



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

**November 5,  
2015 1:30 PM**  
(Packet revised 11/2/15)

**Clackamas Community College  
Wilsonville Training Center, Room 112  
29373 SW Town Center Loop E, Wilsonville, Oregon,  
97070**

# Section 1.0

## Call to Order

**AGENDA (REVISED)**

**EVIDENCE-BASED GUIDELINES SUBCOMMITTEE (EbGS)**

**November 5, 2015**

**1:30pm - 4:30pm**

Room 112, Clackamas Community College

Wilsonville Training Center

29353 SW Town Center Loop E

Wilsonville, Oregon 97070

*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.*

<b>#</b>	<b>Time</b>	<b>Item</b>	<b>Presenter</b>
1	1:30 PM	Call to Order	Wiley Chan
2	1:35 PM	Review of September 2015 minutes	Wiley Chan
3	1:40 PM	Staff update	Darren Coffman
4	1:45 PM	Review public comments <ul style="list-style-type: none"><li>• Nitrous oxide for use in labor pain management</li></ul>	Valerie King Cat Livingston
5	2:00 PM	Review need for updates on coverage guidances approved in 2013 <ul style="list-style-type: none"><li>• Induction of labor</li><li>• Recurrent acute otitis media</li><li>• Neuroimaging for headache</li></ul>	Robyn Liu Cat Livingston
6	2:30 PM	Review initial draft coverage guidance <ul style="list-style-type: none"><li>• Skin substitutes for chronic skin ulcers</li></ul>	Robyn Liu Cat Livingston
7	4:20 PM	Confirmation of the next meeting, February, 2016	Wiley Chan
8	4:25 PM	Next Topics	Cat Livingston
9	4:30 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  
September 3, 2015  
2:00-5:00pm

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**Members Present:** Wiley Chan, MD, Chair; Vern Saboe, DC; Beth Westbrook, PsyD; George Waldmann, MD

**Members Absent:** Eric Stecker, MD, MPH, Vice-Chair; Bob Joondeph, JD

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

**Also Attending:** Adam Obley, MD, Val King MD, MPH and Aasta Thielke (OHSU Center for Evidence-based Policy); Judith Rooks; Sharron Fuchs; Joe Badolato (Family Care); Mellony Berdal (OHA Public Health); Kim Wentz, MD (OHA Health Systems Division); Carl Stevens (CareOregon).

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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

No changes were made to the June 4, 2015 minutes.

**Minutes approved 4-0.**

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#### 3. STAFF REPORT

Coffman reported that Kathryn Leukin has resigned from the subcommittee as she took a different job. Alison Little, former CeBP staff member and now a medical director for PacificSource, has volunteered to join the subcommittee pending approval by HERC. If appointed by HERC, her first meeting would be in November.

Livingston reported about changes to the coverage guidance process, including a new format for the GRADE table. She asked for feedback after the meeting on the format and level of detail. There is more detail available in the appendices.

She also provided an update on the Coverage Guidance on Planned Out-of-Hospital Birth. The subcommittee had recommended that HIV and Hepatitis B status would need to be known to be

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negative prior to a planned out-of-hospital birth, but there are a number of other indications where the subcommittee did not specify the need to rule them out prior to birth. Implementers want to have each risk factor addressed and ruled out for coverage.

There was an extensive discussion about whether it was the HERC versus implementers role to define how to rule in or out each of the criteria. It was clarified that documentation would be required, but clarity around whether each and every risk factor would have to be documented to rule out a risk condition was unclear. It was decided that discussing this with the ad hoc experts, to determine if every risk criteria was equal in requiring assessment and/or testing, was desirable and which tests may be required. . Plans and LDMs are both interested in clarity around what is required. Livingston asked whether EbGS had an expectation of whether each condition would need to be ruled out. Committee members agreed their discussion had not been this explicit except around specific issues such as whether to require a certain number of prenatal visits or testing for HIV and Hepatitis B. Livingston said that VbBS would discuss a staff proposal that every single condition would need to be addressed and ruled out. Wentz said she was working with an internal implementation committee to develop clear guidelines, and wanted to make sure only the key issues need to be addressed, and that no lower-priority items were included so that there would be no doubt about what was required. Waldmann expressed concern about requiring overly technical proof of something such as twin gestation, which he used to routinely detect before ultrasound was available. He said an experienced practitioner will recognize twins long before labor. After brief discussion, the subcommittee agreed that these concerns can be dealt with in the implementation process outside the coverage guidance process.

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#### **4. REVIEW OF DRAFT COVERAGE GUIDANCE ON NITROUS OXIDE USE FOR LABOR PAIN MANAGEMENT**

Livingston introduced Judith Rooks, who will serve as the ad hoc expert for this topic. Rooks is a certified nurse midwife and an epidemiologist. She also assisted with the development of the AHRQ report which served as the primary research source for this coverage guidance. Her only declared conflict of interest was nonfinancial; she has a long history of advocating the use of nitrous oxide for labor pain in the United States. King and Livingston provided an overview of the draft coverage guidance.

Livingston reviewed the GRADE table. Waldmann asked King whether any of the studies showed how often nitrous oxide administration is followed up with an epidural. King said she couldn't quote a number, but that in U.S. hospitals with limited anesthesia resources, there is often difficulty getting epidural anesthesia in a timely manner, so it may be of advantage for a woman to have nitrous oxide while waiting for an epidural. It was confirmed that studies also examined safety of nitrous oxide use in a home birth setting, but that many of the studies are non-U.S. studies, so standards for care in home birth are different than in the United States. Safety results were consistent across studies. There was general agreement that having a safe, effective alternative available to women in labor was valuable. The subcommittee briefly discussed the need for safe use of nitrous oxide (such as adequate ventilation and scavenging systems). These would need to be provided by the facilities in question, but these are regulatory issues, not coverage issues in the HERC's purview. Livingston invited public comment.

Sharron Fuchs offered comment. She noted that she was the one who suggested the topic for consideration by the HERC. She thanked the subcommittee for recommending a choice for women of an

additional effective, low cost treatment. She said her life would have been different if she had been provided with adequate pain relief in her first birth.

Chan commented that the values and preferences portion of the GRADE table in this case is different than is often the case. Where high variation in values and preferences generally leads to a weak recommendation, in this case because some women would want it and because the harms are low, it would argue for a statement that the values and preferences would strengthen the recommendation for coverage rather than weaken it. The same could happen under resource allocation; a high cost item could still be worthwhile. King noted that the values and preferences section may be influenced by public comment. Livingston asked whether there is an argument for a strong recommendation. After brief discussion the subcommittee made no change to the draft coverage guidance, as the underlying evidence is weak by normal standards.

**The draft coverage guidance was referred for posting for public comment as presented, 4-0.**

#### DRAFT HERC COVERAGE GUIDANCE

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

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## 5. TOPIC RESCAN—SCOPE REVIEW

Livingston explained that the topic rescan will now include an a priori scope statement, which will outline the search parameters and key questions for each topic prior to creating the literature search. For several topics (coronary artery calcium scoring, coronary CT angiography tomography and attention deficit/hyperactivity disorder), the HERC has already approved the scope statements, so the subcommittee can review the results of the literature scan based on the approved scope. For the remaining topics (neuroimaging for headache, cervical cancer screening, induction of labor and recurrent acute otitis media), HERC delegated the task of reviewing and approving the scope statements to EbGS.

Neuroimaging for Headache—Obley reviewed the draft scope document from the meeting packet. There was minimal discussion. Wentz asked about the outcome of harms from radiation—would it be reported by the amount of radiation or incidence of brain cancer. Obley said that the scan would retrieve both outcomes, but he suspects that most often it would be reported as the amount of radiation which could be cross-referenced with models to predict tumor incidence, though there is controversy in the literature about those models. After brief discussion the subcommittee changed the outcome to “harms from radiation exposure.” Westbrook said her husband, who is a neurologist, believes imaging for headache tends to be overused but the harms are mostly the expense, or sometimes a delay in needed emergency care. Livingston said that during the previous review of the coverage guidance, the subcommittee asked which were the evidence-based indications for neuroimaging for headache, but the list was much shorter than any of the clinicians believed appropriate, so the current approved coverage guidance has a somewhat longer list based on trusted sources and evidence-based clinical guidelines. Because of this, key question 2 captures the red flag features, and that they will likely be based on evidence-based guidelines, not primary research.

Waldmann said he appreciated the inclusion of incidental findings. Chan suggested clarifying that the outcome should be “harms from incidental findings,” as some incidental findings may be perceived as benefits; the subcommittee agreed to this change. It was clarified that comparative efficacy (such as between CT, PET, or MRI) would be identified by the search. After discussion the subcommittee made no additional changes to the scope document.

Cervical cancer screening—Livingston reviewed the recommendation to defer to the United States Preventive Services Task Force (USPSTF) on cervical cancer screening. Westbrook asked whether it would be reviewed in another two years. Livingston said the intent was to retire the coverage guidance and defer to the USPSTF going forward without any additional HERC review. Several concerns and issues were discussed, including the potential that a USPSTF recommendation may be out-of-date, differ from professional guidelines, or be out of line with the evidence in the future. There was also discussion about controversy regarding the impact of increased human papilloma virus vaccination on the need for screening. This question is currently under review by USPSTF. In addition the subcommittee heard about Federal requirements that most health plans must cover USPSTF “A” and “B” level services, and discussed whether services with an “I” (Insufficient evidence) rating might be appropriate coverage guidance topics. They agreed that taking on “I” recommendations may be appropriate, but not to take on “A” and “B” level recommendations with the intent that those recommendations would be followed. **The subcommittee voted 3-0, with Saboe abstaining, to recommend that HERC retire this coverage guidance.**

Induction of labor—Obley reviewed the scope document. Chan questioned the use of elective cesarean section as a comparator for induction of labor. After a brief discussion, including the lack of comparative trials, the fact that these are clinically not necessarily appropriate comparators, and the lack of current OHP coverage of elective cesarean, the group decided to remove elective cesarean as a comparator. It was also confirmed that elective induction with a favorable cervix after 39 weeks is a currently covered condition for OHP. **The subcommittee approved the revised scope document 4-0.**

Management of recurrent acute otitis media—Livingston drew the subcommittee’s attention to a revised version which had been posted as a handout to the original meeting materials. Obley reviewed the draft and there was brief discussion. Wentz raised concerns about the harm of antibiotic resistance. There was a discussion about the potential lack of literature on this, but that it may be an important consideration that would sway coverage. They decided to have treatment related harms as an important outcome as this could change the recommendation. Wentz also raised the concern of age, as this problem occurs most often before the age of six, making the impact on school performance difficult to assess at the time a decision is made.

Carl Stevens, a medical director at CareOregon and professor of medicine at UCLA, provided public comment. He said that audiometry results are available during preauthorization conversations while speech delay can only be seen later. It would be a mistake to combine those. Wentz said that audiometry might not pick up intermittent hearing loss which may still lead to speech delay.

After additional discussion, the subcommittee edited the coverage guidance and settled on critical outcomes of severe infection (e.g. systemic infection, sepsis, meningitis, locally invasive infection), clinically significant hearing loss, and speech delay. Important outcomes were treatment-related harms and acute otitis media episodes. **The scope statement was approved as edited, 4-0.**

For the approved scope documents, see Appendix A.

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## 6. TOPIC RESCAN—SCANNING RESULTS REVIEW

Livingston clarified that for these topics, HERC already set the scope parameters. The subcommittee's task was not to review the evidence at this meeting, but rather to determine whether an update to the existing coverage guidance is warranted based on the search which was conducted due to the rescan.

Coronary Artery Calcium Scoring—Obley reviewed the meeting materials. **After brief discussion, the subcommittee voted 4-0 to delay review of this topic until the AHRQ report is complete.** At that point the coverage guidance may or may not be re-opened depending on the results of that report. This could happen earlier than two years.

