



**Health Evidence Review  
Commission's  
Evidence-based Guideline  
Subcommittee**

**September 3, 2015  
2:00 PM**

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

# Section 1.0

## Call to Order

## AGENDA

### EVIDENCE-BASED GUIDELINES SUBCOMMITTEE (EbGS)

September 3, 2015

2:00pm - 5:00pm

Meridian Park Medical Center  
Community Health Education Center Room 117B&C  
Tualatin, Oregon

*Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed. Please sign-in to testify.*

#	Time	Item	Presenter
1	2:00 PM	Call to Order	Wiley Chan
2	2:05 PM	Review of June, 2015 minutes	Wiley Chan
3	2:10 PM	Staff update	Darren Coffman
4	2:15 PM	Nitrous oxide for labor pain <ul style="list-style-type: none"><li>Review initial draft Coverage Guidance and approve for public comment posting</li></ul>	Val King Cat Livingston
5	3:40 PM	<b>Topic rescan</b> Scope documents <ul style="list-style-type: none"><li>Neuroimaging for headache</li><li>Cervical cancer screening</li><li>Induction of labor</li><li>Recurrent acute otitis media</li></ul> Search results <ul style="list-style-type: none"><li>Coronary Artery Calcium Scoring</li><li>Coronary CT angiography</li><li>ADHD</li></ul>	Adam Obley
6	4:50 PM	Confirmation of the next meeting, November 5, 2015	Wiley Chan
7	4:55 PM	Next Topics	Cat Livingston
8	5:00 PM	Adjournment	Wiley Chan

*Note: All agenda items are subject to change and times listed are approximate*

## MINUTES

### Evidence-based Guidelines Subcommittee

Meridian Park Community Health Education Center, Room 117B&C

19300 SW 65th Avenue, Tualatin, OR

June 4, 2015

2:00-5:00pm

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**Members Present:** Wiley Chan, MD, Chair; Eric Stecker, MD, MPH (joined at 2:30), Vice-Chair; Kathryn Lueken, MD (by phone); Vern Saboe, DC; Beth Westbrook, PsyD; George Waldmann, MD; Bob Joondeph, JD (by phone).

**Members Absent:** None

**Staff Present:** Darren Coffman; Catherine Livingston, MD, MPH; Jason Gingerich.

**Also Attending:** Adam Obley, MD, Val King MD, MPH, and Aasta Thielke, OHSU Center for Evidence-based Policy, Carol Levanda, Sharron Fuchs, Duncan Neilson, MD (Legacy Health), Kimberly Kincade and Silke Akerson (Oregon Midwifery Council), Colleen Forbes (Direct Entry Midwifery Board).

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### 1. CALL TO ORDER

Wiley Chan called the meeting of the Evidence-based Guidelines Subcommittee (EbGS) to order at 2:00 pm.

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### 2. MINUTES REVIEW

In review of the April 2, 2015 minutes, Leda Garside's transition from EbGS to HTAS was omitted.

**Minutes approved as corrected 6-0 (Stecker not present).**

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### 3. STAFF REPORT

Coffman reported that George Waldmann has officially joined the subcommittee. In addition he reported that HERC authorized staff to remove the Coverage Guidance Development Framework from coverage guidances, as it was causing confusion. HERC also authorized staff to work on a revised GRADE table format that will hopefully aid in decisionmaking and presentation of factors leading to a decision. Furthermore, an updated evidence search and clearer definitions of scope (including identification of critical and important outcomes) will be added to the coverage guidance process to minimize rework and simplify public comment.

He also reported that Stecker volunteered to be vice-chair. Chan nominated Stecker as vice-chair. The motion was approved 6-0 (Stecker not present).

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#### 4. PLANNED OUT-OF-HOSPITAL BIRTH

Valerie King reported the results of a new systematic review she performed in order to address the subcommittee's questions about the safety of out-of-hospital birth for primiparous women. Regardless of planned birth location, risk of adverse neonatal outcomes is higher when the mother has not given birth before. Increased risk for planned out-of-hospital birth for primiparous women appears higher than planned in-hospital birth, though the differences are not statistically significant. There was minimal discussion.

Livingston then led the discussion of the High Risk Conditions List/Dispo document. The subcommittee discussed row 9 regarding intrapartum third- and fourth-degree lacerations. After discussion the subcommittee made intrapartum fourth-degree lacerations and third-degree lacerations requiring hospital repair a criterion for transfer, with intrapartum third-degree lacerations not requiring hospital repair requiring consultation.

A member of the audience said that the concern underlying her comment on the intrapartum lacerations was that some midwives have arrangements with providers who can do these repairs in the home setting. Therefore there would be a transfer of care but not to a hospital setting; however, the coverage recommendation language requires transfer to a hospital. Waldmann said it would be difficult to make a black and white delineation because providers' skill levels vary widely. Chan asked if the proposed change to allow third-degree not requiring hospital repair to be done in the home would address the concern. Cheyney said that it would. In this situation a third-degree laceration not requiring hospital repair could be repaired in the home by an experienced licensed direct-entry midwife, a certified nurse midwife or a physician.

Discussion then moved to rows 31 and 32 regarding small for gestational age and fetal growth retardation. The subcommittee accepted staff recommendations for these items as exclusion criteria without discussion. For prelabor rupture of membranes, the recommendation for exclusion of coverage will remain at 24 hours per the staff recommendation.

For genital herpes, the subcommittee clarified that only a current active infection (outbreak) would necessitate a hospital birth. As discussion progressed, the subcommittee decided to separate the recommendations for chickenpox and rubella, as rubella anytime during pregnancy requires planned hospital birth, whereas chickenpox only requires hospital birth if the infection is active at the time of birth. The subcommittee discussed varicella syndrome but agreed that fetuses with varicella syndrome due to exposure early in pregnancy has a relatively low risk of harm but if harm occurred there would be a different qualifying reason for a hospital birth.

Livingston discussed the comment regarding thick meconium staining with the possibility of imminent birth. After brief discussion the subcommittee accepted the staff recommendation of hospital transfer. The guidance has language for a variety of indicators where transfer is appropriate but not practical due to imminent birth.

For retained placenta, the subcommittee accepted the staff recommendation to require transfer but discussed that a home birth attendant might initiate care at home. The subcommittee agreed with the staff recommendation to add a time limit of 60 minutes, following the NICE definition of retained placenta, rather than the 3 hours used by the Oregon Birth Center criteria. Regarding the suggestion to require a defined system of transfer, the subcommittee affirmed its previous decision not to require this because it may be difficult for home birth attendants to obtain this due to liability concerns of hospital-based providers.

For low maternal hemoglobin levels, the subcommittee accepted the staff recommendations in the meeting materials. On the public comment regarding history of a strep B septic infant, the subcommittee decided to make no change. This recommendation differs from the NICE recommendation because there is no antenatal strep testing in Britain. Livingston noted that some women who choose home birth may refuse strep testing or antibiotics. Others noted that these women might refuse antibiotics in the hospital as well, though hospital management might help the infant in such cases. A member of the audience said she found it difficult to believe a mother whose prior infant had this condition would refuse antibiotics.

For hypertension (exclusion), thrombocytopenia/thrombopenia (exclusion) and chorioamnionitis (transfer to hospital), the group decided to follow the staff recommendation.

For blood group compatibility, the subcommittee decided to change the language to “Blood group incompatibility with atypical antibodies, or Rh sensitization” as a requirement for planned hospital birth.

For substance abuse, the subcommittee had extensive discussion about the risks associated with various substances at various levels of use and times of pregnancy. Westbrook suggested requiring consultation for mild or moderate levels of substance use or dependence, with higher levels requiring hospital birth. After discussion, the subcommittee decided not to require consultation for these levels, because home birth attendants may not be trained in the nuances of DSM-5. After discussion the subcommittee authorized Livingston to refine language for the criterion requiring hospital birth after consulting with members with behavioral health expertise and the Chair before the draft is sent to HERC.

For primiparity, Livingston reviewed the request to make it an indication for hospital birth. Based on the review presented by King earlier in the meeting, the subcommittee elected to make no change to the coverage guidance.

Livingston offered an opportunity for additional public comment but no one wished to comment.

Livingston then reviewed the changes to the coverage recommendation (box) language, including the extensive revisions to the first two paragraphs to clarify that this is a coverage recommendation, not a clinical practice guideline. Chan expressed some concern that the transfer criteria still sound like a guideline, but no better proposal was suggested. After correction of a typographical error, the subcommittee accepted the recommended language.

