epstein's pearls, Bohn's nodules, and dental lamina cysts typically present as asymptomatic 1 mm to 3 mm nodules or papules. They are smooth, whitish in appearance, and filled with keratin. No treatment is required, as these cysts usually disappear during the first 3 months of life.

Congenital epulis of the newborn, also known as granular cell tumor or Neumann's tumor, is a rare benign tumor seen only in newborns. This lesion is typically a protuberant mass arising from the gingival mucosa. It is most often found on the anterior maxillary ridge. Patients typically present with feeding and/or respiratory problems. Congenital epulis has a marked predilection for females at 8:1 to 10:1. Treatment normally consists of surgical excision. The newborn usually heals well, and no future complications or treatment should be expected.

Eruption Cyst (Eruption Hematoma)

The eruption cyst is a soft tissue cyst that results from a separation of the dental follicle from the crown of an erupting tooth. Fluid accumulation occurs within this created follicular space. Eruption cysts most commonly are found in the mandibular molar region. Color of these lesions can range from normal to blue-black or brown, depending on the amount of blood in the cystic fluid. The blood is secondary to trauma. If trauma is intense, these blood filled lesions sometimes are referred to as eruption hematomas.

Because the tooth erupts through the lesion, no treatment is necessary. If the cyst does not rupture spontaneously or the lesion becomes infected, the roof of the cyst may be opened surgically.

Mucocoele

The mucocoele is a common lesion in children and adolescents resulting from the rupture of a minor salivary gland excretory duct, with subsequent leakage of mucin into the surrounding connective tissues that later may be surrounded in a fibrous capsule. Most mucocoeles are well-circumscribed bluish translucent fluctuant swellings (although deeper and long-standing lesions may range from normal in color to having a whitish keratinized surface) that are firm to palpation. Local mechanical trauma to the minor salivary gland is often the cause of rupture. Mucocoeles most frequently are observed on the lower lip, usually lateral to the midline. Mucocoeles also can be found on the buccal mucosa, ventral surface of the tongue, retromolar region, and floor of the mouth (ranula).

Superficial mucocoeles and some other mucocoeles are short-lived lesions that burst spontaneously, leaving shallow ulcers that heal within a few days. Many lesions, however, require treatment to minimize the risk of recurrence.

Structural Anomalies

Maxillary Frenum

A prominent maxillary frenum in children, although a common finding, is often a concern, especially when associated with a diastema. A comparison of attached frena with and without diastemas found no correlation between the height of the frenum attachment and diastema presence and width. Treatment is suggested when the attachment exerts a traumatic force on the gingiva causing the papilla to blanch when the upper lip is pulled or if it causes a diastema to remain after eruption of the permanent canines. Interference with oral hygiene measures, esthetics, and psychological reasons are contributing factors that relate to treatment of the maxillary frenum. Treatment options can include orthodontics, restorative dentistry, surgery, or a combination of these. When a diastema is present, the objectives for treatment involve managing both the diastemas or permanent teeth and its cause while maintaining stable results in the future. It is recommended that treatment be delayed until the permanent incisors and cuspids have erupted and the diastema has

recommended that treatment be delayed until the permanent incisors and cuspids have erupted and the diastema has had an opportunity to close naturally. If orthodontic treatment is indicated, the frenectomy (complete excision [i.e., removal of the whole frenulum]) should be performed only after the diastema is closed as much as possible to achieve stable results. When indicated, a maxillary frenectomy is a fairly simple procedure and can be performed in the office setting.

Mandibular Labial Frenum

A high frenum can sometimes present on the labial aspect of the mandibular ridge. This is most often seen in the central incisor area and frequently occurs in individuals where the vestibule is shallow. The mandibular anterior frenum, as it is known, occasionally inserts into the free or marginal gingival tissue. Movements of the lower lip cause the frenum to pull on the fibers inserting into the free marginal tissue, which, in turn, can lead to food and plaque accumulation. Early treatment can be considered to prevent subsequent inflammation, recession, pocket formation, and possible loss of the alveolar bone and/or tooth. However, if factors causing gingival/periodontal inflammation are controlled, the degree of recession and need for treatment decreases.

Mandibular Lingual Frenum/Ankyloglossia

When indicated, frenuloplasty (various methods to release the tongue tie and correct the anatomic situation) or frenectomy (simple cutting of the frenulum) may be a successful approach to facilitate breastfeeding; however, there is a need for evidence-based research to determine indications for treatment. This indicates that there is a need to standardize a classification system and justify parameters for surgical correction of ankyloglossia among neonates.

Limitations in tongue mobility and speech pathology have been associated with ankyloglossia. There has been varied opinion among health care professionals regarding the correlation between ankyloglossia and speech disorders. Frenuloplasty or frenectomy in conjunction with speech therapy can be a treatment option to improve tongue mobility and speech. Further evidence is needed to determine the benefit of surgical correction of ankyloglossia in resolving speech pathology.

There is limited evidence to show an association between ankyloglossia and Class III malocclusion. Speculations have been made that the abnormal tongue position may affect skeletal development. Although there are no clear recommendations in the literature, a complete orthodontic evaluation, diagnosis, and treatment plan are necessary prior to any surgical intervention.

Reports also have been made regarding the association between frenal attachment and gingival recession; further clinical evidence, however, is warranted to show a clear relationship between these 2 factors. Elimination of plaque-induced gingival inflammation can minimize gingival recession without any surgical intervention.

The significance and management of ankyloglossia are very controversial due to the lack of evidence-based studies to support frenotomy, frenectomy, and frenuloplasty among children and adults affected by ankyloglossia. Studies have shown a difference in treatment recommendations among speech pathologists, pediatricians, otolaryngologists, lactation specialists, surgeons, and dental specialists. Most professionals, however, will agree that there are certain indications for these procedures. A short lingual frenum can inhibit tongue movement and create deglutition problems. If there is no improvement in breastfeeding for a child with ankyloglossia after non-surgical intervention, frenectomy may be indicated. Although there is limited evidence in the literature to promote the timing, indication, and type of surgical intervention, frenectomy for functional limitations due to severe ankyloglossia should be considered on an individual basis. If evaluation shows that function may be improved by surgery, treatment should be considered.