Coronary Computed Tomography Angiography—Obley reviewed the rescanning summary. Chan noted that there is new evidence on this topic, but there is also a pending AHRQ report. Stevens, an emergency doctor by training, said that the use of this technology for evaluation of possible angina versus for acute chest pain is different. The recent increase in use has been in the acute setting. **The motion to delay consideration until the release of the AHRQ report was approved 4-0.**

Attention Deficit/Hyperactivity Disorder—Obley reviewed the rescanning summary. For this topic there is an upcoming NICE report. The recommendation is to wait for the NICE report. The subcommittee discussed the changes in diagnostic criteria with DSM-5, the frequent comorbid conditions in the population with ADHD, and the exclusion of changes in diet. The subcommittee edited the key questions to include explicit consideration of mental health comorbidities to key questions 1 and 4. The issue of stimulant medication diversion was discussed, as this is an increasing problem. **After discussion, the subcommittee agreed to change the scope statement and to delay review pending the release of the NICE guideline, 4-0.** For the revised scope statement, see Appendix B

Chan asked a methodological question. If we are limiting the outcomes to 5, should we limit the interventions to five as well? For ADHD in particular there are a large number of interventions. Gingerich noted that limiting the number of interventions or subpopulations may be useful as well. Obley and King said that limiting the parameters simplifies the search and will help focus the discussion. The subcommittee also discussed that PICO and KQ need to be iterative throughout the process as unforeseen information can arise.

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## 7. NEXT TOPICS

With none of the rescans resulting in an immediate review, the EbGS could take on an additional topic at its November meeting. Topics discussed included acupuncture, hysterectomy, management of chronic non-cancer pain, telepsychiatry, readmissions after hospitalizations for heart failure, bipolar disorder and smoking cessation in pregnancy and postpartum care. Any topics not already approved by HERC would need approval October 1. Livingston requested and received permission for staff to select a topic prior to the next meeting.

## 8. ADJOURNMENT

The meeting was adjourned at 5:00 pm. The next meeting is scheduled for November 5, 2015 in room 112 at the Wilsonville Training Center.

DRAFT

# Section 3.0

## Coverage Guidances

## HERC Coverage Guidance – Nitrous Oxide for Labor Pain Disposition of Public Comments

### Commenters

Identification	Stakeholder
A	Member of the public <i>[Submitted September 21, 2015]</i>

### Public Comments

ID/#	Comment	Disposition
A1	<p>Coverage guidance should state that nitrous oxide is a medical gas and should be handled by staff who are state licensed and acting within their scope of practice when purchasing, setting up equipment, testing equipment, handling the mask, monitoring the equipment during use, and gas scavenging.</p> <p>Coverage guidance should state that nitrous oxide is a medical gas and must be handled, monitored, and used in compliance with regulations and guidelines from:</p> <ul style="list-style-type: none"> <li>• Compressed Gas Association (CGA)</li> <li>• Occupational Safety and Health Administration (OSHA)</li> <li>• The National Fire Protection Association (NFPA)</li> <li>• The Joint Commission for the Accreditation of Healthcare Organizations (JCAHO)</li> <li>• Medical malpractice insurance carriers</li> <li>• Code of Federal Regulations (CFR) Title 41 - Public Contracts and Property Management</li> </ul>	<p>Thank you for your comment. Our coverage guidances make recommendations about coverage, and assume that equipment will be used by qualified and appropriately licensed personnel in accordance with all applicable regulations.</p>

# HEALTH EVIDENCE REVIEW COMMISSION (HERC)

## COVERAGE GUIDANCE: NITROUS OXIDE USE FOR LABOR PAIN MANAGEMENT

**DRAFT for EbGS Meeting Materials 11/5/2015 (rev. 11/2/15)**

### 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-Informed Framework – 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.

## 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:</b> Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
<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 consider an epidural if adverse events occur or if analgesia is insufficient. Other women may prefer	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.
<b>Mode of birth</b> <i>(Critical outcome)</i>	<a href="#">Compared to women using epidural anesthesia, for those using N2O:</a> 15 to 34 more women per 100 are likely to have <a href="#">an unassisted</a> vaginal birth <del>when using N2O</del> ; 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 compared to those using epidural anesthesia for labor pain.  ●●○○ <i>(Low certainty based on prospective cohort and cross sectional studies with consistent findings)</i>			

<b>Coverage question:</b> Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
<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>Maternal adverse effects</b> <i>(Important outcome)</i>	Women may experience unpleasant side effects when using N2O. <u>(These data come from studies of women using N2O as the sole form of labor analgesia and are not compared to any other methods.)</u> 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.  ●●●○ <i>(Moderate certainty based on multiple RCTs and other studies with consistent findings)</i>		epidural anesthesia because of its greater effect in reducing labor pain.	
<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. <u>(These data come from studies where multiple labor pain management modalities are readily available and women using N2O or epidural were asked if they would want to use that method for a future birth.)</u>  ●●○○ <i>(Low certainty based on prospective cohort and cross-sectional studies with consistent findings)</i>			
<b>Use of neuraxial (e.g., epidural) anesthesia</b> <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			

<b>Coverage question:</b> Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
<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>
	<p><u>availability or</u> use of N2O changes the use of neuraxial anesthesia.</p> <p>●○○○ (Very low certainty based on cross-sectional studies with consistent findings)</p>			
<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-informed framework elements are described in Appendix A. Appendix B provides a GRADE Evidence Profile.

## 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<sup>®</sup>) or as a premixed gas (e.g., Entonox<sup>®</sup>). Entonox<sup>®</sup> 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 C.

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**

<b>Citation</b>	<b>Total Studies Included</b>	<b>Included Studies Specifically Addressing Coverage Guidance Scope</b>
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 N<sub>2</sub>O; parenteral opioids and non-pharmacologic techniques not widely available or used in the U.S.). Many of the studies used different concentrations of N<sub>2</sub>O compared to the 50% N<sub>2</sub>O/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 [availability or](#) use of N<sub>2</sub>O 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 N<sub>2</sub>O 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 N<sub>2</sub>O 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 N<sub>2</sub>O use in labor, that 16 of these were conducted prior to 1980 when it was usual practice to combine N<sub>2</sub>O with other sedative, tranquilizing and anesthetic agents. Although N<sub>2</sub>O 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.

## 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).

## REFERENCES

### Evidence Sources

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

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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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## 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. 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 C. 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 D. APPLICABLE CODES

CODES	DESCRIPTION
<b>ICD-9 Diagnosis Codes</b>	
760.0-760.5,760.61-760.9,761.0-761.9,762.0-762.9,763.0-763.7,763.81-763.9,764.00-764.99,765.20-765.29,779.32,779.81-779.82,779.84,779.89,V30.00-V30.2,V31.00-V31.2,V32.00-V32.2,V33.00-V33.2,V34.00-V34.2,V35.00-V35.2,V36.00-V36.2,V37.00-V37.2,V39.00-V39.2	Birth of Infant
<b>ICD-10 Diagnosis Codes</b>	
P00.0-P00.7,P00.81-P00.9,P01.0-P01.9,P02.0-P02.1,P02.20-P02.9,P03.0-P03.6,P03.810-P03.9,P04.0-P04.3,P04.41-P04.9,P05.00,P05.10,P05.9,P29.0,P29.11-P29.2,P29.4,P29.81-P29.9,P36.0,P36.10-P36.9,P78.89,P92.01-P92.09,P94.1-P94.9,P96.0,P96.3-P96.5,P96.82-P96.89,Q27.0, Z38.00-Z38.8	Birth of Infant
<b>CPT Codes</b>	
01960	Anesthesia for vaginal delivery only
01961	Anesthesia for cesarean delivery only
01967	Neuraxial labor analgesia/anesthesia for planned vaginal delivery
01968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia
01969	Anesthesia for cesarean hysterectomy following neuraxial labor analgesia/anesthesia
01996	Daily management of epidural, not to include the day that the catheter is placed

Note: Inclusion on this list does not guarantee coverage

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# Section 4.0

## Coverage Guidances

# HEALTH EVIDENCE REVIEW COMMISSION (HERC)

## COVERAGE GUIDANCE: SKIN SUBSTITUTES FOR CHRONIC SKIN ULCERS

**DRAFT for 11/5/2015 EbGS meeting materials (rev. 11/2/2015)**

### HERC Coverage Guidance

Skin substitutes for chronic venous leg ulcers and chronic diabetic foot ulcers are recommended for coverage (*weak recommendation*) when all of the following criteria are met:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable
3. Appropriate offloading has been performed
4. Wound has adequate arterial flow, no ongoing infection and a moist wound healing environment
5. Multilayer compression dressings are used (when clinically appropriate)
6. Patient has not used tobacco products 4 weeks prior to placement
7. For patients with diabetes, Hba1c level is < 12.
8. No prior failure of the same skin substitute for the ulcer being treated
9. Prior appropriate wound care therapy has failed to result in significant improvement of the wound over at least 30 days
10. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, required for coverage of ongoing applications
11. Patients is able to adhere to the treatment plan

The following products are recommended/not recommended for coverage as shown below. All recommendations are weak recommendations except as specified.

Product	Diabetic foot ulcers	Venous leg ulcers
Dermagraft	Recommended	Not recommended
Apligraf	Recommended	Recommended
OASIS Wound Matrix	Not recommended	Recommended
Epifix	Not recommended	Not recommended
Grafix	Not recommended	Not recommended
Graftjacket	Not recommended	Not recommended
Talymed	Not recommended	Not recommended
Theraskin	Not recommended	Not recommended
Other skin substitutes	Not recommended	Not recommended

The use of skin substitutes is not recommended for coverage of chronic skin ulcers other than venous leg ulcers and diabetic foot ulcers (e.g. pressure ulcers, ~~other types~~) (*weak recommendation*).

Implementation considerations:

1. Consider reference-based pricing or bundling (application and product costs)
2. Products preferred by payers may vary based on price and number of applications expected

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework 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 standard methodology to translate evidence reviews into a policy decision. Coverage guidances are based on a thorough review of the evidence by the Evidence-based Guideline Subcommittee or the Health Technology Assessment Subcommittee. The evidence review used in the coverage guidance development process may use existing systematic reviews of the evidence on a given topic and incorporate additional individual studies published more recently than the included systematic reviews. Included evidence sources are generally published within the last three to five years. A full description of the evidence review methodology is included in each coverage guidance as an appendix. The translation of the evidence review to a policy decision is based on a GRADE-informed framework, as described below.

## 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.

Note: The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee. The GRADE framework elements are described in Appendix A. A GRADE Evidence Profile is provided in Appendix B.

### Apligraf® / Graftskin

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	DFU <sup>1</sup> : osteomyelitis 2.7% vs 10.4% (p = 0.4) ●●○○ (low certainty of no benefit, based on one good quality RCT) <a href="#">DFU (Apligraf vs Theraskin): One amputation due to infection with Theraskin vs none for Apligraf (p-value not reported)</a> ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)	Incremental cost for adding Apligraf to a patient's course of treatment for a small leg ulcer (<25 cm <sup>2</sup> ) under Medicare FFS (using average national prices for October, 2015) would range from \$771.20 for a single application in an ambulatory surgery center to \$4,553.81 for three applications in the physician's office setting. Prices are

<sup>1</sup> DFU: Diabetic Foot Ulcer; VLU: Venous Leg Ulcer

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
	<p><u>VLU</u>: osteomyelitis 8.1% vs 0% (no statistical analysis) ●○○○ (very low certainty of benefit, based on one good quality RCT)</p>	<p>somewhat higher for foot ulcers due to higher physician fees/bundled fees for application. Product is sold in 44 cm<sup>2</sup> sheets. Up to 3 applications appear to be the maximum necessary based on included studies.</p>
<b>Complete wound healing</b> (Critical outcome)	<p><u>DFU</u>: RR 1.5, 1.96 (p = 0.01, 0.03) ●●○○ (moderate certainty of benefit, based on two good quality RCTs)</p> <p><a href="#">DFU (Apligraf vs Theraskin): 47.1% vs 66.7% (p-value not reported)</a> ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p><u>VLU</u>: RR 2.38 (p &lt; 0.001) ●●○○ (low certainty of benefit, based on one good quality RCT)</p> <p><u>Unspecified non-healing ulcers</u>: 100% vs 75% (p &lt; 0.01) ●○○○ (very low certainty of benefit, based on one poor quality RCT)</p>	
<b>Quality of life</b> (Critical outcome)	No evidence identified.	
<b>Time to complete wound healing</b>	<p><u>DFU</u>: No evidence identified.</p> <p><u>VLU</u>: 61 vs 191 days (statistical analysis not provided) ●●○○ (low certainty of benefit, based on one good quality RCT)</p>	