The subcommittee made changes to the coverage recommendations to match the decisions made above, and reviewed the changes made in response to discussion during the last meeting. A member of the audience said that many patients electing out of hospital birth have low risk for HIV, and expressed concern that there would be an outcry if they were ‘forced’ to have an HIV test. The subcommittee elected not to make a change because of the preventable risk to the baby if there were an undetected HIV infection.

Cheyney raised a concern about the inclusion of prior cesarean section in the criteria for which hospital birth is required in order for there to be coverage. There had been a report that women with a prior cesarean who had also had a vaginal birth had lower risk than primiparous women. King said she consulted with the author and got additional information on this study. The adjusted risk for nulliparous women is actually lower than for trial of labor after cesarean (TOLAC). She also said that in review of world literature, she found numerous studies reporting

neonatal death in home births. Most frequently, the pregnancies resulting in neonatal death met one of the following risk criteria: >42 weeks gestation, breech presentation, twins, prior c-section or myomectomy through the uterine wall. In addition, unlike the risks for nulliparous women, the risk with TOLAC is uterine rupture, which happens suddenly, without time for a safe transfer to hospital.

Neilson asked whether a prior successful vaginal birth after cesarean might lower the risk. King said these women have a significantly lower rate of cesarean than a primiparous woman. However the rapidity with which a complication would occur is still quite different.

An audience member then asked whether the definition of history of retained placenta requiring surgical removal included a manual removal. Livingston said manual removal requires consultation, while a surgical removal would require hospital birth.

There was further public comment and discussion regarding the HIV test. The subcommittee discussed the alternative of requiring the baby to be tested, but this might not be practical in the out-of-hospital setting. While recognizing strong preferences of some women to avoid HIV testing, the subcommittee based their rationale on the risks of vertical transmission outweighing cultural preferences of the mother in cases where the health plan would pay for the out-of-hospital birth. The subcommittee decided that for both HIV and hepatitis B, because of the ethical duty and medical ability to intervene, results of this testing would be required for out of hospital birth to be recommended for coverage.

The subcommittee discussed some ambiguity with the criteria related to prior pregnancy; in some cases the bulleted language includes the words “history of,” and in other cases it does not. The subcommittee asked staff to make this consistent before sending to the HERC.

A member of the audience asked that the language around hypertension be clarified with specific blood pressure levels greater than or equal to 140 systolic or 90 diastolic and be in line with the NICE guidelines both as a requirement for planned hospital birth as well as a criteria for transfer if it occurs during labor. The subcommittee clarified this as their intent.

The subcommittee discussed that a number of licensure and practical issues have arisen in the course of development of this coverage guidance. There was a proposal to make a formal request of the licensure board to think about distance from the hospital (is 30 minutes too long?) and to address some of the other practice issues that arose during conversation.

#### **DRAFT HERC COVERAGE GUIDANCE**

Planned out-of-hospital (OOH) birth is recommended for coverage for women who do not have high-risk coverage exclusion criteria as outlined below (*weak recommendation*). This coverage recommendation is based on the performance of appropriate risk assessments<sup>1</sup> and the OOH birth attendant’s compliance with the consultation and transfer criteria as outlined below.

Planned OOH birth is not recommended for coverage for women who have high risk coverage exclusion criteria as outlined below, or when appropriate risk assessments are not performed, or where the attendant does not comply with the consultation and transfer criteria

as outlined below (*strong recommendation*).

**High-risk coverage exclusion criteria:**

*Complications in a previous pregnancy:*

- Cesarean section or other hysterotomy
- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy
- HELLP syndrome
- Placental abruption with adverse outcome
- Pre-eclampsia requiring preterm birth
- Eclampsia
- Uterine rupture
- Retained placenta requiring surgical removal
- Fourth-degree laceration without satisfactory functional recovery

*Complications of current pregnancy:*

- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Pre-existing chronic hypertension
- Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Multiple gestation
- Non-cephalic fetal presentation
- Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa
- Eclampsia or pre-eclampsia
- Placental abruption/abnormal bleeding
- Anemia – hemoglobin less than 8.5 g/dL
- Induction of labor
- Drug or alcohol use with high risk for adverse effects to fetal or maternal health
- Recurrent antepartum hemorrhage
- IUGR (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)
- Abnormal fetal heart rate/Doppler/surveillance studies
- Oligohydramnios or polyhydramnios
- Blood group incompatibility with atypical antibodies, or Rh sensitization
- Prelabor rupture of membranes > 24 hours
- Life-threatening congenital anomalies
- Unknown HIV or Hepatitis B status
- Current active infection of varicella
- Rubella infection anytime during pregnancy
- Active infection (outbreak) of genital herpes
- Refractory hyperemesis gravidarum
- Thrombosis/thromboembolism/ thrombocytopenia (platelets <100,000), or other maternal bleeding disorder
- Uteroplacental insufficiency
- Molar pregnancy

- Maternal mental illness requiring inpatient care
- Diabetes, type I or II, uncontrolled gestational diabetes, or gestational diabetes controlled with medication

**Transfer criteria:**

If out-of-hospital birth is planned, certain intrapartum and postpartum complications may necessitate transfer to a hospital to meet coverage criteria. For these indications, an attempt should be made to transfer the mother and/or her newborn; however, imminent fetal delivery may delay or preclude actual transfer prior to birth.

- Non-cephalic fetal presentation
- Eclampsia or pre-eclampsia
- Placental abruption/abnormal bleeding
- Anemia – hemoglobin less than 8.5 g/dL
- Current active infection of varicella at the time of labor
- Current active infection (outbreak) of genital herpes at the time of labor
- Repetitive or persistent abnormal fetal heart rate pattern
- Thick meconium staining of amniotic fluid
- Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or raised systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Chorioamnionitis or other serious infection (including toxoplasmosis, rubella, CMV, HIV, etc.)
- Failure to progress/failure of head to engage in active labor
- Prolapsed umbilical cord
- Uterine rupture, inversion or prolapse
- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Temperature  $\geq 38.0$  C
- Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourth-degree trauma)
- Enlarging hematoma
- Infection (endometritis, UTI, wound, breast)
- Thrombophlebitis/thromboembolism
- Bladder or rectal dysfunction

If the infant is delivered out-of-hospital, the following complications require transfer to a hospital for the out-of-hospital birth to meet coverage criteria:

- Low Apgar score (< 5 at 5 minutes, < 7 at 10 minutes)
- Temperature instability, fever, suspected infection or dehydration
- Hypotonia, tremors, seizures, hyperirritability
- Respiratory or cardiac irregularities, cyanosis, pallor
- Weight less than 5th percentile for age
- Unexpected significant or life-threatening congenital anomalies
- Excessive bruising, enlarging cephalohematoma, significant birth trauma
- Hyperglycemia/hypoglycemia unresponsive to treatment
- Vomiting/diarrhea

**Consultation criteria:**

Certain high risk conditions require consultation (by a provider of maternity care who is credentialed to admit and manage pregnancies in a hospital) for coverage of a planned out-of-hospital birth to be recommended. These complications include (but are not limited to) patients with:

*Complications in a previous pregnancy:*

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- Blood group incompatibility
- Pre-eclampsia, not requiring preterm birth
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy
- Cervical insufficiency/prior cerclage
- Unresolved intrauterine growth restriction (IUGR) or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)
- Third degree laceration; Fourth-degree laceration with satisfactory functional recovery
- Perinatal death
- Child with congenital and/or hereditary disorder
- Baby > 4.5 kg or 9 lbs 14 oz
- Unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty
- Shoulder dystocia, with or without fetal clavicular fracture
- Postpartum hemorrhage requiring additional pharmacologic treatment or blood transfusion
- Retained placenta requiring manual removal

*Complications of current pregnancy:*

- Fetal macrosomia (estimated weight >4.5 kg or 9 lbs 14 oz)
- Family history of genetic/heritable disorders
- History of maternal seizure disorder (excluding eclampsia)
- Laparotomy during pregnancy
- Cervical dysplasia requiring evaluation
- Gestational diabetes, diet-controlled
- Maternal mental illness under outpatient psychiatric care
- Maternal anemia with hemoglobin < 10.5 g/dL
- Third-degree laceration not requiring hospital repair
- Confirmed intrauterine death
- Maternal seizure disorder (excluding eclampsia)
- Inadequate prenatal care (defined as less than five prenatal visits or care began in the third trimester)
- Body mass index at first prenatal visit of greater than 35 kg/m<sup>2</sup>

<sup>1</sup>Risk assessment should be done initially when planning the location of birth, and updated throughout pregnancy, labor, and delivery to determine if out-of-hospital birth is still appropriate (*weak recommendation*).