Frenectomy Techniques

Frenectomy involves surgical incision, establishing hemostasis, and suturing of the wound. Dressing placement or the use of antibiotics is not necessary. Recommendations include maintaining a soft diet, regular oral hygiene, and analgesics as needed. Although there is minimal evidence-based research available, the use of laser technology and electrosurgery for frenectomies have demonstrated a shorter operative working time, the ability to control bleeding quickly, reduced pain and discomfort, fewer postoperative complications (e.g., pain, swelling, infection), and no need for suture removal, as well as increasing patient acceptance. These procedures require skilled technique and patient management.

Natal and Neonatal Teeth

Natal and neonatal teeth can present a challenge when deciding on appropriate treatment. Natal teeth have been defined as those teeth present at birth, and neonatal teeth are those that erupt during the first 30 days of life. The occurrence of natal and neonatal teeth is rare; the incidence varies from 1:1,000 to 1:30,000. The teeth most often affected are the mandibular primary incisors. In most cases, anterior natal and neonatal teeth are part of the normal complement of the dentition. Natal or neonatal molars have been identified in the posterior region and may be associated with systemic conditions or syndromes (e.g., Pfeiffer syndrome, histiocytosis X). Although many theories exist as to why the teeth erupt prematurely, currently no studies confirm a causal relationship with any of the proposed theories. The superficial position of the tooth germ associated with a hereditary factor seems to be the most accepted possibility.

If the tooth is not excessively mobile or causing feeding problems, it should be preserved and maintained in a healthy condition if at all possible. Close monitoring is indicated to ensure that the tooth remains stable.

Riga-Fede disease is a condition caused by the natal or neonatal tooth rubbing the ventral surface of the tongue during feeding leading to ulceration. Failure to diagnose and properly treat this lesion can result in dehydration and inadequate nutrient intake for the infant. Treatment should be conservative and focus on creating round, smooth incisal edges. If conservative treatment does not correct the condition, extraction is the treatment of choice.

An important consideration when deciding to extract a natal or neonatal tooth is the potential for hemorrhage. Extraction is contraindicated in newborns due to risk of hemorrhage. Unless the child is at least 10 days old, consultation with the pediatrician regarding adequate hemostasis may be indicated prior to extraction of the tooth.

Clinical Algorithm(s)

None provided

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

When data did not appear sufficient or were inconclusive, recommendations were based upon expert and/or consensus opinion by experienced researchers and clinicians. In addition, the manual *Parameters of Care: Clinical Practice Guidelines for Oral and Maxillofacial Surgery*, developed by the American Association of Oral and Maxillofacial Surgeons (AAOMS), was consulted.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management and early treatment of infant, child, and adolescent oral health problems and prevention of oral disease

Potential Harms

All intraoperative complications of third molar removal (e.g., nerve injury, unexpected hemorrhage, unplanned transfusion or parenteral drugs, compromised airway, fracture, other injuries to adjacent teeth/structures) occurred at a frequency less than 1%. Excluding alveolar osteitis, postoperative complications (e.g., paresthesia, infection, trismus, hemorrhage) were similarly low. Factors that increase the risk for complications (e.g., coexisting systemic conditions, location of peripheral nerves, history of temporomandibular joint disease, presence of cysts or tumors) and position and inclination of the molar in question should be assessed.

Contraindications

Contraindications

Tooth extraction is contraindicated in newborns due to risk of hemorrhage.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Chart Documentation/Checklists/Forms

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

American Academy of Pediatric Dentistry (AAPD). Guideline on pediatric oral surgery. Chicago (IL): American Academy of Pediatric Dentistry (AAPD); 2010. 8 p. [77 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2005 (revised 2010)

Guideline Developer(s)

American Academy of Pediatric Dentistry - Professional Association

Source(s) of Funding

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Guideline Committee

Council on Clinical Affairs

Composition of Group That Authored the Guideline

Not stated

Financial Disclosures/Conflicts of Interest

Council members and consultants derive no financial compensation from the American Academy of Pediatric Dentistry for their participation and are asked to disclose potential conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: American Academy of Pediatric Dentistry (AAPD). Guideline on pediatric oral surgery. Chicago (IL): American Academy of Pediatric Dentistry (AAPD); 2005. 9 p. [61 references]

Guideline Availability

Electronic copies: Available from the [American Academy of Pediatric Dentistry Web site](#) .

Print copies: Available from the American Academy of Pediatric Dentistry, 211 East Chicago Avenue, Suite 700, Chicago, Illinois 60611.

Availability of Companion Documents

The following are available:

- Overview. American Academy of Pediatric Dentistry 2010-11 definitions, oral health policies, and clinical guidelines. Chicago (IL): American Academy of Pediatric Dentistry; 2010. 2 p. Electronic copies: Available in Portable Document Format (PDF) from the [American Academy of Pediatric Dentistry Web site](#) .
- Post-operative instructions for extractions/oral surgery. Chicago (IL): American Academy of Pediatric Dentistry; 2010. 1 p. Electronic copies: Available in PDF from the [American Academy of Pediatric Dentistry Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on August 19, 2005. This NGC summary was updated by ECRI Institute on December 30, 2010. The updated information was verified by the guideline developer on May 9, 2011.

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Readers with questions regarding guideline content are directed to contact the guideline developer.