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
(Important outcome)	<p><u>Unspecified non-healing ulcers</u>: 7 vs 51 weeks (statistical analysis not provided)</p> <p>●○○○ (very low certainty of benefit, based on one poor quality RCT)</p>	
<p><b>Adverse effects</b> (Important outcome)</p>	<p><u>DFU</u>: Pooled data from 4 RCTs showed similar incidence of cellulitis, dermatitis, and peripheral edema with Apligraf® vs control (statistical analysis not reported)</p> <p>●●○○ (low certainty of no harm, based on four good quality RCT)</p> <p><u>VLU</u>: Infection rates of 8.2% vs 7.8% (statistical analysis not reported)</p> <p>●○○○ (very low certainty of no harm, based on one good quality RCT)</p>	
<p><b>Rationale:</b> Apligraf is recommended for coverage for venous leg ulcers and diabetic foot ulcers, based on improved complete wound healing, low variability in patient preference, and despite its cost. A strong recommendation was not made because only 2/5 of the predefined critical/important outcomes were addressed by the evidence and in favor of Apligraf for DFU. Coverage is recommended only when other conditions exist for wound healing (see Other Considerations section, below).</p>		
<p><b>Recommendation:</b> Apligraf is recommended for coverage for diabetic foot ulcers and venous leg ulcers (<i>weak recommendation</i>) when conditions necessary for wound healing are present. Payers may wish to consider bundled payment, reference pricing, or other effective alternatives for smaller ulcers, as this product is sold in units of 44 cm<sup>2</sup> and has a short shelf life, which may lead to waste.</p>		

## DermaGraft®

Coverage question: Should DermaGraft® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	<p><u>DFU</u>: Osteomyelitis incidence 8.6% in both intervention and control groups</p> <p>●○○○ (very low certainty of no benefit, based on one fair quality RCT)</p>	<p>Incremental cost for adding DermaGraft® to a patient's course of treatment for a small leg ulcer (&lt;25 cm<sup>2</sup>) under Medicare FFS (using average national prices for October, 2015) would range from \$771.20 for a single application in an ambulatory surgery center to \$11,960.80 for eight applications in the hospital outpatient setting. Up to 4 applications total appears equivalent efficacy to 8 applications.</p> <p>Product is sold in 37.5 cm<sup>2</sup> sheets.</p>
<b>Complete wound healing</b> <i>(Critical outcome)</i>	<p><u>DFU</u>: OR 1.64 (95% CI, 1.10 to 2.43) in pooled data from 3 fair quality RCTs; one poor quality RCT with 38.5% versus 31.7% (p = 0.138)</p> <p>●●○○ (low certainty of benefit, based on three fair quality concordant RCTs and one poor quality discordant RCT)</p> <p><u>DFU (DermaGraft vs OASIS): 84.6% vs 76.9%, p = 0.62</u></p> <p>●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p><u>VLU</u>: RR 1.83 (95% CI, 0.47 to 7.21) and RR 3.04 (95%, CI 0.95 to 9.68) ●○○○ (very low certainty of no benefit, based on two fair quality RCTs)</p>	
<b>Quality of life</b> <i>(Critical outcome)</i>	No evidence identified.	
<b>Time to complete wound healing</b> <i>(Important outcome)</i>	<p><u>DFU</u>: 13 weeks vs 28 weeks (statistical analysis not reported)</p> <p>●●○○ (low certainty of benefit, based on four low to fair quality RCTs)</p> <p><u>DFU (DermaGraft vs OASIS): 40.90 vs 35.67 days, p = 0.73</u></p>	

	<p>●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p><u>VLU</u>: 35 weeks vs 74 weeks, (statistical analysis not reported)</p> <p>●○○○ (very low certainty of benefit, based on one fair quality RCT)</p>
<p><b>Adverse effects</b> (Important outcome)</p>	<p><u>DFU</u>: 19% vs 32%, p = 0.007; second RCT no difference in rates of AE.</p> <p>●○○○ (very low certainty of benefit, based on two fair quality RCTs)</p> <p><u>VLU</u>: Similar number of AEs in all groups, statistical analysis not reported</p> <p>●○○○ (very low certainty of no harm, based on one fair quality RCT)</p>
<p><b>Rationale:</b> Dermagraft is recommended for coverage for diabetic foot ulcers based on evidence of reduced time to wound healing and a higher likelihood of complete wound healing than usual care, with low variability in patient values and preferences. The recommendation is weak because of the low certainty of the evidence, and relatively high cost.</p> <p>Dermagraft is not recommended for coverage for venous leg ulcers based on insufficient evidence of benefit for any critical or important outcome and lack of FDA approval for this indication.</p>	
<p><b>Recommendation:</b></p> <p>Dermagraft is not recommended for coverage for venous leg ulcers (<i>weak recommendation</i>)</p> <p>Dermagraft is recommended for coverage for diabetic foot ulcers (<i>weak recommendation</i>) when conditions necessary for wound healing are present.</p> <p>Payers may wish to consider bundled payment, reference pricing, or other effective alternatives for smaller ulcers, as this product is sold in units of 37.5 cm<sup>2</sup> and has a short shelf life, which may lead to waste.</p>	

## OASIS® Wound Matrix

Coverage question: Should OASIS® Wound Matrix be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	No evidence identified.	Incremental cost for adding OASIS Wound Matrix to a patient’s course of treatment for a small leg ulcer (<25 cm <sup>2</sup> ) under Medicare FFS (using average national prices for October, 2015) would be \$235.69 for a single application in an ambulatory surgery center. In a physician’s office, the cost would be \$10.72 per cm <sup>2</sup> plus physician’s fees of \$143.73. The manufacturer recommends re-application every three to seven days as needed. Product is sold in units of varying sizes, the smallest of which is 10.5 cm <sup>2</sup> .
<b>Complete wound healing</b> <i>(Critical outcome)</i>	<p><u>DFU</u>: 49% vs 28% (p = 0.06)            ●○○○ <i>(very low certainty of benefit, based on one fair quality RCT)</i></p> <p><u>DFU (OASIS vs Dermagraft)</u>: 76.9% vs 84.6%, p = 0.62            ●○○○ <i>(very low certainty of no comparative benefit, based on one fair quality RCT)</i></p> <p><u>VLU</u>: 80% vs 65% at 8 weeks (p &lt; 0.05); 83% vs 46% at 16 weeks (p &lt; 0.001); 55% vs 34% at 12 weeks, (p = 0.02)            ●●○○ <i>(low certainty of benefit, based on three fair to good quality RCTs with inconsistency in comparator groups)</i></p>	
<b>Quality of life</b> <i>(Critical outcome)</i>	No evidence identified.	
<b>Time to complete wound healing</b>	<u>DFU</u> : 5.4 vs 8.3 weeks, statistical analysis not reported; <del>35.67 ± 41.47 vs 40.90 ± 32.32 days</del> ; 67 vs 73 days (p = 0.245)	

Coverage question: Should OASIS® Wound Matrix be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
(Important outcome)	<p>●●○○ (low certainty of no benefit, based on <a href="#">three</a> fair quality RCTs)</p> <p><a href="#">DFU (OASIS vs Dermagraft): 35.67 vs 40.90 days, p = 0.73</a></p> <p>●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p><a href="#">VLU</a>: 63% vs 40% expected to heal at 12 weeks, p = 0.0226</p> <p>●○○○ (very low certainty of benefit, based on one good quality RCT)</p>	
<b>Adverse effects</b> (Important outcome)	<p><a href="#">DFU</a>: Approximately equal number of AEs between groups, statistical analysis not reported</p> <p>●○○○ (very low certainty of no benefit, based on fair quality RCT)</p> <p><a href="#">VLU</a>: Approximately equal number of AEs between groups, statistical analysis not reported</p> <p>●○○○ (very low certainty of no benefit, based on good quality RCT)</p>	
<p><b>Rationale:</b> OASIS Wound Matrix is recommended for coverage for venous leg ulcers based on low-certainty evidence that it improves complete wound healing and time to complete wound healing, with low variability in values and preferences. OASIS Wound matrix is not recommended for coverage for diabetic foot ulcers based on inadequate evidence of benefit, other alternatives available, and its costliness.</p>		
<p><b>Recommendation:</b> OASIS is not recommended for coverage for diabetic foot ulcers (<i>weak recommendation</i>). OASIS is recommended for coverage for venous leg ulcers (<i>weak recommendation</i>), when conditions necessary for wound healing are present.</p>		

## EpiFix®

Coverage question: Should EpiFix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	No evidence identified.
<b>Complete wound healing</b> <i>(Critical outcome)</i>	DFU: 92% versus 8% (p < 0.0001) ●○○○ <i>(very low certainty of benefit, based on one RCT of fair quality)</i>
<b>Quality of life</b> <i>(Critical outcome)</i>	No evidence identified.
<b>Time to complete wound healing</b> <i>(Important outcome)</i>	No evidence identified.
<b>Adverse effects</b> <i>(Important outcome)</i>	No evidence identified.
<b>Rationale:</b> EpiFix is not recommended for coverage due to insufficient evidence of effectiveness and the availability of effective alternatives <i>(weak recommendation)</i> .	
<b>Recommendation:</b> EpiFix is not recommended for coverage for chronic skin ulcers <i>(weak recommendation)</i> .	

## Grafix®

Coverage question: Should Grafix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Deep soft tissue or bone infection (Critical outcome)	DFU: "Wound-related infection" (undefined) 18.0% vs 36.2%, $p = 0.044$ ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
Complete wound healing (Critical outcome)	DFU: 62% vs 21%, $p < 0.01$ ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
Quality of life (Critical outcome)	No evidence identified.
Time to complete wound healing (Important outcome)	DFU: 42 days vs 69.5 days (statistical analysis not reported) ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
Adverse effects (Important outcome)	DFU: 44% vs 66% ( $p = 0.031$ ) ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
<b>Rationale:</b> Grafix is not recommended for coverage for any indication due to insufficient evidence of effectiveness and the availability of effective alternatives ( <i>weak recommendation</i> ).	
<b>Recommendation:</b> Grafix is not recommended for coverage for chronic skin ulcers ( <i>weak recommendation</i> ).	

## Graftjacket®

Coverage question: Should Graftjacket® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> (Critical outcome)	One trial had a single pt with hallux amputation due to infection in the treatment group and zero in control. ●○○○ (very low certainty of harm, based on one RCT of poor quality)
<b>Complete wound healing</b> (Critical outcome)	<u>DFU, vs moist dressing</u> : 70% vs 46% (p = 0.03) <u>DFU, vs Curasol</u> : 86% vs 29% (p = 0.006) ●●○○ (very low certainty of benefit, based on two low to fair quality RCTs)
<b>Quality of life</b> (Critical outcome)	No evidence identified.
<b>Time to complete wound healing</b> (Important outcome)	<u>DFU</u> : 11.92 vs 13.5 weeks and 5.7 vs 6.8 weeks, not significant ●○○○ (very low certainty of no benefit, based on two low to fair quality RCTs)
<b>Adverse effects</b> (Important outcome)	<u>DFU</u> : Wound infection 21.4% vs 35.7%, statistical analysis not reported ●○○○ (very low certainty of no harm, based on one poor quality RCT)
<b>Rationale:</b> Graftjacket is not recommended for coverage because of the very low evidence of benefit for the critical outcome of complete wound healing, and a lack of efficacy for improving time to complete wound healing. Given only one application is required, fewer resources would be needed which would be an argument in favor, however, there is insufficient evidence to justify if even at the lower cost, this would provide significant benefit to patients.	
<b>Recommendation:</b> Graftjacket is not recommended for coverage for chronic skin ulcers ( <i>weak recommendation</i> ).	

## Talymed®

Coverage question: Should Talymed® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> (Critical outcome)	No evidence identified.
<b>Complete wound healing</b> (Critical outcome)	<u>VLU</u> : 86% vs 45% (p = 0.0005) ●○○○ (very low certainty of benefit, based on one good quality RCT)
<b>Quality of life</b> (Critical outcome)	No evidence identified.
<b>Time to complete wound healing</b> (Important outcome)	No evidence identified.
<b>Adverse effects</b> (Important outcome)	<u>VLU</u> : No significant treatment-related AEs ●○○○ (very low certainty of no benefit, based on one good quality RCT)
<b>Rationale:</b> Talymed is not recommended for coverage because of very low certainty of benefit, a lack of strong patient preferences for this, alternatives available, and its high cost.	
<b>Recommendation:</b> Talymed is not recommended for coverage for chronic skin ulcers ( <i>weak recommendation</i> ).	