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## 5. ADJOURNMENT

The meeting was adjourned at 5:00 pm. The next meeting is scheduled for September 3, 2015 from 2:00-5:00pm in Room 117B&C of the Meridian Park Hospital Community Health Education Center in Tualatin.

DRAFT

# Section 2.0

## Coverage Guidance Review

**HEALTH EVIDENCE REVIEW COMMISSION (HERC)**  
**COVERAGE GUIDANCE: NITROUS OXIDE FOR LABOR PAIN**  
**DRAFT for EbGS Meeting Materials 9/3/2015**

**HERC Coverage Guidance**

Nitrous oxide for labor pain is recommended for coverage (*weak recommendation*).

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

## **PLAIN LANGUAGE SUMMARY**

[Staff will insert lay language summary once the coverage guidance has been reviewed by subcommittee]

## **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 OVERVIEW**

### **Clinical background**

Annually, approximately 45,000 births occur in Oregon (Oregon Health Authority, 2015) and childbirth pain is a major concern among women (Likis et al., 2012). Pain relief is most commonly delivered through epidural anesthesia in the United States, with 61% of women who had singleton births through vaginal delivery electing an epidural anesthesia (Centers for Disease Control and Prevention, 2011; Likis, et al., 2012). For women interested in other types of pain relief or in delaying the timing of an epidural, there are several options including inhaled nitrous oxide (N<sub>2</sub>O, also known as "laughing gas"), other

inhaled anesthetic gases, opioids, paracervical or pudendal block, transcutaneous electrical nerve stimulation, hydrotherapy, sterile water injections, and psychoprophylaxis (Likis et al., 2012).

Inhaled nitrous oxide is a non-invasive form of pain relief. Commonly used in dentistry, nitrous oxide provides a diminished sense of pain and provides some antianxiety effects (Likis et al., 2012). In comparison to epidural anesthesia, women using nitrous oxide for pain management retain their full mobility. Individuals experience the maximum effect of nitrous oxide 30 to 60 seconds after inhalation. The effects of nitrous oxide wear off quickly and other types of pain management methods can be used in a relatively short time period after the use of nitrous oxide (Likis et al., 2012).

In the Portland-Metro region, an epidural adds an additional \$1,050 to \$2,400 to the cost of a hospital birth (Providence Health Services, 2015). The use of nitrous oxide costs significantly less with estimates ranging from \$15 to \$100 per patient.

## Indications

Inhaled nitrous oxide can be used in the first or second stages of labor and is indicated for pregnant women in labor intending a vaginal birth. Nitrous oxide can also be used in the third stage of labor to assist with managing pain that may occur during immediate postpartum procedures (e.g., perineal repair, manual placenta removal).

## Technology description

Inhaled nitrous oxide is widely used for childbirth pain relief outside of the United States and is a common form of non-invasive pain relief during childbirth (Klomp, van Poppel, Jones, Lazet, Di Nisio & Lagro-Janssen, 2012). Nitrous oxide is a non-flammable, tasteless, odorless gas that is self-administered on demand by laboring women through a mouth piece or facemask (Collins, Starr, Bishop, Baysiner, 2012; Klomp et al., 2012). Inhaled nitrous oxide is typically administered as a 50% nitrous oxide / 50% oxygen combination. It can be administered at this concentration using a blender device (e.g., Nitronox®) or as a premixed gas (e.g., Entonox®). Entonox® is not currently available in the U.S., but appropriate types of blender equipment are available for hospital and out-of-hospital use.

## Key questions

The following key questions (KQ) guided the evidence search and review described below. For additional details about the review scope and methods please see Appendix B.

KQ1: What are the effects on mode of birth, use of neuraxial (e.g. epidural) analgesia and maternal satisfaction when nitrous oxide is used for labor analgesia?

KQ2: What are the maternal and fetal/neonatal harms of nitrous oxide used for labor pain?

## Evidence review

Two systematic reviews (SR) (Klomp et al., 2012; Likis et al., 2012) identified in the core source search address the use of nitrous oxide for pain management during labor. Both SRs were of good methodological quality. The AHRQ SR (Likis, 2012; Likis, 2014) was selected as the index SR and is the

primary evidence source for this coverage guidance because it is more comprehensive and matches the scope of the HERC’s key questions better. In addition, the Cochrane SR (Klomp, 2012) did not add eligible studies or other information which were not included in the AHRQ SR. For further details on the methods of this evidence review please see Appendix B. The included study characteristics for the AHRQ SR are outlined below in Table 1.

**Table 1. Overview of Index Systematic Review**

Citation	Total Studies Included	Included Studies Specifically Addressing Coverage Guidance Scope
Likis et al (2012, 2014) [AHRQ SR]	59 studies (13 RCTs, 7 crossover RCTs, 4 non-randomized clinical trials, 14 prospective cohorts, 1 retrospective cohorts, 3 case series, 4 case-control studies, 11 cross sectional studies, and 2 trend studies)	<ul style="list-style-type: none"> <li>• 14 studies (5 RCTs; 8 prospective cohorts 1 case-series) for fetal/neonatal harms</li> <li>• 3 studies (2 prospective cohort studies, 1 cross-sectional study) for mode of delivery</li> <li>• 10 studies (7 RCTs; 2 prospective cohorts; 1 cross-sectional study) for maternal adverse effects</li> <li>• 2 studies (both cross-sectional studies) for use of neuraxial (e.g. epidural) anesthesia</li> </ul>

### Evidence from additional sources

No additional evidence sources were included in this review. A MEDLINE® (Ovid) search based on the search strategy of the AHRQ SR did not locate any additional eligible studies.

### EVIDENCE SUMMARY

The AHRQ SR (Likis, 2012) included a total of 59 studies reported in 58 publications (13 RCTs, 7 crossover RCTs, 4 non-randomized clinical trials, 14 prospective cohorts, 1 retrospective cohorts, 3 case series, 4 case-control studies, 11 cross sectional studies, and 2 trend studies) to answer five key questions on the following issues: 1) effectiveness for pain (21 studies); 2) comparative effectiveness for women’s satisfaction with their birth experience and pain management (9 studies); 3) effect on mode of birth (6 studies); 4) maternal and fetal/neonatal adverse effects (49 studies); and 5) health system factors influencing the use of nitrous oxide (no studies). Key Questions 2, 3 and 4 are directly applicable to this coverage guidance.

Most of the studies in the full AHRQ SR included comparator interventions that are not of interest for this guidance (comparators included other inhaled anesthetic gasses, most of which are not used in the U.S., alternative concentrations of N2O; parenteral opioids and non-pharmacologic techniques not widely available or used in the U.S.). Many of the studies used different concentrations of N2O compared to the 50% N2O/50% oxygen mix that is used in most labor and delivery settings in countries such as the United Kingdom (U.K.) and which is the concentration used in U.S. settings that have

adopted it for obstetric use. Most included studies did not report on populations or outcomes of interest for this guidance (e.g. pain scores, occupationally exposed workers). Some populations of interest (e.g. women in the third stage of labor requiring procedural analgesia such as for manual placental removal) were not explicitly included among the studies identified in the AHRQ SR. No study directly addressed or was designed to address whether use of N2O reduces the use of neuraxial (e.g. epidural) analgesia; we were only able to address this outcome descriptively. None of the included studies that did address the questions of interest for this evidence review were conducted in the U.S., although all were conducted in developed countries with modern maternity care systems. However, differences in health systems, provider training, hospital routines and patient expectations may limit the applicability of these studies to the U.S. context.

Although pain was not selected as a key outcome for this guidance, for background context, the AHRQ SR found that N2O is less effective than epidural anesthesia for measures of pain in labor, but that the evidence was insufficient to determine the effectiveness compared with other, non-epidural pain management interventions. The studies are limited because of poor quality, use of varying outcome measures, and inconsistency. The review found no studies that met inclusion criteria and studied the systems factors related to using N2O for management of labor pain, including provider preferences, availability, settings and resource utilization.