Section 7

Straightforward Items (Consent Agenda)

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
51102	Aspiration of bladder; with insertion of suprapubic catheter	88 INJURY TO INTERNAL ORGANS	DMAP is requesting that 51102 be added to line 88 to pair with 867.0 (Injury to bladder and urethra, without mention of open wound into cavity). 51102 is currently on lines 78, 96, and 351.	Add 51102 to line 88.
25310	Tendon transplantation or transfer, flexor or extensor, forearm and/or wrist, single; each tendon	216 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	DMAP is requesting that 25310 be added to line 216 to pair with 881.22 (Open wound of wrist, with tendon involvement). 25310 is currently on lines 143,318,406.	Add 25310 to line 216
38571 38572	Laparoscopy, surgical; with bilateral total pelvic lymphadenectomy Laparoscopy, surgical; with bilateral total pelvic lymphadenectomy	252 CANCER OF OVARY	DMAP is requesting that 38571 be added to line 252 to pair with 183.0 (Malignant neoplasm of ovary). 38571 is currently on lines 123, 144, 218, 287, 311, and 356 and in the DMAP Diagnostic Procedure File. 38572 is located on these same lines and the Diagnostic Procedure File.	Add 38571 and 38572 to line 252 Advise DMAP to remove 38571 and 38572 from the Diagnostic Procedure File.
20610	Arthrocentesis, aspiration and/or injection; major joint or bursa (eg, shoulder, hip, knee joint, subacromial bursa)	326 GOUT AND CRYSTAL ARTHROPATHIES	DMAP is requesting that 20610 be added to line 326 to pair with 274.03 Chronic gouty arthropathy with tophus (tophi). 20610 is on 16 lines.	Add 20610 to line 326

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
94640	Pressurized or nonpressurized inhalation treatment for acute airway obstruction or for sputum induction for diagnostic purposes (eg, with an aerosol generator, nebulizer, metered dose inhaler or intermittent positive pressure breathing [IPPB] device)	424 INFLUENZA	DMAP is requesting that 94640 be added to line 424 to pair with 487.0 Influenza with pneumonia. 94640 is on 15 lines.	Add 94640 to line 424
46900-46924	Destruction of lesion(s), anus (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), various techniques	165 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS	DMAP is requesting that 46900 be added to line 165 to pair with 569.44 Dysplasia of anus. 46900-46924 are currently on line 426 ANOGENITAL VIRAL WARTS. Per guidelines for management of anal dysplasia, the lesions may be treated with cautery, chemical destruction, or surgical resection depending on the degree of dysplasia, size of lesion, etc. Surgical resection codes are on line 165.	Add 46900-46924 to line 165
25652	Open treatment of ulnar styloid fracture	143 OPEN FRACTURE /DISLOCATION OF EXTREMITIES	DMAP is requesting that 25652 be added to line 143 to pair with 813.53 Fracture of distal end of ulna (alone), open. 25652 is currently on line 382 CLOSED FRACTURE OF EXTREMITIES (EXCEPT TOES).	Add 25652 to line 143

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
15004-15005	Surgical preparation or creation of recipient site by excision of open wounds, burn eschar, or scar or incisional release of scar contracture, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, ...	91 DEEP OPEN WOUND OF NECK, INCLUDING LARYNX; FRACTURE OF LARYNX OR TRACHEA, OPEN 292 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA	DMAP is requesting that 15004 and 15120 be added to line 91 to pair with 874.8 (Open wound of neck; Other & unspecified parts, without mention of complication) and requesting that 15120 be added to line 292 to pair with a number of types of skin cancer. Skin graft codes are on multiple lines. Similar codes 15115, 15116, 15040, 15121, 15135, 15136, 15155-15157, 15240, 15241 should also be added to line 91. Most of these codes are on line 292, but 15120-15121 are missing.	Add 15004, 15005, 15040, 15115, 15116, 15120, 15121, 15135, 15136, 15155-15157, 15240, 15241 to line 91. Add 15120-15121 to line 292
15040	Harvest of skin for tissue cultured skin autograft			
15115-15116	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits			
15120-15121	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits			
15135-15136	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits			
15155-15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits			
15240-15241	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet less			

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
31237	Nasal/sinus endoscopy, surgical; with biopsy, polypectomy or debridement	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX	DMAP is requesting that 31237 be added to line 312 to pair with 160.9 Malignant neoplasm of accessory sinus, unspecified. 31237 is currently on lines 498 CHRONIC SINUSITIS, 532 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES.	Add 31237 to line 312
17272-17276	Destruction, malignant lesion (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), scalp, neck, hands, feet, genitalia; various lesion sizes	275 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS	DMAP is requesting that 17272 be added to line 275 to pair with 233.6 Carcinoma in situ of other & unspecified male genital organs. 17272 is currently on lines 257 and 292.	Add 17272-17276 to line 275
35476	Transluminal balloon angioplasty, percutaneous; venous	87 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	DMAP is requesting that 35476 be added to line 87 to pair with 453.40 Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity. 35476 is on lines 303,308,378.	Add 35476 to line 87
44055	Correction of malrotation by lysis of duodenal bands and/or reduction of midgut volvulus (eg, Ladd procedure)	48 INTUSSUSCEPTION, VOLVULUS, INTESTINAL OBSTRUCTION, AND FOREIGN BODY IN STOMACH, INTESTINES, COLON, AND RECTUM	DMAP is requesting that 44055 be added to line 48 to pair with 560.2 Volvulus. 44055 is currently on line 111.	Add 44055 to line 48.

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
31545-31546 31560-31561	Laryngoscopy, direct, operative, with operating microscope or telescope, with submucosal removal of non-neoplastic lesion(s) of vocal cord; reconstruction with various techniques Laryngoscopy, direct, operative, with arytenoidectomy; with or without operating microscope or telescope	49 CONGENITAL AIRWAY OBSTRUCTION WITH OR WITHOUT CLEFT PALATE	DMAP is requesting that 31545 and 31561 be added to line 49 to pair with 748.3 (Other anomalies of larynx, trachea, and bronchus). 31545 and 31561 are currently on 214 SUPERFICIAL ABSCESES AND CELLULITIS and 31545 is also on line 402 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS. Arytenoidectomy is widening of the larynx.	Add 31545-31561 to line 49
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications	340 CANCER OF LIVER	DMAP is requesting that 77301 be added to line 340 to pair with 197.7 Secondary malignant neoplasm of the liver, specified as secondary. 77301 is on many lines	Add 77301 to line 340
27598	Disarticulation at knee	271 CHRONIC OSTEOMYELITIS	DMAP is requesting that 27598 be added to line 271 to pair with 730.17 Chronic osteomyelitis, ankle and foot. 27598 is on lines 146, 190, 208, 250, 297, 346, 355, 410.	Add 27598 to line 271
25210-25215	Carpectomy	384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE	DMAP is requesting that 25215 be added to line 384 to pair with 733.49 Aseptic necrosis of bone. 25215 is on lines 143, 190, 208, 271, 382, 549.	Add 25210 and 25215 to line 384