## TheraSkin®

Coverage question: Should TheraSkin® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> (Critical outcome)	<a href="#">No evidence identified. DFU (TheraSkin vs Apligraf): One amputation for infection, compared to none with Apligraf</a> ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
<b>Complete wound healing</b> (Critical outcome)	DFU: <a href="#">(TheraSkin vs Apligraf): 66.7% vs 41.3% (p = 0.21)</a> <del>compared to Epifix (p-value not reported)</del> ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
<b>Quality of life</b> (Critical outcome)	No evidence identified.
<b>Time to complete wound healing</b> (Important outcome)	No evidence identified.
<b>Adverse effects</b> (Important outcome)	No evidence identified.
<b>Rationale:</b> TheraSkin is not recommended for coverage because of insufficient evidence of benefit (limited evidence suggesting it is comparable to another <a href="#">effective</a> product <del>which does not have sufficient evidence to recommend it</del> ), a lack of strong patient preferences for this, alternatives available, and its moderate cost.	
<b>Recommendation:</b> TheraSkin is not recommended for coverage for chronic skin ulcers ( <i>weak recommendation</i> ).	

## EVIDENCE OVERVIEW

### Clinical background

Diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and decubitus ulcers can be serious wounds, leading to severe health outcomes such as amputations and death. Diabetic foot ulcers are the result of atherosclerosis that impedes blood flow to the extremities and peripheral neuropathy that reduces the ability to sense injuries from extended pressure or other causes. Diabetic foot ulcers can lead to infections such as osteomyelitis and amputation. Appropriate treatment of these wounds can minimize the negative health outcomes and improve patient quality of life. Treatment for diabetic foot ulcers include cleaning, dressing, debridement, and pressure relief (Wound, Ostomy, and Continence Nurses Society, 2012). During the past 20 years, the prevalence of diabetes among adults in Oregon has more than doubled, to 9% in 2011. Among adults covered by the Oregon Health Plan, 17% have diabetes (Oregon Heart Disease and Stroke and Diabetes Prevention Programs, 2013). The annual incidence of foot ulcers among Medicare patients with diabetes is 6% (Margolis et al., 2011).

Venous leg ulcers are caused by chronic venous insufficiency. Treatment for venous leg ulcers include cleaning and dressing the wound, hemodynamic support to control the underlying disorder that caused the ulcer (e.g., medication or vascular bypass procedures), compression bandages, and compression stockings. The lifetime incidence of venous leg ulcers is about 1% (O'Meara, Al-Kurdi, & Ovington, 2008).

Decubitus ulcers or pressure ulcers (commonly called bed sores or pressure ulcers) occur when patients are unable to reposition themselves, most commonly in hospitals, long-term care facilities, and at home. Sustained pressure on a specific part of the body (often a bony prominence such as hip or sacrum) for long periods of time can cause a pressure ulcer. Treatment includes removing the pressure from the affected area, skin protection, debridement of necrotic tissues, cleaning, and dressing. Data from the National Nursing Home Survey indicate that 11% of nursing home residents had pressure ulcers (Park-Lee & Caffrey, 2009).

Skin substitutes have been used to treat ulcers that do not heal with the standard treatments. The most common use for skin substitutes is for the treatment of diabetic foot ulcers, venous leg ulcers, and decubitus ulcers. The etymologies of these ulcers make the wounds slower to heal, and the usual wound treatments are not always sufficient to ensure complete healing.

### Indications

Skin substitutes are indicated for the treatment of chronic wounds, usually defined as having not healed within 30 days, having not responded to initial treatment, or persisting despite appropriate care. Skin substitutes were originally designed to treat burns, but now the most common usage is treating diabetic foot ulcers, venous leg ulcers, and decubitus ulcers.

## Technology description

Skin substitutes promote healing and wound closure by mimicking or substituting for the skin structure. The skin substitute is designed to help the healing process by stimulating the host to regenerate lost tissue and replace the wound with functional skin. Skin substitutes can be categorized (Snyder, Sullivan, & Schoelles, 2012) based upon how they are derived or produced:

- Products derived from human donor tissue
- Products derived from living human or animal tissues and cells
- Acellular animal –derived products
- Biosynthetic products

Currently, there are over 73 skin substitute products approved by the FDA for use in humans. While skin substitute products can be broadly grouped according to their source materials, the products are all sufficiently unique as to make generalization of efficacy across categories impracticable.

Table 1 shows skin substitute products available in the United States, categorized by how the product is derived and thus regulated by the FDA. This list of skin substitutes was created from the evidence and policy sources, and may not be complete. Products in the same category may not be equivalent in terms of effectiveness (Snyder, Sullivan, & Schoelles, 2012).

Human-derived skin substitute products that are minimally processed are regulated by the FDA as human cells, tissues, and cellular and tissue-based products (HCT/Ps). With HCT/Ps, tissue is obtained from human donors then processed and used in the same role in the patient (e.g., skin for skin, tendon for tendon). These HCT/Ps are regulated as human tissue intended for transplantation as long as the processing and clinical use are consistent with “Minimal Manipulation” and “Homologous Use” as defined in 21 CFR 1271. Products regulated as HCT/Ps must be registered with the FDA but are not required to demonstrate safety or effectiveness.

Cellular-derived material for wound healing cultured from human-derived tissues are regulated using the Biologics License Application (under the Federal Public Health Service Act) or with premarket approval (PMA) or as a Humanitarian Use Device obtained through a humanitarian device exemption depending on their composition and primary mode of action. The application for products regulated under the PMA process must include scientifically valid clinical studies demonstrating that the product is effective and safe.

Acellular animal-derived products and synthetic products are regulated under Section 510(k) of the Food, Drug and Cosmetic Act. This requires a premarket submission to the FDA to demonstrate that the device is substantially equivalent, i.e., at least as safe and effective, to a legally marketed device that is not subject to PMA. Submitters can compare their device to a device that was legally marketed prior to May 28, 1976 or a device which has been previously found to be substantially equivalent through the 510(k) process (Snyder, Sullivan, & Schoelles, 2012).

**Table 1: Skin Substitutes**

Products derived from human donor tissue, minimally processed	Products derived from living human and/or animal tissue	Acellular animal-derived products	Biosynthetic products
AlloDerm Regenerative Tissue Matrix Allpatch HD™ Alloskin™ Cymetra® Micronized AlloDerm Dermacell® and Arthroflex® Flex HD® GammaGraft® Graftjacket® Regenerative Tissue Matrix Graftjacket® Express Scaffold Matrix HD™ Memoderm™ Puros® Dermis Repliform® TheraSkin®	Apligraf®/Graftskin Dermagraft® AlloMax™ Celaderm® OrCel™ TransCyte™	Acell UBM Hydrated Wound Dressing Acell UMB Lyophilized Wound Dressing Aongen™ Collagen Matrix Atlas Wound Matrix Avagen Wound Dressing Biobrane® Collagen Sponge (Innocoll) Collagen Wound Dressing (Oasis Research) Collaguard® CollaSorb™ CollaWound™ Collexa® Collieva® Coreleader Colla-Pad Dermadapt™ Wound Dressing DressSkin EndoForm Dermal Template™ Excellagen E-Z Derm™ FortaDerm™ Wound Dressing Helicoll Integra® Dermal Regeneration Template	Epicel™ Hyalomatrix® (Laserskin®) Hyalomatrix® Jaloskin® Suprathel® Talymed®

Products derived from human donor tissue, minimally processed	Products derived from living human and/or animal tissue	Acellular animal-derived products	Biosynthetic products
		Integra™ Bilayer Matrix Wound Dressing Integra™ Flowable Wound Matrix LTM Wound Dressing MatriStem Matristem Micromatrix® Matristem® Burn Matrix MatriStem® Wound Matrix Matrix Collagen Wound Dressing Medline Collagen Wound Dressing OASIS Burn Matrix™ OASIS Wound Matrix™ Primatrix™ Primatrix™ Dermal Repair Scaffold SIS Wound Dressing II SS Matrix™ Stimulen™ Collagen TheraPorm™ Standard/Sheet Unite® Biomatrix Unite™ Biomatrix	

The following skin substitute products may not be available for chronic wounds in the US: Dermagen, EpiDex, Hyalograft, Kaloderm, Matriderm, PermaDerm, StrataGraft/ExpressGraft, and Xelma.

### Key Questions and Outcomes

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 D.

1. What is comparative effectiveness of different types of skin substitutes compared with wound care alternatives for individuals with chronic skin ulcers? Include consideration of:
  - a. Age
  - b. Body mass index (BMI)
  - c. Comorbidities
  - d. Site of ulcer
  - e. Ulcer etiology (e.g. infectious, pressure or circulatory).
  - f. Wound severity
  - g. Prior need for skin substitute
  - h. Failure of prior therapies
2. What adverse events are associated with skin substitutes?
3. What are contraindications to the use of skin substitutes?

*Critical outcomes* selected for inclusion in the GRADE table: deep soft tissue or bone infection, complete wound healing, and quality of life. *Important outcomes* selected for inclusion in the GRADE table: time to complete wound healing and adverse effects.

## Evidence overview

Four systematic reviews and two additional RCTs address the use of skin substitutes for chronic skin ulcers; they are summarized in Tables 2 and 3. The outcomes considered critical for purposes of this coverage guidance are deep soft tissue or bone infection, complete wound healing, and quality of life. Time to complete wound healing and adverse effects are considered important outcomes. Complete wound healing is generally defined as “full epithelialization with no drainage, no exudate or eschar (scab) present” (Snyder, Sullivan & Schoelles, 2012, p. 48).

Although some products may have similar components or substrates, “[t]he results obtained from studies of a single product [...] cannot be extrapolated to all products in a group because of differences in product components and healing properties” (Snyder, Sullivan & Schoelles, 2012, p. 48). Therefore, the results are organized by product type below.

Results are also separated by indication (diabetic foot ulcer or venous leg ulcer; the search did not identify any evidence for skin substitutes in the treatment of decubitus ulcers). Effectiveness for one type of wound cannot be extrapolated across indications “because of the difference in etiology and pathophysiology” between different types of wounds (Snyder, Sullivan & Schoelles, 2012, p. 56).

One limitation of the body of evidence is a lack of standardization of comparators. Some trials compare one skin substitute versus another, but many use “usual care” in the control group. Some treatments that fall into the category of usual care can include (but are not limited to):

- Diabetic Foot Ulcers – usual care techniques:
  - Nonadherent gauze dressing (Mepitel), covered with a secondary dressing including saline-moistened gauze and dry gauze

- Saline-moistened, nonadherent gauze (Teapore) covered with a layer of saline-moistened gauze followed by dry gauze and petrolatum gauze layer
- Nonadherent interface + saline moistened gauze
- Saline moistened gauze
- Venous Leg Ulcers – usual care techniques:
  - Tegapore (gauze bolster), zinc oxide-impregnated, paste bandage (Unna boot), and self-adherent elastic wrap
  - Multilayered compression therapy

The body of evidence is also limited in the evidence addressing the considerations in Key Question 1. Where possible, discussion of study inclusion/exclusion criteria are presented.