### **Critical Outcome: Fetal/neonatal adverse effects**

The AHRQ SR (Likis, 2012) noted that while 49 studies reported on maternal, fetal, neonatal, or occupational harms associated with N2O use in labor, that 16 of these were conducted prior to 1980 when it was usual practice to combine N2O with other sedative, tranquilizing and anesthetic agents. Although N2O is transmitted via the placenta to the fetus, it is also quickly eliminated via maternal circulation and neonatal respiration. Twenty-nine studies included fetal or neonatal harms as outcomes. The SR found no significant differences between any comparison groups in Apgar scores at either one or five minutes after birth. Eight studies reported umbilical cord blood gasses. There was one study that compared infants of women using 50% N2O/50% oxygen to epidural anesthesia. It found that 7% of the N2O group had Apgar scores less than or equal to seven at one minute after birth compared to 6% of infants of women who used epidurals. At five minutes, the proportions with low Apgar scores were 1% and 4%, respectively (p values not reported). There was a statistically significant finding in one study of lower arterial cord blood gasses among infants of primiparous women who used N2O plus meperidine (a parenteral opioid) compared to those who used an epidural (pH 7.21 vs. pH 7.29, p<0.01). Use of meperidine alone has been associated with lower umbilical cord gasses and so it is not clear whether this finding can be attributed to N2O use or only to use of meperidine. The AHRQ SR was unable to analyze neonatal intensive care unit admission because of the varying definitions of intensive care across countries and lack of reporting of this outcome.

Only one study included in the AHRQ SR compared neonatal neurobehavioral outcomes among infants of women using N2O and who used other methods of labor pain management, including epidurals, opioids, TENS, and non-pharmacologic methods. This study reported no significant differences between groups in neonatal adaptive capacity scores (NACS).

## Critical Outcome: Mode of birth

Six studies in the AHRQ review compared the mode of birth among women who used N2O to women who used other methods of pain relief and determined that there was insufficient evidence, primarily due to poor quality studies and inconsistent results. However, only three studies compared the intervention and comparator of interest for this guidance. One prospective cohort study from Ireland, published in 1987, enrolled primiparous women in an academic hospital. Twenty women used N2O and 50 women used epidural anesthesia. Other comparison groups in the study used TENS or parenteral opioids. Another prospective cohort study from Finland, published in 1994, included 210 women (27% primiparas) using N2O and 82 women (71% primiparas) using epidural anesthesia. This study also found higher rates of vaginal birth among women using N2O. No analysis of the results by parity was provided in the AHRQ SR. These two studies found the following proportions of women with vaginal, assisted vaginal (vacuum or forceps), Cesarean, or vaginal breech births as described in Table 2 below. No statistical testing of differences between pain management groups were reported in either study.

**Table 2. Mode of Birth According to Pain Management Approach**

Mode of Birth	Nitrous Oxide*	Epidural*
Vaginal	60%/95%	26%/80%
Assisted	35%/2%	62%/11%
Cesarean	0%/3%	6%/9%
Breech	5%/NR	6%/NR

NR: not reported

\* The first percentage in each cell represents the Irish study and the second percentage is from the Finnish study.

One cross sectional study conducted in the U.K. and published in 1982 also reported the mode of birth. This U.K.-based study included women (51.4% primiparous) who had vaginal births and found that women who used N2O (n=128) were more likely to have a spontaneous vaginal birth and less likely to have an assisted vaginal birth compared with women who used epidural anesthesia (n=423) or women who used an epidural and N2O together (n=38). Proportions who had a vaginal birth for each of these three groups were 93.7%, 48.7%, and 60.5% and for assisted vaginal birth the proportions were 6.3%, 51.3%, and 39.5%.

Consistent with reported mode of birth outcomes, three of these studies (two prospective cohort studies and one cross sectional study) also reported shorter duration of labor for women in the N2O groups compared to the epidural groups. The reported duration of labor in the N2O groups ranged from a mean of 5.2 hours +/- 1.7 (standard deviation [S.D.]) to 6.7 +/- 3.0 hours. The reported range among women using epidural anesthesia was 7.7 +/- 2.4 hour to 10.8 +/- 4.9 hours.

## Important Outcome: Maternal adverse effects

Most harms reported by studies included in the AHRQ SR were unpleasant side effects of N2O such as nausea, vomiting, dizziness and drowsiness. Some commonly reported adverse effect outcomes (e.g.

nausea and oxygen desaturation) are reported often among women in labor regardless of pain management strategies used. Studies did not have adequate power to detect rare outcomes. Eight studies of women receiving N2O as the sole pain management agent report rates of nausea from 0% to 28%. Four of these studies also reported vomiting with a range of 0% to 14%. Four studies of women using N2O as the sole analgesia agent reported dizziness or lightheadedness, with rates ranging from 3% to 23%. Four studies reported drowsiness or sleepiness with sole use of N2O and proportions ranged from 0% to 67%.

## **Important Outcome: Maternal satisfaction**

Nine studies in the AHRQ SR evaluated women's satisfaction with their birth experience or pain management, although most were of poor quality and reported varying outcome measures, making it difficult to synthesize results. However, the AHRQ authors concluded that there was low strength of evidence to support the equivalence or superiority of N2O relative to maternal satisfaction outcomes. Among the three studies that specifically evaluated use of 50% N2O / 50% oxygen compared with epidural anesthesia, two studies (two prospective cohorts) evaluated women's satisfaction with labor pain management at various points in time between one hour and three days post-delivery. They both reported that women who used N2O were somewhat less satisfied with the adequacy of pain relief for N2O compared to epidural anesthesia. Satisfaction scores ranged from 60% to 90% for the N2O group and 98% to 100% for the epidural group in the prospective cohort study. Because N2O is not assumed or designed to achieve the same degree of pain relief as epidural anesthesia this is not considered by the AHRQ researchers to be as robust of an outcomes as is women's assessment of whether they would use the method again. One prospective cohort study conducted in Ireland found that 80% of women who used N2O would request the method again in a subsequent pregnancy compared with 88% of women who used an epidural. In a cross-sectional study performed in Sweden that evaluated this outcome, 69.9% of women who used N2O would request it in another pregnancy compared to 45.3% of women who used an epidural.

## **Important Outcome: Use of neuraxial analgesia in labor**

The AHRQ SR did not report on this outcome. However, the two cross sectional studies (one from the U.K. and one from Sweden) that reported outcomes for groups of women choosing N2O and epidural anesthesia, respectively, do give some information on the methods that women choose when both choices are freely available. The U.K. based study, published in 1982, included only women who had a vaginal birth and approximately half were primiparous. Of 1000 women, about 13% used N2O, 42% used epidurals, and 4% used both methods. Other methods used in this study included parenteral opioids, pudendal or regional anesthetic blocks, no pharmacologic pain management, and combinations of these methods. The Swedish cross-sectional study, published in 1996, gathered data on women who had used N2O, epidural, local anesthesia, acupuncture, hydrotherapy, and breathing techniques as their primary pain management technique. About 79% of women used N2O and 34% used epidural (categories were not mutually exclusive and thus some women who started with N2O may have also used epidurals or other techniques).

## **OTHER DECISION FACTORS**

### **Resource Allocation**

The cost of N2O for labor is low (\$15 to \$100 per patient). The major cost is for the delivery equipment, which is borne by the facility or provider. The costs of the comparator intervention are relatively high (\$1,050 to \$2,400 per patient per epidural in the Portland metropolitan area). Use of N2O is associated with lower rates of assisted vaginal birth and cesarean delivery which would potentially result in significantly lower intrapartum costs. For some women who use both N2O and an epidural during the same labor, anesthesia costs of care could increase over use of an epidural alone. However, this combination may still result in higher vaginal birth rates and thus lower total costs of care. The literature review found that the length of labor was consistently shorter (about 2 to 4 hours shorter) among women using N2O analgesia compared to women using epidural anesthesia such that increased use of N2O may also result in somewhat shorter length of stay on labor and delivery units.

### **Values and preferences**

Some women and clinicians have a strong preference to avoid or delay neuraxial anesthesia and would potentially desire an intervention that may decrease their risk of assisted vaginal delivery or cesarean section. If N2O were available in Oregon facilities, many women would likely try it. Most women would not be concerned about potential harms because there do not appear to be adverse fetal/neonatal harms and women who experience adverse effects themselves can stop using N2O and their symptoms would resolve. Its quick onset would also be desired by women who are waiting for an epidural in labor and who would use it as a bridging technology. However, other women may strongly prefer neuraxial anesthesia (epidural) because of its greater effect in reducing labor pain, so the net assessment is that values and preferences would be highly variable.

### **Other considerations**

There is currently no specific CPT code for N2O use in labor except for an anesthesia-specific code. Benefit plans may need to consider alternative payment methodologies and/or innovative mechanisms to encourage use by providers. Facilities and clinicians may have to invest in equipment and staff training to implement N2O for labor pain. Facilities may experience shorter length of stay on labor and delivery units with increased use of N2O that may result in higher bed availability and/or decreased staffing needs in some hospitals.