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
23650-23680	Open or closed treatment of shoulder dislocation, with or without manipulation; with or without anesthesia	143 OPEN FRACTURE/DISLOCATION OF EXTREMITIES 297 DEFORMITY/CLOSED DISLOCATION OF JOINT 443 DISORDERS OF SHOULDER,POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT	DMAP is requesting that 23650 be added to line 443 to pair with 718.31 Recurrent dislocation of shoulder joint. The shoulder dislocation treatment codes are currently on line 297 or a combination of line 297 and 143. Shoulder diagnoses are now all on line 443.	Add 23650-23680 to line 443 Remove 23650-23680 from line(s) 143 and 297
43653	Laparoscopy, surgical; gastrostomy, without construction of gastric tube (eg, Stamm procedure)	Ancillary	DMAP requested several diagnoses be paired with CPT 43653. All other feeding tube codes, including the open equivalent to 43653 are on the Ancillary List.	Advise DMAP to place 43653 on the Ancillary List Remove 43653 from lines 78, 111, 409
20600 20610	Arthrocentesis, aspiration and/or injection; small joint or bursa (eg, fingers, toes) Arthrocentesis, aspiration and/or injection; major joint or bursa (eg, shoulder, hip, knee joint, subacromial bursa)	326 GOUT AND CRYSTAL ARTHROPATHIES	DMAP is requesting that 20610 be added to line 326 to pair with 274.02 Chronic gouty arthropathy without mention of tophus (tophi). 20610 is currently on more than 10 lines. Similar code 20605 (medium joints) is on line 326. 20600 is missing from this line.	Add 20600 and 20610 to line 326
29445	Application of rigid total contact leg cast	410 CHRONIC ULCER OF SKIN	DMAP is requesting that 29445 be added to line 410 to pair with 707.14 Ulcer of heel and midfoot. 29445 is currently on lines 143,297,382,406,455.	Add 29445 to line 410

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
33910 33915	Pulmonary artery embolectomy; with cardiopulmonary bypass without cardiopulmonary bypass	226 ACUTE PULMONARY HEART DISEASE AND PULMONARY EMBOLI	DMAP is requesting that 33910 be added to line 226 to pair with 415.19 Pulmonary embolism and infarction. 33910 and 33915 are currently on line 385 ANEURYSM OF PULMONARY ARTERY. There are no emboli ICD-9 codes on line 385.	Add 33910 and 33915 to line 226 Remove 33910 and 33915 from line 385
37204	Transcatheter occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck	62 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE	DMAP is requesting that 37204 be added to line 62 to pair with 578.9 Hemorrhage of gastrointestinal tract, unspecified. 37204 is on lines 50,77,85,98,141,247,270,340.	Add 37204 to line 62
38564	Limited lymphadenectomy for staging (separate procedure); retroperitoneal (aortic and/or splenic)	123 CANCER OF TESTIS	DMAP is requesting that 38564 be added to line 123 to pair with 186.9 Other and unspecified testis. 38564 is on lines 144, 218, 287, 311, 356. Similar procedures (38571-2) are on line 123.	Add 38564 to line 123
50840	Replacement of all or part of ureter by intestine segment, including intestine anastomosis	186 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER	DMAP is requesting that 50840 be added to line 186 to pair with 593.4 Other ureteric obstruction. 50840 is on lines 96,228,287.	Add 50840 to line 186

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
58562	Hysteroscopy, surgical; with removal of impacted foreign body	448 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 58562 be added to line 448 to pair with 996.32 Mechanical complication of genitourinary device, implant, and graft; Due to intrauterine contraceptive device.	Add 58562 to line 448
33223	Revision of skin pocket for cardioverter-defibrillator	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 33223 be added to line 308 to pair with 996.61 Infection and inflammatory reaction due to cardiac device, implant, and graft. 33223 is on lines 76,109,195,304,376.	Add 33223 to line 308
19328	Removal of intact mammary implant	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 19328 be added to line 308 to pair with 996.69 Infection & inflammatory reaction due to other internal prosthetic device, implant, and graft. 19328 is on lines 197,448,665. 996.69 includes breast prosthesis per coding guidelines.	Add 19328 to line 308
26990 27603	Incision and drainage, pelvis or hip joint area; deep abscess or hematoma Incision and drainage, leg or ankle; deep abscess or hematoma	448 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	DMAP is requesting that 26990 and 27603 be added to line 448 to pair with 998.12 Hematoma complicating a procedure. 26990 is on lines 84, 214, 216, 250, 384. 27603 is on lines 84, 214, 216, 250, 297.	Add 26990 and 27603 to line 448

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
36825	Creation of arteriovenous fistula by other than direct arteriovenous anastomosis (separate procedure); autogenous graft	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 36825, 36830, 37205, 37206, and 37607 be added to line 308 to pair with 996.73 Other complications of internal (biological)(synthetic) prosthetic device, implant, and graft; Due to renal dialysis device, implant, and graft. These procedures are currently on lines 110, 270, 307, 349, 366. 37607 is currently on line 331. 37205 and 37206 are on lines 35,270,278,303,350,378,472. On review, 37208 is missing from line 308	Add 36825, 36830, 37205, 37206, 37208, and 37607 to line 308
36830	Creation of arteriovenous fistula by other than direct arteriovenous anastomosis (separate procedure); nonautogenous graft (eg, biological collagen, the			
37205	Transcatheter placement of an intravascular stent(s) (except coronary, carotid, vertebral, iliac, and lower extremity arteries), percutaneous; initial vessel each additional vessel			
37206	Transcatheter placement of intravascular stent(s), open, each additional vessel.			
37208	Ligation or banding of angioaccess arteriovenous fistula)			
37607				
49423	Exchange of previously placed abscess or cyst drainage catheter under radiological guidance (separate procedure)	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 49423 be added to line 308 to pair with 998.59 Other postoperative infection. 49423 is on lines 84,111,389,593,597,598.	Add 49423 to line 308