**Table 2. Summary of Included Systematic Reviews**

<b>Systematic Review (Quality) Total N</b>	<b>Population No. and Type of Included Studies</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
Game (2015) (Fair) N = 1461	Diabetic foot ulcers: 11 RCTs 1 Cohort 1 Case-control	<ul style="list-style-type: none"> <li>● Allogeneic fetal fibroblasts on polyglactic matrix (Dermagraft)</li> <li>● Tissue engineered sheet of fibroblast/keratinocyte co-culture (Graftskin)</li> <li>● Living keratinocytes and fibroblasts (Apligraf®)</li> <li>● Amniotic membrane wound graft (Epifix)</li> </ul>	<ul style="list-style-type: none"> <li>● Complete wound healing</li> <li>● Time to complete wound healing</li> </ul>
Felder (2012) (Fair) N = 2043	Chronic foot ulcers (diabetic, angiopathic, venous stasis, pressure-induced, or infected): 15 RCTs 1 Cohort 5 SRs	<ul style="list-style-type: none"> <li>● Bilayer of neonatal keratinocytes and fibroblasts on hyaluronic acid matrix (Apligraf/Graftskin)</li> <li>● Neonatal fibroblasts and keratinocytes cultured onto bovine collagen matrix (OrCel)</li> </ul>	<ul style="list-style-type: none"> <li>● Complete wound healing</li> <li>● Time to complete wound healing</li> <li>● Infection rate</li> <li>● Complications</li> <li>● Ulcer recurrence</li> </ul>

<b>Systematic Review (Quality)</b>	<b>Population No. and Type of Included Studies</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
<b>Total N</b>		<ul style="list-style-type: none"> <li>• Cryopreserved split-thickness skin allograft (TheraSkin)</li> <li>• Allogeneic fetal fibroblasts on polyglactic matrix (Dermagraft)</li> <li>• Autologous cultured keratinocytes on hyaluronic acid-derived, perforated lamina (Laserskin)</li> <li>• Decellularized cadaveric dermis (Graftjacket®)</li> <li>• Bovine collagen and chondroitin-6-sulfate scaffold with silicone covering (Synthetic Integra)</li> </ul>	
Jones (2013) (Good) N = 438	Venous leg ulcers: 5 RCTs	<ul style="list-style-type: none"> <li>• Allogenic bilaminar Composite Cultured Skin (OrCel™)</li> <li>• Cultured epidermal allograft (Autoderm™)</li> <li>• Products derived from live human/animal tissue (Apligraf®, Dermagraft®)</li> </ul>	<ul style="list-style-type: none"> <li>• Complete wound healing</li> <li>• Time to complete healing</li> <li>• Rate of change in ulcer area</li> <li>• Pain</li> <li>• Adverse events</li> </ul>
Snyder (2012) (Good) N = 1,829	Diabetic foot ulcers: 12 RCTs Vascular leg ulcers: 6 RCTs	<ul style="list-style-type: none"> <li>• Products derived from human donor tissue (Graftjacket®)</li> <li>• Products derived from live human/animal tissue (Apligraf®, Dermagraft®)</li> </ul>	<ul style="list-style-type: none"> <li>• Wound infection</li> <li>• Complete wound healing</li> <li>• Time to complete wound healing</li> </ul>

<b>Systematic Review (Quality)</b>	<b>Population No. and Type of Included Studies</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
<b>Total N</b>		<ul style="list-style-type: none"> <li>• Acellular animal derived products (OASIS® Wound Matrix)</li> <li>• Biosynthetic products (Talymed®)</li> </ul>	<ul style="list-style-type: none"> <li>• Adverse events</li> <li>• Quality of life surrogate outcomes (return to baseline activities of daily living and function, pain reduction)</li> </ul>

**Table 3. Summary of Included Randomized Controlled Trials identified in additional Medline search**

<b>RCT (Quality)</b>	<b>Population</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
<b>Total N</b>			
Lavery 2014 (Poor) N = 97	Diabetic foot ulcers	<ul style="list-style-type: none"> <li>• Placenta-derived human viable wound matrix (Grafix®)</li> </ul>	<ul style="list-style-type: none"> <li>• Complete wound healing</li> <li>• Time to complete healing</li> <li>• Adverse events</li> <li>• Wound-related infections</li> </ul>

## EVIDENCE SUMMARY

*Snyder [AHRQ] (2012)*

The AHRQ systematic review by Snyder, Sullivan and Schoelles (2012) included 18 RCTs (12 on DFUs, 6 on VLUs). Of the 18 studies, eight were assessed as a low risk of bias, nine as a moderate risk of bias, and one with an unclear risk of bias. The review authors limited study inclusion to RCTs that had a minimum of 10 patients per treatment arm. In addition to the outcomes described in Table 1, the AHRQ review evaluated wound recurrence, need for amputation, need for hospitalization, return to baseline activities of daily living and function, pain reduction, and exudate and odor reduction.

### *Felder (2012)*

The systematic review by Felder, Goyal, and Attinger (2012) included 15 RCTs and one prospective cohort study as well as five systematic reviews. This SR was concerned with chronic foot ulcers of any origin. There is significant overlap in included studies (nine RCTS) between the AHRQ SR (Snyder, Sullivan and Schoelles, 2012) and this SR. Felder and colleagues (2012) included five additional studies (3 DFU, 1 VLU, 1 non-healing foot ulcer) that were not included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012). Of these five, one was assessed at low risk of bias, one at moderate risk of bias, and three at high risk of bias. Rate of complete wound healing was the primary outcome; secondary outcomes included time to complete wound healing, infection rates, and ulcer recurrence.

### *Jones [Cochrane] (2013)*

The Jones systematic review (Jones, Nelson and Al-Hity, 2013) focused on the treatment of VLUs and included five RCTs on the use of skin substitutes, two of which overlap with the AHRQ review (Snyder, Sullivan and Schoelles, 2012). Of the remaining three studies, one is rated as unclear risk of bias, one at low risk of bias, and one at moderate risk of bias. Authors included any randomized study, regardless of publication status or language, in which skin grafts or skin replacements for venous leg ulcers were compared against any other intervention (only studies involving skin substitutes are summarized in this coverage guidance), and which reported on the primary outcomes of wound healing, time to complete healing, or absolute rate of change of ulcer area.

### *Game (2015)*

A systematic review by Game and colleagues (2015) assessed the effectiveness of various interventions for diabetic foot ulcers. This is the second update of a systematic review undertaken by the International Working Group of the Diabetic Foot (IWGDF) in 2006 and first updated in June 2010. Game and colleagues (2015) included all controlled studies, both prospective and retrospective, that evaluated treatment of chronic foot ulcers in adults (age 18 and older) with type 1 or type 2 diabetes. Primary outcomes were healing, time to healing, and reduction in wound area. The 2015 review included 11 RCTs relevant to skin substitutes; all but three of them overlap with the other SRs included in this report. Of those three, one was rated at medium risk of bias and the others at high risk of bias.

## **Apligraf® / Graftskin**

Apligraf®, known previously as Graftskin, is a “living cell based bilayered skin substitute derived from bovine type 1 collagen and human fibroblasts and keratinocytes derived from neonatal foreskins” (Snyder, Sullivan, and Schoelles, 2012, pg 38).

The FDA has approved Apligraf®

For use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment

of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure.

Apligraf is contraindicated for use on clinically infected wounds. Apligraf is contraindicated in patients with known allergies to bovine collagen. Apligraf is contraindicated in patients with a known hypersensitivity to the components of the Apligraf agarose shipping medium.” of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure (Snyder, Sullivan, and Schoelles, 2012, pg 38).

The prescribing information contains a caution; “The safety and effectiveness of Apligraf have not been established for patients receiving greater than 5 device applications.”

Inclusion criteria for trials of Apligraf® varied in the size and severity of wounds. Minimum duration was 2-4 weeks. Patients were excluded for conditions that would impair wound healing such as poor glycemic control (identified in one trial as hemoglobin A1c  $\geq 12$ ), active infection, immunocompromise (either from underlying disease, radiation, chemotherapy, or recent corticosteroid use), evidence of skin cancer at or near the wound, renal or hepatic impairment, drug or alcohol abuse, and Charcot foot or inability to offload the ulcer. Some studies excluded patients whose ulcers responded to usual care in a 7-14 day run-in period. The majority of patients were male and in their 50s or 60s.

Three early studies (Sabolinski, 1996; Falanga, 1998; Falanga & Sabolinski, 1999) all used the same protocol of up to five applications within the first 21 days of treatment. Ulcers were re-examined every few days and if less than 50% of the previous application “took,” researchers applied the product again, up to five times in total. The earliest study reported that 70% of patients got 1-3 grafts; the others did not report how many applications were required. A 2009 study re-examined patients at 4 and 8 weeks after initial application and re-applied as necessary. “In the Apligraf group, 13 of the 33 subjects required only 1 application of Apligraf, and 15 and 5 subjects received 2 or 3 applications, respectively. On average, subjects received 1.8 Apligraf applications during the course of the study” (Edmonds, 2009, pg. 14). The comparative study of Apligraf® vs TheraSkin® (DiDomenico, 2011) put no limits on the number of applications and allowed them at clinician discretion, they report an average of 1.53 applications (SD = 1.65).

Chang, 2000 used only a single application for all subjects, and reported on costs thusly:

At our institution, professional fee reimbursement for all skin graft procedures averages \$1 350. A single 7-inch disk of Apligraf costs \$1000 to the third-party insurer or the patient. The reimbursement for a 3- to 5-day hospital stay, including operating room and recovery room costs, average \$8000-\$11,000 for a Medicare patient. Therefore, Apligraf application in these patients costs \$7000 to \$10,000 less than an autologous skin graft. Moreover, further cost reductions may be possible as demand for this product increases. Finally, wound closure yields may further be improved with multiple applications of TEGS and as the optimal dressing and management of TEGS-treated wounds in this patient population become better defined (Chang, 2000, pg. 49).

#### ***Critical Outcome: Deep Soft Tissue or Bone Infection***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included one trial that reported cases of osteomyelitis in patients with DFUs treated with either Apligraf®/Graftskin or usual care. The RCT compared Apligraf® to saline-moistened gauze (treatment group, n = 112; usual care group, n = 96). There was a significantly lower incidence of osteomyelitis in the Apligraf® group compared to usual care (2.7% vs 10.4%, p = 0.04).

For VLU, the AHRQ review included a single RCT comparing Apligraf® to compression therapy (treatment group, n = 161; usual care group, n = 136) that reported incidence of osteomyelitis. Approximately eight percent of patients receiving Apligraf® developed osteomyelitis at the study site, compared with no patients in the comparison group developing a bone infection (no statistical analysis conducted).

#### ***Critical Outcome: Complete Wound Healing***

Snyder and colleagues (2012) included three RCTs comparing Apligraf® to usual care. Two of the trials included patients with DFUs (total n = 280) and the third trial focused on VLUs (n = 275). The AHRQ review (Snyder, Sullivan and Schoelles, 2012) found the use of Apligraf® was associated with significantly greater percentage of wound closures compared to usual care for patients with DFUs at 12 weeks (Trial 1, n=72, 52% vs 26%, p=0.03, relative risk 1.96, 95% CI 1.05 to 3.66; Trial 2, n=208, 56% vs 38%, p=0.01, relative risk 1.5, 95% CI 1.11 to 2.04) and patients with VLUs at 12 weeks (53% vs 22%, p<0.001, relative risk 2.38, 95% CI 1.67 to 3.39).

Felder and colleagues (2012) included two additional RCTs comparing Apligraf® to usual care. The first was a subgroup analysis of a larger study which looked at 120 patients whose ulcers had been present for at least one year, comparing Apligraf® to multilayer compression wrap. In this hard-to-heal subgroup, complete healing occurred by six months in 47% of subjects receiving Apligraf® versus 19% of the control subjects. The second study included by Felder (2012) compared Apligraf® against saline gauze dressing in patients with chronic foot ulcers of any etiology who had undergone limb revascularization within 60 days. Complete closure by six months occurred in 100% of Apligraf® patients, compared to 75% of usual care patients (p < 0.01).

## Apligraf® vs Theraskin®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Apligraf® and Theraskin® for DFUs (n = 28). Average wound size was similar between groups. There were no significant differences reported in complete wound closure between the two products (Apligraf® 41% vs Theraskin® 67%, p=0.21).

### *Critical Outcome: Quality of Life*

No SRs or RCTs reported on the effect of Apligraf® on validated quality of life indicators. One RCT included in the AHRQ review reported on pain, noting that it improved significantly in both Apligraf® and control groups (Snyder, Sullivan and Schoelles, 2012).

### *Important Outcome: Time to Complete Wound Healing*

Snyder and colleagues (2012) included one RCT that reported on the time to complete wound healing in the use of Apligraf® for VLU. In the single RCT, patients who received Apligraf® experienced shorter median time to wound closure (61 days) compared with usual care (i.e., Unna boot) (191 days).