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## 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 several 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. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by the Commission based on assessment of two independent reviewers from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of the Commission.

<b>Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?</b>				
<b>Outcomes</b>	<b>Estimate of Effect for Outcome/ Confidence in Estimate</b>	<b>Resource allocation</b>	<b>Values and Preferences</b>	<b>Other considerations</b>
<b>Fetal/neonatal adverse effects</b> <i>(Critical outcome)</i>	No significant differences in Apgar scores at 1 and 5 minutes, or umbilical cord gasses after birth when maternal N2O is compared to epidural anesthesia use.  ●●●○ <i>(Moderate certainty, based on multiple RCTs and other studies with consistent findings)</i>	Use of N2O is likely to be cost-saving compared to epidural anesthesia. The cost of N2O is low. Use of N2O is associated with lower rates of assisted vaginal birth and cesarean delivery, and shorter length of stay on labor and delivery units.	High variability: Some women would want this additional option because of the reduced risk of caesarean section or assisted delivery. Concerns about harms would be mitigated because they could easily discontinue it and	There is no specific CPT code for this service, other than an anesthesia code, so reimbursement to providers may require use of a non-specific code that may require manual review.

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	Estimate of Effect for Outcome/ <i>Confidence in Estimate</i>	Resource allocation	Values and Preferences	Other considerations
<b>Mode of birth</b> <i>(Critical outcome)</i>	15 to 34 more women per 100 are likely to have a vaginal birth when using N2O compared to those using epidural anesthesia for labor pain. 9 to 27 fewer women per 100 would experience assisted vaginal (forceps/vacuum) birth, and there would be about 6 fewer Cesarean births per 100.  ●●○○ (Low certainty based on prospective cohort and cross sectional studies with consistent findings)		consider an epidural if adverse events occur or if analgesia is insufficient. Other women may prefer epidural anesthesia because of its greater effect in reducing labor pain.	
<b>Maternal adverse effects</b> <i>(Important outcome)</i>	Women may experience unpleasant side effects when using N2O. Nausea (0-28%), vomiting (0-14%), dizziness/lightheadedness (3-23%), and drowsiness/sleepiness (0-67%) were commonly reported side effects. Effects dissipated quickly when N2O use is stopped.  ●●●○ (Moderate certainty based on multiple RCTs and other studies with consistent findings)			
<b>Maternal satisfaction</b> <i>(Important outcome)</i>	70 to 80% of women who used N2O said they would want to use it in a subsequent pregnancy compared to 45 to 88% of women who would request an epidural again.  ●●○○ (Low certainty based on prospective cohort and cross-sectional studies with consistent findings)			

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	Estimate of Effect for Outcome/ <i>Confidence in Estimate</i>	Resource allocation	Values and Preferences	Other considerations
Use of neuraxial (e.g., epidural) anesthesia <i>(Important outcome)</i>	When multiple pain management methods are available for women 13% to 79% will use N2O, compared to 34 to 42% who will select epidural anesthesia. There is no direct evidence on whether use of N2O changes the use of neuraxial anesthesia.  ●○○○ <i>(Very low certainty based on cross-sectional studies with consistent findings)</i>			
<p><b>Rationale:</b> On balance, there are potential benefits to the use of N2O and no serious harms to its use. Costs are low and variable maternal preferences argue for increased availability of N2O for management of labor pain. Coverage is recommended because of the potential benefits of fewer cesarean and assisted deliveries, the lack of significant harms, maternal preferences, and low costs. The recommendation is a weak recommendation because there are few studies available for benefit outcomes, and the external validity of the data and its applicability in U.S. settings is limited. The confidence in the quality of evidence for most outcomes is low to moderate certainty.</p> <p><b>Recommendation:</b> Nitrous oxide for labor pain is recommended for coverage (<i>weak recommendation</i>).</p>				

Note: GRADE framework elements are described in Appendix A

## POLICY LANDSCAPE

### Quality measures

No quality measures related to the use of nitrous oxide during labor were identified when searching the [National Quality Measures Clearinghouse](#).

### Payer coverage policies

No public or private payer coverage policies<sup>1</sup> were identified for the use of nitrous oxide during labor.

### Professional society guidelines

The National Institute for Health and Care Excellence (NICE) found there to be moderate evidence of benefit for the use of nitrous oxide during labor (NICE, 2014). The guideline notes that nitrous oxide can cause nausea and light-headedness for the mother. NICE did not find any evidence of harm to the baby. The use of 50:50 mixture oxygen and nitrous oxide is recommended to be available in all birth settings in the United Kingdom.

The American College of Nurse-Midwives (ACNM) has a Position Statement that supports the increased availability and use of nitrous oxide analgesia (ACNM, 2011).

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.

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<sup>1</sup> Washington Medicaid, Aetna, Cigna, Regence Blue Cross Blue Shield, and Moda

## APPENDIX A. GRADE INFORMED FRAMEWORK - ELEMENT DESCRIPTIONS

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
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
Other considerations	Other considerations include issue about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

### Confidence in the quality of the evidence, across studies, about an outcome

**High:** The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

**Moderate:** The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

**Low:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

**Very low:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

### 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.

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## APPENDIX B. METHODS

### Scope Statement

#### Populations

Pregnant women intending a vaginal birth in the first and second stages of labor and their fetus/neonate, women in the third stage of labor or immediate postpartum period

Population scoping notes: *Exclude women planning a Cesarean birth*

#### Interventions

Self-administered nitrous oxide used for labor analgesia or third stage/immediate postpartum management

Intervention exclusions: *Concentration of nitrous oxide blended with oxygen for analgesia other than 50%; non-self-administration of nitrous oxide*

#### Comparators

Neuraxial analgesia (e.g. epidural, combined spinal/epidural)

#### Outcomes

Critical: Mode of birth; Fetal/neonatal adverse effects (e.g. low Apgar score, low cord blood gasses)

Important: Maternal adverse effects (e.g. nausea/vomiting, dizziness, loss of consciousness); Use of neuraxial (e.g. epidural) analgesia; Maternal satisfaction

*Considered but not selected for the GRADE table*: Use of non-neuraxial analgesia

#### Key Questions

KQ1: What are the effects on mode of birth, use of neuraxial (e.g. epidural) analgesia and maternal satisfaction when nitrous oxide is used for labor analgesia?

KQ2: What are the maternal and fetal/neonatal harms of nitrous oxide used for labor pain?

#### Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “nitrous oxide,” and “labor pain management.” Searches of core sources were limited to citations published after 2004.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence
- Canadian Agency for Drugs and Technologies in Health (CADTH)

Cochrane Library (Wiley Interscience)  
Hayes, Inc.  
Institute for Clinical and Economic Review (ICER)  
Medicaid Evidence-based Decisions Project (MED)  
National Institute for Health and Care Excellence (NICE)  
Tufts Cost-effectiveness Analysis Registry  
Veterans Administration Evidence-based Synthesis Program (ESP)  
Washington State Health Technology Assessment Program

Based on this initial search, the AHRQ report (Likis, 2012) was selected as the index systematic review.

We also identified another good quality SR from the Cochrane Collaboration in the core source search. The Cochrane SR (Klomp, 2012) included four RCTs that were not included in the AHRQ SR. They were excluded from the AHRQ SR because they were not published in English. In total, five RCTs in the Cochrane SR, compared varying or unspecified concentrations of N<sub>2</sub>O to oxygen alone or no treatment. Only one of these RCTs evaluated the comparison, relevant to this coverage guidance, of 50% N<sub>2</sub>O/50% oxygen with epidural anesthesia. This RCT also included a no treatment control group. The Cochrane SR did not present outcomes for the comparison of N<sub>2</sub>O vs. epidural groups, but only the comparison of the N<sub>2</sub>O and no treatment groups. We were unable to incorporate the results of the N<sub>2</sub>O vs. epidural comparison to this evidence report due to this RCT being published in Chinese.

A MEDLINE® (Ovid) search was then conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of the AHRQ report (Likis, 2012). The search was limited to publications in English published after 2010 (the end search date for the AHRQ SR).

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)  
Centers for Disease Control and Prevention (CDC) – Community Preventive Services  
Choosing Wisely  
Institute for Clinical Systems Improvement (ICSI)  
National Guidelines Clearinghouse  
New Zealand Guidelines Group  
NICE  
Scottish Intercollegiate Guidelines Network (SIGN)  
United States Preventive Services Task Force (USPSTF)  
Veterans Administration/Department of Defense (VA/DOD)

## **Inclusion/Exclusion Criteria**

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, or clinical practice guidelines.