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
35475 37183	Transluminal balloon angioplasty, percutaneous; brachiocephalic trunk or branches, each vessel Revision of transvenous intrahepatic portosystemic shunt(s) (TIPS)	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 35475, and 37183 be added to line 308 to pair with 996.74 Other complications of internal (biological)(synthetic) prosthetic device, implant, and graft due to other vascular device, implant, and graft. 35475 is on line 378 ATHEROSCLEROSIS, PERIPHERAL. 37183 is on lines 224, 230, 303, 360. On review, other balloon angioplasty codes are missing from line 308 (35471, 35472). Similar code 37182 is missing from line 308 as well.	Add 35471, 35472, 37182, and 37183 to line 308
15002-15005 15100-15101	Surgical preparation or creation of recipient site by excision of open wounds, burn eschar, or scar (including subcutaneous tissues), or incisional release of scar contracture Split-thickness autograft, trunk, arms, legs	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 15002 and 15100 be added to line 308 to pair with 998.32 Disruption of external operation (surgical) wound. These codes are on multiple lines.	Add 15002-15005 and 15100-15101 to line 308
V20.2	Routine infant or child health check	4 PREVENTIVE SERVICES, OVER AGE OF 10	DMAP is requesting that V20.2 be added to line 4, to allow children over age 10 to receive routine well child care. Currently, V20.2 is only on line 3.	Add V20.2 to line 4

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
736.1	Mallet finger	406 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT 407 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF- DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION 550 DEFORMITIES OF UPPER BODY AND ALL LIMBS	Tracy Muday, OHP Medical Director is requesting that mallet finger be moved from its current lines (407, 550) to line 406. Other hand extensor tendon injuries and the repair for mallet finger (CPT 26433) are located on 406.	Add 736.1 to line 406 Remove 736.1 from line 407 and 550
626.8	Disorders of menstruation & other abnormal bleeding from female genital tract; Other	446 MENSTRUAL BLEEDING DISORDERS	DMAP is requesting that 626.8 pair with 58300 Insertion of intrauterine device (IUD). Currently 626.8 is only on line 403 IMPERFORATE HYMEN; ABNORMALITIES OF VAGINAL SEPTUM. This ICD9 code includes dysfunctional uterine bleeding as a subdiagnosis.	Add 626.8 to line 446 Add 626.8 to GN88 (see below)
97140	Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes	493 BRACHIAL PLEXUS LESIONS	DMAP is requesting that 97140 pair with 353.0 Brachial plexus lesions. Most other PT/OT procedure codes are on line 492. 97140 is currently on multiple lines.	Add 97140 to line 493

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
99241-99245 99251-99255	Office consultation Inpatient consultation		Currently, the consultation CPT codes are on many lines on the Prioritized List. In 2010, CMS determined that these codes should no longer be utilized. They have not been reimbursable by DMAP since 2010.	Remove 99241-99245 and 99251-99255 from all lines on the List Advise DMAP to place 99241-99245 and 99251-99255 on the Excluded List
10160	Puncture aspiration of abscess, hematoma, bulla, or cyst	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 509 BREAST CYSTS AND OTHER DISORDERS OF THE BREAST	DMAP is requesting that 10160 be added to line 308 to pair with 998.51 Infected postoperative seroma and to line 509 to pair with 610.0 Solitary cyst of breast. Currently, 10160 is on lines 84,214,415,448,623.	Add 10160 to lines 308 and 509
14301 14302	Adjacent tissue transfer or rearrangement, any area; defect 30.1 sq cm to 60.0 sq cm each additional 30.0 sq cm, or part thereof	197 CANCER OF BREAST	DMAP is requesting that 14301 be added to line 197 to pair with 174.3 Malignant neoplasm of female breast. 14000 and 14001 (equivalent codes for defect <30 sq cm) are on this line. Similar code 14302 is also missing. These codes are on multiple lines.	Add 14301 and 14302 to line 197
38100	Splenectomy; total	349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	DMAP is requesting that 38100 be added to line 349 to pair with 442.83 Other aneurysm; Splenic artery. 38100 is currently on lines 166, 177, 181, 199, 221, 224, 328.	Add 38100 to line 349

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
69110 69120 69145 69150 69155	Excision external ear; partial, simple repair Excision external ear; complete amputation Excision soft tissue lesion, external auditory canal Radical excision external auditory canal lesion; without neck dissection with neck dissection	207 CANCER OF SOFT TISSUE	DMAP is requesting that 69110 be added to line 207 to pair with 171.0 Malignant neoplasm of connective & other soft tissue of head, face & neck. This ICD9 code includes neoplasms of ear cartilage. 69110 is currently on lines 257,292,312,355,632. Similar codes 69120, 69145, 69150 and 69155 are also not included on line 207.	Add 69110, 69120, 69145, 69150 and 69155 to line 207
37205 37206	Transcatheter placement of an intravascular stent(s) (except coronary, carotid, vertebral, iliac, and lower extremity arteries), percutaneous; initial vessel each additional vessel	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 331 DISORDERS OF ARTERIES, OTHER THAN CAROTID OR CORONARY	DMAP is requesting that 37205 be added to line 308 to pair with 996.73 (Other complications of internal (biological)(synthetic) prosthetic device, implant & graft; Due to renal device, implant & graft and 331 to pair with 593.81 Vascular disorders of kidney. 37205 is on lines 35,270,278,303,350,378,472.	Add 37205 and 37206 to lines 308 and 331
61885 61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array with connection to 2 or more electrode arrays	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 61885 be added to line 308 to pair with 996.2 Mechanical complication of nervous system device, implant, and graft. 61885 is currently only on line 182 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS. Similar code 61888 is on line 308.	Add 61885 and 61886 to line 308