Felder and colleagues (2012) included one RCT of patients with chronic foot ulcers who had recently (60 days) undergone limb revascularization, which found mean time to healing with Apligraf® was seven weeks, compared to 15 weeks in the group treated with saline-gauze dressing (p = 0.0021).

### *Important Outcome: Adverse Effects*

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included four studies that reported on adverse effects from Apligraf® for a total of 332 patients treated with the product and 283 patients treated with usual care. Two RCTs (N = 28 and N = 72) reported only “serious adverse events” in the treatment and follow-up phases, and these were roughly equivalent (3-5 patients in each group). One trial only reported on osteomyelitis, which is discussed above. In the fourth RCT (N = 297), there were approximately equal incidences of cellulitis (15.5% vs 13.2%), dermatitis (8.7% vs 8.8%), and peripheral edema (5.0% vs 5.0%) in the Apligraf® group compared to usual care.

Although not explicitly stated as a critical outcome, one trial reported on the incidence of death. Six cases of death reported in the Apligraf® group compared with five cases in the usual care group (reasons not described); there were no other deaths reported across the three other trials.

Felder and colleagues (2012) included one additional study (a subgroup of a previous study, separating out 120 patients with hard-to-heal venous ulcers present longer than one year) that reported infection rates of 8.2% in the Apligraf® treatment group (n = 72) versus 7.8% in the usual care control group (n = 48).

In addition to the adverse effects described above, trials also reported relatively rare incidence of rashes, pain, urinary tract infection, pain, dyspnea, congestive heart failure, accidental injury, pharyngitis, asthenia, arrhythmia, arthralgia, increased cough, erythema, and kidney failure.

## **Dermagraft®**

Dermagraft® is a “cryopreserved human fibroblast-derived dermal substitute on a bioabsorbable polyglactin mesh scaffold. The fibroblasts are obtained from human newborn foreskin tissue” (Snyder, Sullivan and Schoelles, 2012, pg 38). It is indicated by the FDA

[f]or use in the treatment of full-thickness diabetic foot ulcers greater than six weeks’ duration which extend through the dermis, but without tendon muscle, joint capsule or bone exposure. Dermagraft® should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot. Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts. Dermagraft is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution (Snyder, Sullivan and Schoelles, 2012, pg 38).

The FDA prescribing information contains a caution that Dermagraft has not been studied in patients receiving greater than 8 device applications.

Trials of Dermagraft® included patients with adequate glycemic control and evidence of adequate circulation as measured by ankle brachial pressure index (ABPI). Patients were excluded for evidence of active infection, impaired mobility, and significant comorbidities such as HIV, severe peripheral vascular disease, or a bleeding disorder. Patients were also generally excluded if their ulcers responded to usual care during a run-in or screening period. Average age ranged from 55 to 72 years.

Application regimens for Dermagraft® are diverse in the literature. Earlier trials involved weekly applications for up to 7 or 8 treatments (Gentzkow, 1996; Naughton, 1997; Marston, 2003). A study in 2003 divided patients into three different treatment arms; weekly applications for up to 12 weeks and a total of four applications at 0, 1, 4, and 8 weeks had identical efficacy (5/13 wounds healed). The most recent trial in this report (Omar, 2004) used this same 0, 1, 4, and 8 protocol and had a similar result (5/10 ulcers healed).

#### ***Critical Outcome: Deep Soft Tissue or Bone Infection***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT comparing Dermagraft® to saline-moistened gauze in the treatment of DFU that reported on incidence of osteomyelitis. Rates were 8.6% in both the intervention and the control groups.

#### ***Critical Outcome: Complete Wound Healing***

Snyder and colleagues (2012) included three RCTs that reported on complete wound healing in the use of Dermagraft® for DFUs. All three RCTs on DFUs found that patients receiving Dermagraft® experienced greater rates of complete wound healing compared to usual care at 12 weeks. A meta-analysis found Dermagraft to be more effective for achieving wound closure compared to usual care (saline-moistened gauze) for patients with DFUs (odds ratio 1.64; 95% CI 1.10 to 2.43).

Felder and colleagues (2012) identified one additional RCT of Dermagraft® in care of DFUs, in which the metabolic activity of the graft was assessed and patients in the treatment arm were stratified by whether or not the Dermagraft® was “metabolically active within the therapeutic range” (Felder, 2012, p. 150). At twelve weeks, the rate of complete healing was 38.5% in the entire treatment group and 31.7% in the control group (p = 0.138), but was 50.8% in the “metabolically active” Dermagraft® group.

Snyder and colleagues (2012) identified one RCT that included patients with VLUs, which found greater rates of complete wound healing in the Dermagraft® group at 12 weeks, although this finding was not statistically significant (28% vs 15%, p=0.30, relative risk 1.83, 95% CI 0.47 to 7.21).

Jones and colleagues (2013) identified one additional RCT of Dermagraft® versus usual care in VLUs that used a four-piece protocol. They pooled this data with the results of the aforementioned RCT and found that “There was no evidence of overall benefit associated with four pieces of dermal skin replacement (at baseline, one, four and eight weeks) in the two studies (RR 3.04, 95% CI 0.95 to 9.68), when pooled using a fixed-effect model (44 participants)” (Jones, Nelson, and Al-Hity, 2013, p. 10).

#### Dermagraft® vs OASIS®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® for DFUs (n = 26). Average wound size was similar between groups (p = 0.94). There were no significant differences reported in complete wound closure between the two products (Dermagraft 84.6% vs OASIS® 76.9%, p = 0.62).

#### *Critical Outcome: Quality of Life*

No SRs or RCTs reported on the effect of Dermagraft® on validated quality of life indicators or surrogate measures.

#### *Important Outcome: Time to Complete Wound Healing*

Felder and colleagues (2012) identified four RCTs that reported on time to complete healing for DFUs treated with Dermagraft®. In all four trials, generally speaking, healing was faster in the Dermagraft® group than in the control. A fair quality small RCT testing three different Dermagraft® regimens against usual care (N=50) found that weekly application of Dermagraft® resulted in mean time to healing of 12 weeks, while less frequent applications and usual care led to healing times greater than 12 weeks. A second, fair quality RCT (N=235) assessed the metabolic activity of the Dermagraft® product prior to application and found an improvement in healing time (13 weeks vs 28 weeks) only when the product was “metabolically active within the therapeutic range” (Felder, Goyal, and Attinger, 2012, p. 150). A poor quality RCT (N=281) published the same year had identical results (13 weeks vs 28 weeks), while the final RCT in this review (also poor quality, N=245) demonstrated that time to healing was significantly faster with Dermagraft than with control (p = 0.04)

Similarly, the one RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) on the use of Dermagraft® for patient with VLUs found shorter wound closure time in the Dermagraft group compared with usual care (35 weeks vs 74 weeks).

## Dermagraft® vs OASIS®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® for DFUs (n = 26). There were no significant differences reported in complete wound closure between the two products (Dermagraft 40.90 ± 32.32 days vs OASIS® 35.67 ± 41.47 days, p = 0.73).

### *Important Outcome: Adverse Effects*

Two trials identified by Felder and colleagues (2012) reported on adverse effects with Dermagraft®. One trial (n = 314) found that compared to usual care (saline-moistened gauze), patients who received Dermagraft® had lower rates of adverse effects (i.e., infection, osteo and cellulitis) (19% vs 32%, p=0.007). In the second trial, patients in the Dermagraft® groups had similar rates of adverse events (undefined, statistical significance not reported in the AHRQ review). Unrelated AEs in this study (N = 53) included syncope, skin excoriation, bleeding from biopsy site, latex allergy, development of bullous pemphigoid, and cerebrovascular accident.

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) reported adverse events from one fair quality RCT (N=53) of Dermagraft® in treatment of VLU. With 13-14 subjects in each treatment group, total number of adverse events was 15-18 per group, Serious adverse events were not reported in the control group; the three treatment groups each had at least one serious adverse event, with four serious events in the most intensive treatment arm.

## **EpiFix®**

EpiFix® is derived from human amniotic membrane and is marketed both in a skin allograft form as well as an injectable form. It does not presently have any FDA indications. This evidence review identified one small RCT of EpiFix®. Patients were 56-62 years old, were 69% and 58% male in the intervention and control groups, respectively, and had ulcers averaging 2.8cm<sup>2</sup> in the intervention group and 3.4 cm<sup>2</sup> in the controls. Other inclusion/exclusion criteria were not described and significance of baseline differences were not reported.

In this RCT (Zelen, 2013), patients who had incomplete epithelialization received an additional application at weeks 2, 4, 6, 8, and 10. The authors state, "Five patients (45%) healed with one dHAM application, one (9.1%) healed with two applications, one (9.1%) healed with three applications, two (18%) healed with four applications, and one (9.1%) healed after five applications." This is an average of 2.3 applications.

### *Critical Outcome: Deep Soft Tissue or Bone Infection*

No SRs or RCTs reported on the effect of EpiFix® on deep soft tissue or bone infection.

### *Critical Outcome: Complete Wound Healing*

Game and colleagues (2015) identified one RCT of EpiFix®, an amniotic membrane graft product, in the treatment of DFUs. This was a small pilot study in which 13 patients with an average wound size of 2.8

cm<sup>2</sup> were treated with EpiFix<sup>®</sup> and 12 patients with an average wound size of 3.4 cm<sup>2</sup> were treated with moistened gauze and silver; all patients received compression dressings. At four weeks, complete healing was 77% in the EpiFix<sup>®</sup> group and 0% in the control group ( $p < 0.0001$ ). By six weeks, rates of complete healing were 92% and 8%, respectively ( $p < 0.0001$ ). This is an unexpectedly low rate of healing in the control group.

***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of EpiFix<sup>®</sup> on validated quality of life indicators or surrogate measures.

***Important Outcome: Time to Complete Wound Healing***

No SRs or RCTs reported on the effect of EpiFix<sup>®</sup> on time to complete wound healing.

***Important Outcome: Adverse Effects***

No SRs or RCTs reported on the adverse effects of EpiFix<sup>®</sup>.

## **Grafix<sup>®</sup>**

Grafix<sup>®</sup> is another product derived from cryopreserved human placental membrane. It is approved by the FDA as a “wound cover” for both acute and chronic wounds. According to the manufacturer it intends to submit a Biologics License Application for more clinical indications. This evidence review identified only one RCT of poor quality. Patients in this trial had wounds of four to 52 weeks’ duration, and of one to 15 cm<sup>2</sup> in area. Patients were excluded for A1c  $\geq 12$ , inadequate ABPI, presence of active infection, and response to usual care during a one-week screening period. Other subject characteristics were not reported. Patients received weekly applications for up to 84 days (Lavery, 2014).

***Critical Outcome: Deep Soft Tissue or Bone Infection***

No SRs or RCTs reported on the effect of Grafix<sup>®</sup> on deep soft tissue or bone infection. The RCT by Lavery and colleagues (2014) did report that patients randomized to Grafix<sup>®</sup> did experience significantly fewer wound infections than the usual-care group (18.0% versus 36.2%,  $p = 0.044$ ), and a trend to fewer infection-related hospitalizations (6% versus 15%,  $p = 0.15$ ).

***Critical Outcome: Complete Wound Healing***

Lavery and colleagues (2014) conducted an RCT of Grafix<sup>®</sup> versus standard wound care for DFUs. Patient groups were similar at baseline. Complete wound healing occurred in 62% of patients treated with Grafix<sup>®</sup> and in 21% of the control group ( $p < 0.01$ ). The quality of this study is poor due to having no description of randomization methodology, nor concealment or blinding efforts. The study was funded by manufacturer.

***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of Grafix<sup>®</sup> on validated quality of life indicators or surrogate measures.

### ***Important Outcome: Time to Complete Wound Healing***

In the poor quality RCT by Lavery and colleagues (2014), time to complete healing was a secondary outcome. Patients treated with Graftix® experienced complete wound healing in a median time of 42 days, compared to 69.5 days in the control group ( $p = 0.019$ ).

### ***Important Outcome: Adverse Effects***

Lavery and colleagues (2014) reported that patients treated with Graftix® were less likely to experience any adverse event than patients in the control group (44% versus 66%,  $p = 0.031$ ). One control group subject underwent amputation due to an adverse event; there were no amputations in the intervention arm. There was no discussion of whether any of the adverse events were thought to be related to treatment.