## APPENDIX C. GRADE EVIDENCE PROFILE

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Fetal/Neonatal Adverse Effects (Apgar scores, Cord gasses)<sup>1</sup></b>							
14	5 RCTs; 8 Prospective cohorts; 1 Case-series	High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
<b>Mode of Birth<sup>3</sup></b>							
3	2 Prospective cohort; 1 Cross-sectional	High	Consistent	Direct	Imprecise	Moderate magnitude of effect and some evidence of dose-response relationship	Low confidence in estimate of effect ●●○○
<b>Maternal Adverse Effects (Nausea, Vomiting, Dizziness/Lightheadedness, Drowsiness/Sleepiness)<sup>2</sup></b>							
10	7 RCTs; 2 Prospective cohorts; 1 Cross-sectional	High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
<b>Maternal Satisfaction<sup>3</sup></b>							
4	2 Prospective cohort; 2 Cross-sectional	High	Consistent	Direct	Imprecise	None	Low confidence in estimate of effect ●●○○

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Use of Neuraxial Anesthesia<sup>3</sup></b>							
2	2 Cross-sectional	High	Consistent	Indirect	Imprecise	None	Very low confidence in estimate of effect (●○○○)

<sup>1</sup>Studies from Tables 9, 10, 11 (AHRQ, 2012). Strength of evidence assessment based on AHRQ SR, Table 12 (AHRQ, 2012).

<sup>2</sup>Studies from Table 8 (AHRQ, 2012). Strength of evidence assessment based on AHRQ SR, Table 12 (AHRQ, 2012).

<sup>3</sup>Studies for benefit outcomes selected from AHRQ SR based on HERC review PICO only (neuraxial anesthesia comparator studies only) (AHRQ, 2012). Strength of evidence based on risk of bias assessments included for individual studies in AHRQ SR, Table 6 (AHRQ, 2012) and assessment of other GRADE elements by staff.

## APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
<b>ICD-9 Diagnosis Codes</b>	
<b>ICD-10 Diagnosis Codes</b>	
<b>ICD-9 Volume 3 (Procedure Codes)</b>	
<b>CPT Codes</b>	
<b>HCPCS Level II Codes</b>	

Note: Inclusion on this list does not guarantee coverage

**Section 3.0**  
**Coverage Guidance**  
**Monitoring**

# Neuroimaging for Headache

## PICO & Key Questions for Updated Literature Search

### **Populations**

Adults and children with non-traumatic, acute or chronic headache

### **Interventions**

MRI or CT head/brain, with or without contrast enhancement

### **Comparators**

Usual care, no neuroimaging

### **Outcomes**

*Critical:* Morbidity from significant intracranial abnormalities

*Important:* Headache-free days, quality of life, radiation exposure, incidental findings

*Outcomes considered but not selected for GRADE table:*

### **Key Questions**

KQ1: What is the comparative effectiveness of neuroimaging for headache in improving patient outcomes or detecting significant intracranial abnormalities?

- a. Does the effectiveness of neuroimaging for headache vary based on acuity?

KQ2: What are evidence-supported red flag features which are indications for neuroimaging for headache?

- a. Do the evidence-supported red-flag features which indicate neuroimaging vary based on acuity?

KQ3: What are the harms of neuroimaging for headache?

# Cervical Cancer Screening

PICO & Key Questions for Updated Literature Search

**Staff recommends retiring this coverage guidance and deferring to the United States Preventive Services Task Force (USPSTF).**

The HERC Coverage Guidance, Routine Cervical Cancer Screening, approved in 2013, aligned with the USPSTF recommendations. Staff recommends retiring the coverage guidance because the USPSTF now defines use of preventive services for the Essential Health Benefits. The Essential Health Benefits provide minimum coverage standards on preventive services for most health plans in the United States.

# Induction of Labor

## PICO & Key Questions for Updated Literature Search

### **Populations**

Pregnant adolescents and women

### **Interventions**

IOL without medical or obstetrical indications

### **Comparator**

Expectant management, elective C-section

### **Outcomes**

*Critical:* Perinatal mortality, maternal mortality, neonatal morbidity

*Important:* Mode of birth (stratified by indication for operative delivery), maternal length of stay

*Outcomes considered but not selected for GRADE table:* iatrogenic prematurity, hemorrhage, epidural, patient satisfaction, neonatal length of stay

### **Key Questions**

KQ1: What are the outcomes of IOL versus expectant management for women without medical or obstetrical indications for induction of labor?

KQ2: How do outcomes vary by cervical favorability, gestational age and parity?

### **Contextual Questions**

CQ1: What are the evidence-based medical or obstetrical indications for induction of labor?

# Recurrent Acute Otitis Media

## PICO & Key Questions for Updated Literature Search

### **Population**

Children with recurrent acute otitis media (AOM)

### **Interventions**

Prophylactic or suppressive antibiotics, tympanostomy tubes (grommets), tonsillectomy and/or adenoidectomy (note that these interventions may be used alone, serially or in combination)

### **Comparators**

Usual care, episodic treatment of AOM

### **Outcomes**

*Critical:* Severe infection (e.g systemic infection, sepsis, meningitis, locally invasive infection), school performance/academic achievement

*Important:* Hearing loss, speech delay, treatment-specific harms

*Outcomes considered but not selected for GRADE table:* Missed school days

### **Key Questions**

KQ1: What is the comparative effectiveness of interventions (alone, serially, or in combination) for recurrent acute otitis media?

- a. Are there subpopulations of children with recurrent acute otitis media who are more likely to benefit from prophylactic interventions?

KQ2: What are the harms of interventions for recurrent acute otitis media?

## Coronary Artery Calcium Scoring – 2015 Rescanning Summary

**Subcommittee:** Evidence-based Guidelines Subcommittee (August 2013)

**Bottom Line:** There is little new summary evidence related to the comparative effectiveness, cost-effectiveness or harms related to coronary calcium scoring. The studies that were identified appear to have substantial limitations and would likely not result in a change to the existing HERC coverage guidance. An AHRQ report on non-invasive testing for coronary artery disease that was started in January 2015 will include information on CACS when published.

### Coverage Recommendation (Box Language)

Coronary artery calcium scoring (CACS) should not be covered.

### Scope Statement

<b>Population description</b>	Asymptomatic adults with coronary heart disease (CHD) risk, adults with acute chest pain with normal EKG and negative cardiac enzymes, adults with chronic stable chest pain  <i>Population scoping notes:</i> None
<b>Intervention(s)</b>	Coronary artery calcium scoring (CACS)  <i>Intervention exclusions:</i> None
<b>Comparator(s)</b>	No further risk stratification, other forms of risk stratification (including serial monitoring (EKG, troponins), exercise EKG, stress echocardiography, stress myocardial perfusion scanning, coronary angiography, clinical risk prediction tools
<b>Outcome(s) (up to five)</b>	<b>Critical:</b> All-cause mortality, major adverse cardiovascular events <b>Important:</b> Incidental findings, avoidance of invasive procedure  <i>Considered but not selected for GRADE table:</i> Length of stay
<b>Key questions</b>	<ol style="list-style-type: none"><li>1. What is the comparative effectiveness of CACS in improving outcomes for asymptomatic patients with CHD risk or patients with chest pain (either acute chest pain with normal EKG and negative cardiac enzymes or chronic stable chest pain)?</li><li>2. What is the cost-effectiveness of CACS?</li></ol>

	3. What are the harms of CACS?
<b>Contextual questions</b>	1. Does CACS alter treatment plans by refining estimates of risk?

### Original Evidence Sources

Hayes, Inc. (2012). *Coronary artery calcium scoring to assess the risk of coronary artery disease in asymptomatic adults*. Lansdale, PA: Hayes, Inc.

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### Summary:

Citation 1 is a joint clinical practice guideline from seven professional societies. The guideline states that coronary artery calcium scoring may be considered for patients who have a low to intermediate pre-test probability of obstructive ischemic heart disease. The recommendation is based on consensus opinion, case studies and/or the determined standard of care.

Citation 2 is a systematic review of eight studies (n=6,521) that focuses on the use of coronary artery calcium scoring for reducing all-cause mortality and cardiovascular events in patients with type 2 diabetes. The overall reported sensitivity and specificity of a calcium score  $\geq 10$  were 94% and 34%, respectively, for detecting all-cause mortality and cardiovascular events at a mean follow-up interval of 5 years. This corresponds to a positive likelihood ratio of 1.67 and a negative likelihood ratio of 0.11. The clinical significance of testing in this population (i.e. whether it influences management decisions or alters clinical outcomes) remains unclear.