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
D1206	Topical application of fluoride varnish	3 PREVENTIVE SERVICES, BIRTH TO 10 YEARS OF AGE 4 PREVENTIVE SERVICES, OVER AGE OF 10	DMAP is requesting that D1206 be added to line 3 to pair with V20.2 Routine infant or child health check. DMAP has this service open to medical providers because it can be done at a well child check. Claims are denying related to non-pairing. D1206 is currently on line 58 PREVENTIVE DENTAL SERVICES.	Check with Tyack about adding to line 4. Also, do we need a guideline for line 4/the ICD10 List prevention line regarding age?
426.82	Long QT Syndrome	304 LIFE-THREATENING CARDIAC ARRHYTHMIAS 376 CARDIAC ARRHYTHMIAS	DMAP is requesting that 426.82 pair with 33249 - Insertion or replacement of permanent pacing cardioverter-defibrillator system with transvenous lead(s), single or dual chamber. Currently, 426.82 is on line 376. The defibrillator CPT codes are on line 304. Long QT syndrome can lead to ventricular fibrillation and sudden death. A standard treatment in the literature is an implantable defibrillator.	Add 426.82 to line 304 Remove 426.82 from line 376
31780-31781	Excision tracheal stenosis and anastomosis	49 CONGENITAL AIRWAY OBSTRUCTION WITH OR WITHOUT CLEFT PALATE	DMAP is requesting that 31781 pair with 519.19 Other diseases of trachea and bronchus. 519.19 includes tracheal stenosis as a subdiagnosis. 31781 and similar code 31780 are on lines 91, 308, 448.	Add 31780 and 31781 to line 49

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
20680	Removal of support implant	467 MALUNION AND NONUNION OF FRACTURE	DMAP is requesting that 20680 be paired with 733.82 Nonunion of a Fracture. There are other removal CPT codes on line 467. 20680 is on multiple lines on the List.	Add 20680 to line 467
649.0x	Tobacco use disorder complicating pregnancy, childbirth, or the puerperium	6 TOBACCO DEPENDENCE	DMAP is requesting that 649.0x be paired with S9453 Smoking cessation classes. This code is on line 6. 649.0x is on line 1 Pregnancy.	Add 649.0x to line 6
38700	Suprahyoid lymphadenectomy	312 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX	DMAP is requesting that 38700 be paired with 141.9 (Malignant neoplasm of tongue, unspecified) and several other diagnoses which are on line 312. 38700 is currently on lines 220,243,292,597,598.	Add 38700 to line 312
64719	Neuroplasty and/or transposition; ulnar nerve at wrist	216 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	DMAP is requesting that 64719 be paired with 955.2 Injury ulnar nerve. 64719 is currently on lines 441,531,550,557.	Add 64719 to line 216
97022	Application of a modality to 1 or more areas; whirlpool	216 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	DMAP is requesting that 97022 be paired with 891.2 Open wound of knee, leg (except thigh), and ankle with tendon involvement. 97022 is on more than 50 lines.	Add 97022 to line 216

Straightforward Issues—August, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
626.8	Other disorders of menstruation and other abnormal bleeding from female genital tract	446 MENSTRUAL BLEEDING DISORDERS	DMAP is requesting that 626.8 be paired with 58301 Removal of intrauterine device (IUD). 626.8 is currently on line 403 IMPERFORATE HYMEN; ABNORMALITIES OF VAGINAL SEPTUM. However, subdiagnoses of this code include “dysfunctional or functional uterine NOS.” This subdiagnosis is more appropriate for line 446 which contains 58301.	Add 626.8 to line 446

GUIDELINE NOTE 88, USE OF PROGESTERONE CONTAINING IUDS FOR NON-CONTRACEPTIVE INDICATIONS

Lines 197,446,495

Intrauterine device (IUD) insertion and removal (CPT 58300 and 58301) are included on these lines for use only with progesterone containing IUDs. These CPT codes are covered only for 1) menorrhagia (ICD-9 626.2, [626.8](#)); 2) for uterine protection in women taking estrogen replacement therapy after premature ovarian failure (ICD-9 256.3) or menopause (ICD-9 627); and 3) for uterine protection in women taking selective estrogen receptor modulators (SERMs).

V55 “Attention to” Codes

Question: should the V55 series of codes be Ancillary or on lines on the Prioritized List?

Question source: DMAP and HERC staff

Issue: Some of the V55 series of codes are currently Ancillary while others are on Prioritized List lines. In an effort to reduce the size of Line Zero, DMAP and HERC staff would like to move the codes in this series that are current Ancillary to line(s) on the Prioritized List. Note: Line 78 has all the relevant procedure codes for placement and care of the ostomies recommended for placement below.

Recommendations:

- 1) Adopt the placements suggested in the table below
- 2) Advise DMAP to remove these codes from the Ancillary List
- 3) Change title of line 78 to NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS ; ATTENTION TO OSTOMIES

ICD-9 Code	Code Description	Current Placement	Recommended Placement
V55.0	Attention to tracheostomy	Ancillary	78
V55.1	Attention to gastrostomy	Ancillary	78
V55.2	Attention to ileostomy	Ancillary	78
V55.3	Attention to colostomy	Ancillary	78
V55.4	Attention to other artificial opening of digestive tract	Ancillary	78
V55.5	Attention to cystostomy	78 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS 96 CONGENITAL ANOMALIES OF URINARY SYSTEM 351 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION	78
V55.6	Attention to other artificial opening of urinary tract	78,96,351	78
V55.7	Attention to artificial vagina	380 CONGENITAL ABSENCE OF VAGINA	380
V55.8	Attention to other specified artificial opening	Excluded	78
V55.9	Attention to unspecified artificial opening	Excluded	Excluded

Update to the Genetic Testing Guideline

Issue: NCCN has updated their colorectal cancer screening guideline. The highlighted portions of our current guideline are affected. HERC staff recommends changing the reference to the most current NCCN guideline as found in the packet.