## **Graftjacket®**

Graftjacket® is derived from donated human tissue, and is composed of extracellular components of human dermis (collagen, elastin, and proteoglycans). One RCT included patients with non-infected ulcers and a palpable/audible pulse to the affected extremity, but did not describe other inclusion/exclusion criteria. A second RCT included only patients with good diabetic control (Hgb A1c < 12, serum creatinine < 3.0 mg) and adequate ABPI, and excluded patients who had received biomedical or topical growth factors within 30 days. Other subject characteristics were not reported. Both RCTs used a single application in the treatment group (Brigido, 2006; Reyzelman, 2009).

### ***Critical Outcome: Deep Soft Tissue or Bone Infection***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT that reported wound infection rates in the use of Graftjacket®. In 46 patients treated with Graftjacket®, one patient experienced a wound infection that eventually ended with amputation; there were no cases of wound infection in the 39 control group subjects.

### ***Critical Outcome: Complete Wound Healing***

Two RCTs were included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) that evaluated the use of Graftjacket® in patients with DFUs (total  $n = 113$ ). The authors of both studies report a significantly greater proportion of wound closure compared to usual care at 12 weeks (compared with moist-wound therapy dressings: 70% vs 46%,  $p=0.03$ , relative risk 1.51, 95% CI 1.02 to 2.22; compared with Curasol: 86% vs 29%,  $p=0.006$ ). In the AHRQ review, one of these RCTs was assessed at moderate risk of bias; the other was determined to be at low risk of bias after author communications clarified the randomization procedures. However, Felder and colleagues (2012) point out other flaws in this second RCT, specifically that the dropout rate was twice as high in the treatment group as in the control group, that the average pretreatment wound size was biased in favor of the Graftjacket arm (3.6cm<sup>2</sup> in the treatment subjects versus 5.1cm<sup>2</sup> in the control subjects), and that the control group “had a higher percentage of foot wounds, which are more likely to be weight-bearing and therefore more difficult to heal” (Felder, Goyal and Attinger, 2012, p. 60).

### ***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of Graftjacket® on validated quality of life indicators or surrogate measures.

### ***Important Outcome: Time to Complete Wound Healing***

The AHRQ SR (Snyder, Sullivan and Schoelles, 2012) included two RCTs that reviewed the effectiveness of Graftjacket for DFUs. In one trial, time to complete healing was 11.92 weeks in the treatment group versus 13.5 weeks in the control group; in the other, it was 5.7 weeks in the treatment group versus 6.8 weeks in the control. While both studies reported a shortened time to wound closure compared to a usual care group, neither finding was statistically significant.

### ***Important Outcome: Adverse Effects***

One RCT reported wound infection rates of 21.4% versus 35.7% in the treatment and control groups, respectively (Felder, Goyal and Attinger, 2012). The other RCT reported on a control group patient who experienced altered mental status and hypotension and another who developed an abscess; in the treatment group, one patient had an infection leading to amputation (discussed above), and a second required vascular surgery.

## **OASIS® Wound Matrix**

OASIS® is derived from hydrolyzed bovine collagen and is approved by the FDA “[f]or the management of wounds including full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, second-degree burns, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, dehisced surgical incisions” (Snyder, Sullivan and Schoelles, 2012, pg. ES-12). The AHRQ review identified five RCTs evaluating the effectiveness of OASIS®. Patients were enrolled with a wound of >4 weeks duration (in one trial, > 6 months). Patients with conditions that would slow wound healing were excluded from all trials, for example, malnutrition (albumin < 2.5 g/dL), poor glycemic control (A1c >12), active smoker status, inadequate circulation to the affected limb, active infection, immunosuppression, use of steroids, vascular disease, and Charcot foot.

In three trials of OASIS<sup>®</sup> for DFU, the product was re-applied as deemed clinically necessary. One RCT (Niezgoda, 2005) reported an average use of 10 sheets of OASIS per patient. A trial of OASIS compared to Dermagraft<sup>®</sup> (Landsman, 2008) reported that up to eight applications of OASIS was similarly effective to up to three applications of Dermagraft<sup>®</sup>. The third trial (Romanelli, 2010) reported an average of 5.2 days between dressing changes for OASIS patients.

Two RCTs reported on OASIS<sup>®</sup> in treatment of VLU. One (Mostow, 2005) reported an average of eight sheets per patient; the other (Romanelli, 2007) reported an average of 6.4 days between dressing changes but did not report on number of sheets of product used.

***Critical Outcome: Deep Soft Tissue or Bone Infection***

No SRs or RCTs reported on the effect of OASIS<sup>®</sup> on deep soft tissue or bone infection.

***Critical Outcome: Complete Wound Healing***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included one RCT of patients with DFUs (n = 98), comparing OASIS<sup>®</sup> Wound Matrix with Regranex Gel (contains platelet-derived growth factor) and found greater wound closure of plantar ulcers at 12 weeks in the OASIS<sup>®</sup> group (49% vs 28%, p=0.06).

Snyder and colleagues (2012) included three RCTs of patients with VLUs that evaluated the effectiveness of OASIS<sup>®</sup> Wound Matrix (total n = 222). The trials included disparate usual care groups (petrolatum-impregnated gauze with no compression, Jaloskin containing hyaluronan, nonadherent dressing with compression bandages). However, healing rates were greater in the OASIS<sup>®</sup> Wound Matrix arms across all three trials and follow-up periods (80% vs 65% at 8 weeks, p<0.05; 83% vs 46% at 16 weeks, p<0.001; 55% vs 34% at 12 weeks, p=0.02; respectively).

**OASIS<sup>®</sup> Wound Matrix vs Dermagraft<sup>®</sup>**

The AHRQ SR included one RCT that compared OASIS<sup>®</sup> Wound Matrix with Dermagraft<sup>®</sup> for individuals with DFUs (n = 26) (Snyder, Sullivan and Schoelles, 2012). The study found no significant difference in the percentage of wound closure between the two products (~~77~~Dermagraft 84.6% vs ~~85~~OASIS<sup>®</sup> 76.9%, p=0.62).

***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of OASIS<sup>®</sup> on validated quality of life indicators. One RCT identified in the AHRQ review reported fewer wound dressings with OASIS<sup>®</sup> (6.46 ± 1.39 changes vs 2.54 ± 0.78), while a second reported lower pain levels in the intervention group as measured by a 10-point visual analog scale (3.7 vs 6.2, p < 0.05). A third RCT reported that 2/17 patients in the OASIS<sup>®</sup> group experienced pain, compared to 1/10 control patients.

***Important Outcome: Time to Complete Wound Healing***

Of the three RCTs included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) that evaluated OASIS<sup>®</sup> Wound Matrix in patients with DFUs, only one trial reported a shorter time to wound closure

compared to nonadherent dressing with compression bandages (5.4 weeks vs 8.3 weeks, statistical analysis not reported). A second RCT reported  $35.67 \pm 41.47$  days in the OASIS® arm vs  $40.90 \pm 32.32$  days in the control (not significant). The third RCT reported average time of 67 days with OASIS® and 73 days with control ( $p = 0.245$ ). All three RCTs were of fair quality.

One RCT of OASIS® in VLU did not report time to healing, but did estimate using Cox analysis that at twelve weeks, 63% of the treatment group vs 29% of the controls would be expected to achieve complete wound healing (Snyder, Sullivan and Schoelles, 2012).

#### OASIS® Wound Matrix vs Dermagraft®

The AHRQ SR included one RCT that compared OASIS® Wound Matrix with Dermagraft for individuals with DFUs. The study found no significant difference in the time to wound closure between the two products (Snyder, 2012).

#### *Important Outcome: Adverse Effects*

The AHRQ SR included one RCT that compared OASIS® with Regranex growth gel (Snyder, Sullivan and Schoelles, 2012). The authors reported adverse effects in the OASIS® group ( $n=17$ ) including one patient with depression/mood disorder, one patient with gastrointestinal disorder, and three patients with infections in a non-study ulcer. In the Regranex group ( $n=10$ ), there was one instance of infection in a non-study ulcer, two cases of limb injury, one respiratory tract infection, one case of septic arthritis, and one skin injury.

The AHRQ SR also reported on one trial in which eight patients received OASIS® and 15 were treated with compression. In this trial, three patients in each group experienced an allergic reaction or intolerance to the secondary dressing. One patient in the OASIS® group died of cardiovascular disease; one patient in the compression group developed a new ulcer from the compression. One patient in each group developed an infection in another (non-target) wound, one patient receiving compression developed a seroma, and one patient in each group suffered skin injury.

## Talymed®

Talymed® is a wound dressing product containing poly-N-acetyl glucosamine (pGlcNAc) derived from microalgae. (Snyder, Sullivan and Schoelles, 2012, pg. 56). This evidence review identified one small pilot RCT within the AHRQ review. Patients in this trial were 59-63 years old, 25-65% male, and had wounds ranging from 2.7 to 3.6 months duration. Patients in both intervention and control groups had comorbidities including hypertension, diabetes, obesity, arthritis, and blood clotting disorders. Patients were excluded for a variety of more severe indications such as collagen vascular disease, Charcot disease, previous radiation, current hemodialysis, or insufficient ABPI.

The RCT (Kelechi, 2011) included three treatment arms (single application, application every other week, or application every three weeks). Weekly application was equivalent to control (45%,  $n = 9$  of 20).

Complete healing occurred in 86.4% (n = 19 of 22) and 65.0% (n = 13 of 20) with applications every two and every three weeks, respectively. P-value was significant for every other week versus standard care ( $p < 0.01$ ).

***Critical Outcome: Deep Soft Tissue or Bone Infection***

No SRs or RCTs reported on the effect of Talymed® on deep soft tissue or bone infection.

***Critical Outcome: Complete Wound Healing***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included a single RCT that evaluated the use of Talymed® in combination with usual care compared to usual care alone for VLU (n=82). Patients receiving Talymed® with usual care every other week experienced higher wound closure rates than usual care alone at 20 weeks (86% vs 45%,  $p=0.0005$ ). Snyder and colleagues (2012) note that patients receiving Talymed® once every three weeks or only receiving one application did not experience statistically significant results.

***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of Talymed® on validated quality of life indicators or surrogate measures.

***Important Outcome: Time to Complete Wound Healing***

No SRs or RCTs reported on the effect of Talymed® on time to complete wound healing.

***Important Outcome: Adverse Effects***

In the AHRQ review (Snyder, Sullivan and Schoelles, 2012), a single RCT reported “no pain, edema, or significant treatment-related adverse events occurred” (p. C-65).

## **TheraSkin®**

TheraSkin® is a cryopreserved human skin allograft (Snyder, Sullivan and Schoelles, 2012). This evidence review identified one RCT in which TheraSkin® was used as a comparison for Apligraf® for diabetic foot ulcers, discussed above. Patients in this trial had either Type I or Type II diabetes with A1c < 12.0 and the ability to comply with an offloading regimen as well as adequate ABPI (>0.75) and absence of infection, gangrenous tissue, or abscess. The study was rated at moderate risk of bias.

Patients in the RCT ([DiDomenico, 2011](#)) received up to five applications, in accordance with the manufacturer’s recommendations. Authors report that most patients received only a single application and that the mean number of applications was 1.38 (SD = 0.29).

***Critical Outcome: Deep Soft Tissue or Bone Infection***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT in which TheraSkin® was used as the comparator to Apligraf®. In this trial, one patient treated with TheraSkin® was hospitalized due to infection, but no further information is available.

### ***Critical Outcome: Complete Wound Healing***

The RCT identified in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) reported complete wound healing at two time points. By 12 weeks follow up, the TheraSkin® group had 66.7% complete healing, versus 41.3% in the Apligraf® group ( $p = 0.21$ ). The difference was even smaller at 20 weeks, as no more patients in the TheraSkin group experienced complete healing (66.7% vs 47.1%,  $p$  not reported).

### ***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of TheraSkin® on validated quality of life indicators or surrogate measures.

### ***Important Outcome: Time to Complete Wound Healing***

No SRs or RCTs reported on the effect of TheraSkin® on time to complete wound healing.