Citation 3 is a clinical practice guideline that states CT coronary calcium is usually not appropriate for diagnosing chest pain suggestive of acute coronary syndrome and is not validated in the acute setting. The guideline notes that CT coronary calcium has a medium level of relative radiation (1-10 mSv for adults).

Citation 4 is an economic analysis comparing coronary artery calcium scoring with stress electrocardiography. The analysis was based on national prices in the United Kingdom and may be too indirect to influence the HERC coverage guidance.

Citation 5 is a clinical practice guideline that states CT coronary calcium is usually not appropriate for diagnosing chronic chest pain in patients with a low to intermediate pre-test probability of coronary artery disease. The guideline notes that CT coronary calcium has a medium level of relative radiation (1-10 mSv for adults).

Citation 6 is a systematic review and meta-analysis of five studies (n=34,028) evaluating the prognostic performance of coronary artery calcium scoring in asymptomatic patients. Of note, the main data sources are studies of chest CT for lung cancer screening and the highly heterogeneous results in the prognostic studies precluded meta-analysis. The study did not evaluate whether using calcium scoring resulted in a change of care or prevented any major adverse cardiac events or death.

Note: The Agency for Healthcare Research and Quality Effective Health Care Program is currently in the process of reviewing noninvasive testing for coronary artery disease. The [protocol](#) was initiated in January 2015.

## Appendix A. Methods

### *Search Strategy*

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “calcium scor\*,” “computed tomography coronary,” “computed tomography calcium,” and “cardiac CT.” Searches of core sources were limited to citations published after 2011 (the last search date of original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2011 (the last search date of the original evidence sources).

Searches for clinical practice guidelines were limited to those published since 2012 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

*Inclusion/Exclusion Criteria*

Studies were excluded if they were not published in English, , did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

DRAFT

# Coronary Computed Tomography Angiography – 2015 Rescanning Summary

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**Subcommittee:** Evidence-based Guidelines Subcommittee (August 2013)

**Bottom Line:** New summary evidence and clinical practice guidelines pertaining to the use of CCTA are now available. Most of the new data further establishes the diagnostic performance (but not clinical utility) of CCTA, though there is some tentative data on downstream testing utilization and clinical outcomes. An AHRQ report on non-invasive testing for coronary artery disease that was started in January 2015 will include information on CCTA when published.

## Coverage Recommendation (Box Language)

Coronary computed tomography angiography (CCTA) is not recommended for coverage.

## Scope Statement

<b>Population description</b>	Adults with acute chest pain or chronic stable chest pain <i>Population scoping notes:</i> None
<b>Intervention(s)</b>	Coronary CT angiography (CTA) <i>Intervention exclusions:</i> None
<b>Comparator(s)</b>	Usual care (including no additional testing, exercise EKG, stress echocardiography, stress myocardial perfusion scanning, coronary angiography; serial monitoring with EKG/troponin)
<b>Outcome(s) (up to five)</b>	<b>Critical:</b> All-cause mortality, major adverse cardiac events (MACE) <b>Important:</b> Contrast-induced nephropathy, avoidance of invasive procedures <i>Considered but not selected for GRADE table:</i> radiation exposure; need for revascularization procedure
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What is the comparative effectiveness of coronary CTA for improving outcomes among adults with chest pain? <ol style="list-style-type: none"> <li>a. Are there patient characteristics that modify the utility?</li> </ol> </li> <li>2. What are the harms of coronary CTA (including incidental</li> </ol>

	<p>findings)?</p> <p>3. What are the comparative costs and/or cost-effectiveness of coronary CTA?</p>
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### Original Evidence Sources

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### Scanning Results (reviewed for applicability, methodologic quality not assessed)

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## Summary

Citation 1 is a SR and MA of studies examining the use of CTA for the so-called triple rule-out (CAD, PE, dissection) of adults with chest pain in the emergency department. It concludes that CTA is highly accurate for detecting CAD, but that the low prevalence of PE and dissection in the studies provide insufficient data to support the triple-rule out. The meta-analytic information presented on the operating characteristics of CTA for CAD in this selected population would potentially change HERC coverage guidance.

Citation 2 is a CADTH rapid response that summarizes two non-randomized studies on the risk of contrast-induced renal injury from CTA.

Citation 3 is a SR and MA of 4 RCTs examining the use of CCTA in ED patients with chest pain. The main outcomes reported were odds of undergoing a revascularization procedure, time to diagnosis, and costs of ED care. It would potentially change HERC coverage guidance.

Citation 4 is a cost-effectiveness study of CCTA vs conventional angiography using a micro-costing method in 4 French hospitals. Any conclusions are probably too indirect to influence the HERC coverage guidance.

Citation 6 is a SR and MA examining how the operating characteristics of CCTA are affected by the presence of coronary artery calcification detected by CACS and/or the use of 64-slice vs 16-slice MDCT technology. It might provide contextual information if the HERC coverage guidance is updated.

Citation 7 is an AHRQ comparative effectiveness review on the non-invasive diagnosis of CAD in women. It concludes that evidence of low strength supports the diagnostic accuracy of CCTA, but there is insufficient evidence that it improves risk stratification, decision making, or clinical outcomes.

Citation 8 is a SR and MA of CCTA vs standard care for evaluation of low-risk chest pain. It includes data from 4 RCTs and 3 case-control studies and concludes that the use of CCTA is associated with decreased risk of ACS and fewer repeat ED visits. It would potentially change HERC coverage guidance.

Citation 9 is the 2012 ACCF/AHA/et al guideline on the diagnosis and management of stable ischemic heart disease (SIHD). The recommendations concerning CCTA in patients with suspected or known SIHD who require non-invasive testing are all class IIa (is reasonable) or IIb (may be considered) with a levels of evidence B-C. These guidelines would potentially change HERC coverage guidance.

Citation 10 is a decision analytic study comparing the effectiveness and costs of CCTA vs stress EKG based on information from a single prospective cohort of 471 patients. The economic evaluation made assumptions based on the Dutch Health Care Insurance board. The design of the study and the indirectness of the information on cost make it unlikely to influence HERC coverage guidance.

Citation 11 is cost-effectiveness study comparing 64-slice CCTA with conventional angiography. It would probably provide contextual information on resource use if the topic is selected for updating.

Citation 12 is a SR and MA of non-comparative studies that report >3 months of clinical follow-up for patients undergoing 64-slice CCTA. The report provides OR for cardiac death or MI based on the findings of the CCTA. Obstructive and non-obstructive CAD on CCTA had higher OR for the outcomes compared to those without CAD.

Citation 13 is a randomized controlled trial of 1000 patients between the ages of 40-74 years presenting to the ED with symptoms of ACS but without EKG or biochemical evidence of ischemia; they were randomly assigned to either CCTA or standard evaluation. The CCTA strategy resulted in shortened time to diagnosis and length of hospital stay, but the overall cost of care was not significantly different in the two groups. It may provide contextual information about the incorporation of CCTA into clinical workflows if the topic is selected for updating.

Citation 14 is a SR and MA of 4 RCTs comparing CCTA and usual care for patients in the ED with chest pain. It concludes that CCTA use decreased ED costs and length of stay, but increased invasive coronary angiography and revascularization.

Citation 15 is the ACR Appropriateness Criteria for patients with acute chest pain and suspected aortic dissection. It recommends CTA of the chest and abdomen as the definitive test in most patients with suspicion of aortic dissection. This recommendations does not specifically apply to coronary CTA, and thus would be unlikely to change the HERC coverage guidance.

Citation 16 is a SR and MA of non-comparative studies of patients with suspected coronary disease who underwent CCTA with follow-up of at least 12 months. The primary outcomes were test characteristics for predicting MACE. The weighted average annualized MACE rate was 3.49% for patient with “positive” CCTA and 0.21% for patients with “negative” CCTA. It is not clear that information from this study would change HERC coverage guidance.

Citation 17 is a study of CCTA for detecting graft vasculopathy in patients who have had a heart transplant and is thus out of scope.

Citation 18 is a SR and MA of 10 studies examining the diagnostic accuracy of 320-slice CCTA. It provides information on the incremental diagnostic accuracy of more advanced CT technology.

Citation 19 is a SR and MA of studies comparing the diagnostic performance of 64-slice MDCT and post 64-slice MDCT with coronary angiography. It provides information on the comparative diagnostic performance of two CCTA technologies.