Recommendation:

- 1) Changes to the genetic testing guideline as shown below.
 - a. Changes reference to the V1.2013 (5/13/13) NCCN guideline

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

Coverage of genetic testing in a non-prenatal setting shall be determined the algorithm shown in Figure C.1 unless otherwise specified below.

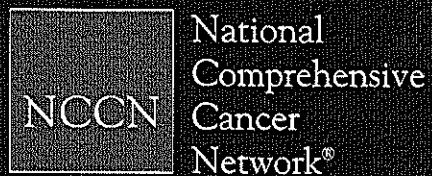
- A) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer suspected to be hereditary, or patients at increased risk to due to family history.
 - 1) Services are provided according to the Comprehensive Cancer Network Guidelines.
 - a) Lynch syndrome (hereditary colorectal and endometrial cancer) services (CPT 81292-81300, 81317-81319) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening. V.1.2013 2.2012 (4/27/12 5/13/13). www.nccn.org
 - b) BRCA1/BRCA2 testing services (CPT 81211-81217) for women without a personal history of breast and/or ovarian cancer should be provided to high risk women as defined in [GuideLineRef,,3] or as otherwise defined by the US Preventive Services Task Force.
 - c) BRCA1/BRCA2 testing services (CPT 81211-81217) for women with a personal history of breast and/or ovarian cancer and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V.1.2011 (4/7/11). www.nccn.org
 - d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V. 1.2013 2.2012 (4/27/12 5/13/13). www.nccn.org.
 - 2) Genetic counseling should precede genetic testing for hereditary cancer. Very rarely, it may be appropriate for a genetic test to be performed prior to genetic counseling for a patient with cancer. If this is done, genetic counseling should be provided as soon as practical.
 - a) Pre and post-test genetic counseling by the following providers should be covered.
 - i) Medical Geneticist (M.D.) - Board Certified or Active Candidate Status from the American Board of Medical Genetics
 - ii) Clinical Geneticist (Ph.D.) - Board Certified or Active Candidate Status from the American Board of Medical Genetics.

- iii) Genetic Counselor - Board Certified or Active Candidate Status from the American Board of Genetic Counseling, or Board Certified by the American Board of Medical Genetics.
 - iv) Advance Practice Nurse in Genetics - Credential from the Genetic Nursing Credentialing Commission.
- 3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81211) analyses is not. There is one exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).
- 4) Costs for rush genetic testing for hereditary breast/ovarian and colon/endometrial cancer is not covered.
- B) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
 - 1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.
 - 2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.
 - 3) CPT 81243, 81244, Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
 - 4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.
- c) Related to other tests with specific CPT codes:

- 1) The following tests are not covered:
 - a) CPT 81225, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
 - b) CPT 81226, CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN).
 - c) CPT 81227, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
 - d) CPT 81291, MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
 - e) CPT 81330, SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
 - f) CPT 81350, UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
 - g) CPT 81355, VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
- 2) The following tests are covered only if they meet the criteria for the Non-Prenatal Genetic Testing Algorithm AND the specified situations:
 - a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
 - b) Diagnostic testing for cystic fibrosis (CF)
 - i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81223, 81222: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
 - c) Carrier testing for cystic fibrosis
 - i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered.
 - d) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
 - e) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromboembolism; for asymptomatic family members of

patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

- f) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.
- g) CPT 81332 SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Generic testing or the alpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.
- 3) Do not cover a more expensive genetic test (generally one with a wider scope or more detailed testing) if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.



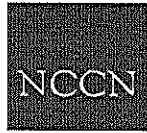
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▸ Internal medicine
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≠ Pathology
¶ Surgery/Surgical oncology
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NCCN Guidelines Panel Disclosures

Complications Involving Need for Vascular Surgery

Question: should all the bypass graft CPT codes be added to the complications of a procedure line (line 308)?

Question source: HERC staff

Issue: DMAP has requested that various bypass procedure codes be added to line 308. Line 308 contains the diagnosis codes 996.1 (Mechanical complication of other vascular device, implant, and graft), 996.62 (Infection and inflammatory reaction due to other vascular device, implant, and graft), and 996.74 (Other complications of internal (biological)(synthetic) prosthetic device, implant, and graft due to other vascular device, implant, and graft). Vascular procedure codes are all located on line 378 ATHEROSCLEROSIS, PERIPHERAL. A subset of these codes are located on line 308. HERC staff has identified many missing codes in the vascular code series which might be paired with the complications diagnosis codes found on line 308.

Recommendations:

- 1) Add all missing “bypass graft, vein” CPT codes to line 308 (CPT code series 35500-35571)
- 2) Add all missing “bypass graft, with other than vein” CPT codes to line 308 (CPT code series 35601-35671)

Epilepsy

Question: Where should various diagnoses of subtypes of epilepsy be placed on the Prioritized List?

Question source: DMAP and HERC staff

Issue: there are currently 2 epilepsy lines on the Prioritized List, one for medical treatment (line 36 EPILEPSY AND FEBRILE CONVULSIONS) and one for surgical treatment (line 182 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS). All of the epilepsy code series (ICD-9 345.x) as well as several other seizure codes are located on line 36. Only some of these codes are located on line 182. DMAP is requesting additional ICD-9 codes be paired with some of the surgical treatments.

On review, petit and grand mal seizures and infantile spasms do not have surgical interventions listed as treatments in the literature. Epilepsia partialis continua is a symptom of another condition, such as a stroke or brain tumor. 345.8x includes cursive and gelastic epilepsy. 345.9x includes epileptic seizures NOS and seizure disorder NOS.

ICD-9 Code	Code Description	Line 36	Line 182	Suggested for addition to line 182
345.1x	Generalized convulsive epilepsy	X	X	
345.2	Petit mal status	X		
345.3	Grand mal status	X		
345.4x	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures	X	X	
345.5x	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures	X	X	
345.6x	Infantile spasms	X		
345.7x	Epilepsia partialis continua	X		
345.8x	Other forms of epilepsy and recurrent seizures	X		
345.9x	Epilepsy, unspecified	X		X

Recommendation

- 1) Add 345.9x (Epilepsy, unspecified) to line 182 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS

Coding Specifications for ICD-10 Prioritized List

Question: What will the new coding specifications look like as part of ICD-10 Prioritized List?

Question Source: HERC Staff

Issue: All the coding specifications needed to be updated with ICD-10 codes. Most of these resulted in minor adjustments, but some coding specifications were added or deleted based on refinement of the codes.

HERC Staff Recommendations:

- 1) Approve the following coding specifications with updated codes and placements:

Line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

CPT code 96110 can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

- **Changes made:** this will be on Lines 3 and 4 in the interim list

Line:30 TYPE II DIABETES MELLITUS

CPT codes 43644-43645 and 43846-43848 (Roux-En-Y gastric bypass) and 43770-43775 (laparoscopic adjustable gastric banding) are only included on this line as treatment according to the requirements in Guideline Note 8 when paired with:

- 1) a primary diagnosis of E11 (Type II Diabetes with or without complication);
 - 2) a secondary diagnosis of E66.01, E66.09, E66.2, E66.8 or E66.9 (Obesity);
- AND,
- 3) a tertiary diagnosis code of Z68.35-Z68.39 or Z68.4.

- **Changes made:** ICD-10 codes replaced ICD-9 codes

Line:88 DIABETES MELLITUS WITH END STAGE RENAL DISEASE

SPK included for type I diabetes mellitus with end stage renal disease (E10.2),

PAK only included for other type I diabetes mellitus with secondary diagnosis of Z94.0.

- Changes made: ICD-10 codes replaced ICD-9 codes

~~Line: 162 NON-HODGKIN'S LYMPHOMAS~~

~~Malignant and systemic mastocytosis (202.3) are included on Line 221. Mastocytosis limited to the skin (757.3) resides on Line 688.~~

- Changes made: Delete entire coding specification. This is no longer necessary as ICD-10 allows the distinction between malignant, systemic, and skin mastocytoses.

Line:209 SUPERFICIAL ABSCESES AND CELLULITIS

Spastic dysphonia (478.79) is not included on this line, but on Line 583.

- See separate issue summary .

Line:231 INTESTINAL MALABSORPTION

ICD-10-CM code K90.89 (Other intestinal malabsorption) is included on this line only for chronic steatorrhea, exudative enteropathy, and protein-losing enteropathy.

- Changes made: ICD-10 code replaced ICD-9 code

Line:266 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS

ICD-10-CM code I87.1 is included on this line for superior vena cava syndrome only.

- Changes made: ICD-10 code replaced ICD-9 code

Line:292 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX

ICD-10-CM code D11.0 is included on this line only for parotid gland pleomorphic adenomas.

- Changes made: ICD-10 code replaced ICD-9 code

Line:297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS

Spinal cord stimulation (63655-63688) is not included on this line when paired with G90.5x Complex regional pain syndrome/reflex sympathetic dystrophy.

- Changes made: ICD-10 code replaced ICD-9 code, and “complex regional pain syndrome” descriptor added

Line:312 CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE

Liver-kidney transplant only included on this line for a documented diagnosis of Q44.6 Caroli's disease

- Changes made: ICD-10 code replaced ICD-9 code

Line:331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION

ICD-10-CM codes N40.1 and N40.3 are only included on this line when post-void residuals are at least 150 cc's.

- Changes made: ICD-10 codes replaced ICD-9 codes

Line:359 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE

Knee arthroscopy (29871, 29873-29876, 29884-29887) is not included on this line

when paired with osteoarthritis/osteoarthrosis of the knee (M17.0-M17.9).

- Changes made: ICD-10 codes replaced ICD-9 codes

Line:364 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND STENOSIS

Chemodenervation with botulinum toxin injection (CPT 64612-64614) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD-10-CM G24.9).

- Changes made: ICD-10 codes replaced ICD-9 codes

~~**Line 440 PREGANEROUS VULVAR CONDITIONS**~~

~~ICD-9 701.0 is included on this line only for the diagnosis of lichen sclerosis.~~

- Changes made: Coding specification deleted as now ICD-10 allows for distinction of vulvar lichen sclerosis

Line:449 ADJUSTMENT DISORDERS

ICD-10-CM codes Z71.89, Other specified counseling, and Z63.4 Disappearance and death of family member are only included in this line when identified as secondary diagnoses with a primary diagnosis of F43.8, Other Specified Adjustment Reactions.

- Changes made: ICD-10 codes replaced ICD-9 codes

Spastic Dysphonia

Question: How should spastic dysphonia be handled on the ICD-10 Prioritized List?

Question source: DMAP/HERC staff

Issue: the ICD-10 code for spastic dysphonia is no longer specific (R49.0 Dysphonia). This code includes “hoarseness” and is in the signs and symptoms portion of the coding schema. R49.0 should be Diagnostic, to allow for the diagnostic work up of hoarseness.

J38.3 (Other diseases of vocal cords) can be used for spastic dysphonia. This code could be placed on the current spastic dysphonia line, 583 SPASTIC DYSPHONIA. It also includes various abscess conditions of the vocal cords, and should be included on line 214 SUPERFICIAL ABSCESES AND CELLULITIS.

HERC Staff Recommendation

- 1) Advise DMAP to place R49.0 on the Diagnostic List
- 2) Place J38.3 on Line 583 SPASTIC DYSPHONIA and keep on line 214
 - a. Add the following coding specification to lines 214 and 583
 - i. “ICD-10 J38.3 is included on line 214 for treatment of abscesses and cellulitis of the vocal cords; it is included on line 583 for treatment of spastic dysphonia,”
 - b. Delete the current coding specification on line 214
 - i. ~~“Spastic dysphonia (478.79) is not included on this line, but on Line 583~~
 - c. Add the following coding specification to line 538
 - i. “R49.0 is located on the Diagnostic List for use for the work-up of hoarseness.”