Citation 20 is an economic evaluation of CCTA in the Italian health care system. Any conclusions are probably too indirect to influence the HERC coverage guidance.

Citation 21 is the ACR Appropriateness Criteria for patients with symptoms suggestive of acute coronary syndrome. It suggests that CCTA can be considered for “those patients with low-to-intermediate likelihood for coronary artery disease in the absence of cardiac enzyme elevation and ischemic ST changes.

Citation 22 is a small (180 patients) prospective multicenter RCT comparing CCTA and myocardial perfusion imaging (MPI) as the initial diagnostic evaluation for patients with stable chest pain and suspected CAD. It concludes that CCTA and MPI show comparable improvements in angina-related QoL. CCTA is associated with more aggressive medical therapy and increased revascularization, but lower total costs and effective radiation dose. It is a small but reasonably well done RCT that could potentially inform HERC coverage guidance.

Citation 23 is a narrative review of evidence and cost-effectiveness data on CCTA in patients with chronic chest pain. It provides a critical review of some of the general limitations of the literature and would provide important contextual information if the topic is selected to be updated.

Citation 24 is a single center retrospective cohort study comparing patients who received CCTA or exercise stress testing in symptomatic patients with low-to-intermediate pretest probability of

CAD. It provides clinical and cost outcomes at 12 months of follow-up for these patients. The design makes it unlikely that this study would change the HERC coverage guidance.

Citation 25 is a SR and MA of studies comparing the diagnostic accuracy and clinical outcomes of exercise EKG and SPECT vs CCTA in patients with suspected stable CAD. It concludes that the diagnostic performance of CCTA is better than exercise EKG or SPECT and that CCTA is associated with lower odds of non-fatal MI and increased downstream testing and coronary revascularization. It would be potentially change the HERC coverage guidance.

Citation 26 is a SR of prospective non-randomized controlled trials and diagnostic accuracy studies of 64-slice CT and coronary angiography. It concludes that 64-slice CT is highly sensitive and specific for the diagnosis of significant coronary stenosis in patients with angina. The authors propose that CCTA should replace angiography as the gold-standard diagnostic test for CAD. It would potentially change HERC coverage guidance.

Citation 27 is a multisociety (ACP/ACCF/AHA/et al) guideline on the diagnosis of stable ischemic heart disease. Pertinent recommendations include a) that CCTA should not be used for risk assessment in patients with stable IHD who are able to exercise and have an interpretable EKG, b) that CCTA should not be used in conjunction with other tests to assess risk in patients with stable IHD. However, CCTA is included in the testing algorithm for ischemic heart disease and would therefore potentially change the HERC coverage guidance.

Citation 28 is an economic analysis of coronary artery calcium scoring compared with stress EKG for the non-invasive diagnosis of CAD. It is therefore out of scope.

Citation 29 is a SR and MA of diagnostic accuracy studies of dual-source CT for CAD. The included studies were published between 2005 and 2011 and would likely have been captured in the summary evidence sources used for the 2013 coverage guidance.

Citation 30 is SR and MA of studies of CCTA for diagnosis of chest pain for patients in the ED with suspected ACS. It concludes that CCTA has high sensitivity and a low negative LR and is therefore effective in ruling out ACS in low-to-intermediate risk ED patients with acute chest pain.

Citation 31 is a SR and MA of studies examining the diagnostic performance of EKG-gated CCTA for the diagnosis of CAD. It concludes that EKG-gated CCTA has favorable diagnostic performance with pooled sensitivity and specificity of 99% and 91% respectively.

Citation 32 is a SR and MA of studies examining the diagnostic performance of combined use of CCTA and computed tomographic perfusion (CTP) for diagnosis of significant coronary stenosis. It is therefore out of scope.

Citation 33 is a SR and MA of dual-source CCTA for the diagnosis of CAD in “difficult to image patients.” It concludes that dual-source CCTA “may be sufficiently accurate to diagnose clinically significant CAD in some or all difficult to image patients.” It could potentially change HERC coverage guidance.

Citation 34 is a SR and MA of studies of CCTA in graft vasculopathy following cardiac transplantation. It is therefore out of scope.

Citation 35 is the ACR Appropriateness Criteria for patients with chronic chest pain and low-to-intermediate probability of CAD. It recommends that CCTA “can be used to assess for coronary atherosclerosis, anomalous coronary artery, and pericardial disease. High negative predictive value will exclude coronary artery disease and allow triage management to focus on more likely diagnoses.” It could potentially change HERC coverage guidance.

Citation 36 is SR of 42 studies examining the comparative effectiveness, cost-effectiveness, and effects on downstream test utilization of CCTA. It concludes that CCTA may be a cost-effective strategy and reduce downstream testing in stable chest pain patients with low-to-intermediate risk. It could potentially change HERC coverage guidance.

Note: The Agency for Healthcare Research and Quality Effective Health Care Program is currently in the process of reviewing noninvasive testing for coronary artery disease. The [protocol](#) was initiated in January 2015.

## Appendix A. Methods

### *Search Strategy*

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “coronary computed tomography” and “coronary CT angiography.” Searches of core sources were limited to citations published after 2011 (last search date of original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2011 (last search date of the original evidence sources).

Searches for clinical practice guidelines were limited to those published since 2012 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

*Inclusion/Exclusion Criteria*

Studies were excluded if they were not published in English, , did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

# Treatment of Attention Deficit / Hyperactivity Disorder in Children – 2015 Rescanning Summary

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**Subcommittee:** Evidence-based Guidelines Subcommittee (December 2013)

**Bottom Line:** Given the vast number of systematic reviews that have been published on the treatment of attention deficit / hyperactivity disorder in children in recent years, the Subcommittee may wish to delay reviewing this coverage guidance until the NICE guideline is published in early 2016.

## Coverage Recommendation (Box Language)

### Children under Age 6

For children under 6 diagnosed with disruptive behavior disorders<sup>1</sup>, including those at risk for ADHD, specific parent behavior training<sup>2</sup> is recommended for coverage as first-line therapy (*strong recommendation*).

Pharmacotherapy<sup>3</sup> 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 ADHD<sup>1</sup>, pharmacotherapy<sup>3</sup> alone (*weak recommendation*) or pharmacotherapy<sup>3</sup> with psychosocial/behavioral treatment (*strong recommendation*) are recommended for coverage.

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

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

<sup>2</sup>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.

<sup>3</sup>Limited to medications that are FDA-approved for the condition.

## Scope Statement

<b>Population description</b>	Children 6 years of age or older diagnosed with ADHD or children under 6 years of age deemed at-risk for ADHD
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	<i>Population scoping notes: None</i>
<b>Intervention(s)</b>	Parent behavior training, teacher consultation, pharmacotherapy (methylphenidate, amphetamine salts, non-stimulant medications, atypical antipsychotics), other pharmacologic treatments, psychosocial and behavioral interventions, dietary supplements, complimentary and alternative medicine (CAM)  <i>Intervention exclusions: Changes in diet</i>
<b>Comparator(s)</b>	Usual care, no intervention
<b>Outcome(s) (up to five)</b>	<b>Critical:</b> Academic achievement, measures of social functioning <b>Important:</b> Measures of impulsiveness, grade retention, growth restriction  <i>Considered but not selected for GRADE table:</i> Measures of inattention, overactivity, non-specific harms
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What is the effectiveness of pharmacologic, behavioral, and psychosocial interventions for children with ADHD? <ol style="list-style-type: none"> <li>a. Does effectiveness vary based on patient characteristics?</li> </ol> </li> <li>2. Is there comparative effectiveness evidence for interventions for children with ADHD?</li> <li>3. What is the effectiveness of interventions for children under 6 years of age deemed at-risk for ADHD?</li> <li>4. What is the evidence of harms associated with the interventions for ADHD in children?</li> </ol>

### Original Evidence Sources

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](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

### **Scanning Results** (reviewed for applicability, methodologic quality not assessed)

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### **Summary**

A large volume of studies have been published since this coverage guidance was developed. An [update](#) to the 2008 NICE guideline on attention deficit hyperactivity disorder is expected to be published in early 2016. In addition, the Agency for Healthcare Research and Quality is in the process of [updating](#) the 2011 report.

## Appendix A. Methods

### *Search Strategy*

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “attention deficit hyperactivity disorder.” Searches of core sources were limited to citations published after 2010 (last search date of original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2013 due to the large amount of information identified in the core source search.

Searches for clinical practice guidelines were limited to those published since 2010 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

*Inclusion/Exclusion Criteria*

Studies were excluded if they were not published in English, , did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

DRAFT