### **Important Outcome: Adverse Effects**

No SRs or RCTs reported on the adverse effects of TheraSkin®

## **Summary of the Evidence**

The field of biologic skin substitutes for treatment of chronic skin ulcers such as venous leg ulcers and diabetic foot ulcers is rapidly expanding with a variety of new innovations and products. An AHRQ review in 2012 identified 57 unique products, while this updated search found 73 and there are likely more. Evidence for the effectiveness and safety of these products has not kept pace with their development, however, as this review was only able to find published trials of nine products (available in the US), and none dealing with pressure ulcers. While early tests are promising for these products in the treatment of serious and occasionally life-threatening wounds, our confidence in the estimates of effectiveness is generally very low. Studies are almost universally limited by small sample size and inconsistency in control groups and what is defined as “usual care.” There is virtually no evidence to illuminate the comparative effectiveness of these products, nor to compare their effectiveness versus other alternative types of wound dressings besides moist saline gauze and compression.

Our key question regarding subgroup analysis (considerations of age, BMI, comorbidities, etc.) went largely unanswered by these studies. Where inclusion/exclusion criteria were reported, in general the patients were predominantly male, between 50-70 years of age, had hemoglobin A1c < 12.0%, had no active infectious process, and had adequate circulation to the extremity as measured by ankle-brachial pressure index (ABPI). Some trials excluded other comorbidities such as immunosuppression.

Most trials did report on the likelihood of complete wound closure, which makes comparison of results across studies possible; however, the limitation is that many studies have a short follow-up time that may miss complete healing that takes place in the usual care group at a later time. The second critical outcome was incidence of deep soft tissue or bone infection; this outcome was not widely reported and could be inferred from some studies only by the occasion of an amputation. No information was

identified related to validated quality of life indicators for any of the products, although there is very limited information about pain and number of dressing changes for a few products. Time to complete healing is another outcome considered important to this review. In these early trials, the skin substitutes do appear to reduce time to wound healing but it should be noted that none of the trials had adequate blinding and many are subject to selection as well as observer bias.

In the AHRQ review, Snyder and colleagues (2012) express concern about the external validity of this body of evidence:

The overall applicability of the evidence base is limited to a small number of skin substitute products examining diabetic foot ulcers and venous and/or arterial leg ulcers and to patients in generally good health. Although these results are consistent in showing a benefit when using skin substitutes and suggest that skin substitutes could be used in treating diabetic foot ulcers and venous leg ulcers, the patients enrolled in these studies were in generally good health and free of infected wounds, medications that would impede wound healing, clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes. The results of these studies may not easily translate to everyday clinical situations. The expected population with chronic wounds is likely to have these conditions; therefore, the results reported in studies without these patients may not extrapolate well. The applicability of the findings to sicker patients may be limited (Snyder, Sullivan and Schoelles, 2012, p. 74).

These products are dissimilar enough that even though they can be broadly categorized by derivation, results from a trial of one product cannot be extrapolated to other products in its category. With such a large number of products, it will be challenging to have high confidence in the evidence of their effectiveness without many, many more trials.

## **OTHER DECISION FACTORS –**

### **Resource Allocation**

Cost for a course of treatment with skin substitutes can vary widely, depending on the product used, the number of applications required, the amount of skin substitute purchased, where it is applied (inpatient hospital, outpatient hospital, ambulatory surgical center, office) and payer reimbursement policies. Costs for a course of treatment can vary from a few hundred dollars for an in-office treatment with a low-cost skin substitute such as OASIS® Wound Matrix to several thousand dollars for multiple applications of higher cost products such as Apligraf and Dermagraft. While these products are sometimes billed separately from the physician fees for applying them (including related debridement), some payers are bundling payment in order to incentivize the use of cost-effective products. For instance, in the ambulatory surgery center setting, Medicare fee for service bundles the professional fee with the product itself. In addition, in a form of reference pricing, Medicare groups these bundles into two groups—for high-cost and low cost products—in order to encourage the use of cost-effective

products. Some other payers follow Medicare's practices, but others have their own reimbursement policies.

When not bundled, prices for the skin substitute product itself are usually based on the number of square centimeters purchased, though some products are only sold in relatively large pieces (creating waste when used for small ulcers), while others can be purchased in a variety of sizes. In addition, some products are perishable and must be ordered to arrive within a few days of use; others have a longer shelf life. If these products are effective at improving time to complete ulcer healing, or preventing amputations, they could be cost-effective. However, given the low quality evidence available on most of these products, it is difficult to determine whether or not the expected improvement is sufficient to justify the cost.

For products recommended for coverage, the GRADE-informed framework above shows examples of pricing for smaller ulcers for Medicare fee-for-service in various settings.

When multiple effective skin substitutes are available for a given indication, strategizing preferred products based on price or using alternative payment strategies may create savings for payers.

## Values and preferences

Ulcers can be painful, distressing, and debilitating to patients and patients would likely be highly motivated to have effective treatment. However, few of these products have any evidence of benefit at this point and patients would be unlikely to strongly prefer skin substitutes if benefit is unclear. Skin substitutes, however, do not appear to add much burden to the patient; they would continue to require frequent wound dressings, offloading, and other mediating treatments regardless of the use of skin substitutes, so adverse effects or impact on convenience would not be a strong consideration against these products.

## Other considerations

Expert input and study inclusion criteria show that skin substitutes can only be effective when other conditions necessary for wound healing exist. These conditions include the following:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable
3. Appropriate offloading has been performed
4. Wound has adequate arterial flow, no ongoing infection and a moist wound healing environment
5. Multilayer compression dressings are used (when clinically appropriate)
6. Patient has not used tobacco products 4 weeks prior to placement
7. For patients with diabetes, Hba1c level is < 12.
8. No prior failure of the same skin substitute for the ulcer being treated
9. Prior appropriate wound care therapy has failed to result in significant improvement of the

- wound over at least 30 days
- 10. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, required for coverage of ongoing applications
- 11. Patients is able to adhere to the treatment plan

## POLICY LANDSCAPE

### Quality measures

No quality measures related to skin substitutes were identified on the National Quality Measures Clearinghouse.

### Payer coverage policies

Among the four private payers reviewed, two payers provide coverage of skin substitute products (Aetna and Cigna) and two payers do not have coverage criteria (Moda and Regence). Washington Medicaid only covers one skin substitute (Theraskin for diabetic foot ulcers) and requires prior authorization. No National Coverage Determinations were identified. However, there are four Local Coverage Determinations (LCDs) that specify coverage of skin substitutes. Two of the LCDs detail specific products covered (L34285 and L34593), while the other two do not (L36377 and L35041). Table 4 summarizes the coverage for skin substitutes to treat diabetic foot ulcers (DFU) and venous leg ulcers (VLU) across payers. None of the skin substitute coverage policies cover decubitus ulcers. All payers reviewed, except the Medicare NCD and Washington Medicaid, cover skin substitutes when a wound has not adequately responded to standard treatments, usually within 30 days. Many coverage policies have additional indications that limit use, such as the ulcer being infection-free (Aetna, L35041, L34593, and L34285), the foot having adequate blood supply (Aetna, Cigna, L 35041, and L34593), and HbA1C < 12% (Cigna). Some payers limit the number of applications of skin substitutes, for example, a maximum of four treatments of Apligraf or Epifix in 12 weeks and wound healing must be present (Cigna), not more than 10 applications per wound (L35041), Apligraf and Epifix limited to five applications (L34593), and Graftjacket is limited to one application (L34285).

**Table 4. Summary of Other Payer Coverage of Skin Substitutes**

Payer	Skin Substitutes						
	Apligraf®	Dermagraft®	Epifix®	Graftjacket®	OASIS®	Primatrix®	Theraskin®
Aetna	DFU, VLU	DFU	X	DFU	DFU, VLU	X	X
Cigna	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	X	DFU
Washington	X	X	X	X	X	X	DFU w/ author- ization

Payer	Skin Substitutes						
	Apligraf®	Dermagraft®	Epifix®	Graftjacket®	OASIS®	Primatrix®	Theraskin®
LCD-Alabama (L34285)	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	X	DFU, VLU
LCD-Iowa (L34593)	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	DFU, VLU	DFU, VLU
LCD-Delaware (L35041)	DFU, VLU – no specific products identified						
LCD-Florida (L36377)	DFU, VLU – no specific products identified						

Key: X – product is not covered

Abbreviations: DFU – diabetic foot ulcer; LCD – local coverage determination; VLU – venous leg ulcer

## Clinical Practice Guidelines

### *Diabetic foot ulcers*

Three clinical practice guidelines address care for diabetic foot ulcers (Braun, Kim, Margolis, Peters, & Lavery, 2006; NICE, 2011; Registered Nurses' Association of Ontario, 2013). The good-quality National Institute for Health and Care Excellence (NICE) clinical practice guidelines recommend to, “Consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service” (2015, p.18). The fair-quality guideline from the Registered Nurses' Association of Ontario and Braun and colleagues (2006) poor-quality update to the Wound Healing Society guideline did not include a recommendation on use of skin substitutes.

### *Venous leg ulcers*

Three clinical practice guidelines address care of venous leg ulcers (AAWC, 2010; Australian Wound Management Association Inc. and the New Zealand Wound Care Society Inc., 2011; SIGN, 2010). One good-quality guideline, Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers, and one poor-quality guideline from the Association for the Advancement of Wound Care (AAWC) recommend skin substitutes for non-healing or persistent venous leg ulcers, but do not provide recommendations on the use of specific products. The good-quality SIGN guideline found that there is insufficient evidence on which to base a recommendation for including skin substitutes, or any skin grafting.

### *Pressure ulcers*

The good-quality Institute for Clinical Systems Improvement (ICSI) guideline recommends that clinicians refer the patient to a wound-focused physician or clinician to select the appropriate skin substitute or

other biological application for the treatment of chronic skin ulcers, such as platelet gels, platelet-derived growth factor therapy, or extracellular matrix sheets.

DRAFT

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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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## 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.

### Strong recommendation

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

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

### Weak recommendation

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

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

### Quality or strength of evidence rating across studies for the treatment/outcome<sup>2</sup>

**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.

<sup>2</sup> Includes risk of bias, precision, directness, consistency and publication bias

**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.

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## APPENDIX B. GRADE EVIDENCE PROFILE<sup>3</sup>

### Apligraf® / Graftskin

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
DFUs	1	RCT	Low	Unknown	Direct	Precise	None	Low confidence in estimate of effect ●●○○
VLUs	1	RCT	Low	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFUs	2	RCT	Low	Consistent	Direct	Precise	None	Moderate confidence in estimate of effect ●●●○
VLUs	1	RCT	Low	Unknown	Direct	Precise	None	Low confidence in estimate of effect ●●○○
Nonhealing foot ulcers – undefined	1	RCT	High	Unknown	Indirect	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								

<sup>3</sup> All GRADE Evidence Profiles in this Appendix are in comparison to usual care.

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Time to Complete Wound Healing</b>								
VLUs	1	RCT	Low	Unknown	Direct	Precise	None	Low confidence in estimate of effect ●●○○
Nonhealing foot ulcers – undefined	1	RCT	High	Unknown	Indirect	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								
DFUs	1	RCT	Low	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
VLUs	1	RCT	Low	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Deep Soft Tissue or Bone Infection</b>								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFUs	4	RCTs	Moderate to high	Inconsistent	Direct	Precise	3 RCTs of moderate ROB are consistent, a high-risk RCT had a discrepant result	Low confidence in estimate of effect ●●○○
VLUs	2	RCTs	Moderate	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
DFUs	4	RCT	Moderate to high	Consistent	Direct	Unknown	None	Low confidence in estimate of effect ●●○○
VLUs	1	RCTs	Moderate	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
								●○○○
<b>Adverse Effects</b>								
DFUs	2	RCT	Moderate	Unknown	Direct	Unknown		Very low confidence in estimate of effect ●○○○
VLUs	1	RCT	Moderate	Unknown	Direct	Unknown		Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

## EpiFix®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
<i>No evidence identified</i>								

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

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Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
DFUs	1	RCT	High	Unknown	Direct	Precise	"Wound-related infection" not defined	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFU	1	RCT	High	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
DFU	1	RCT	High	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								
DFU	1	RCT	High	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

## Graftjacket®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFUs	2	RCT	Moderate to high	Consistent	Unknown	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
DFUs	2	RCTs	Moderate to high	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								
DFUs	1	RCT	High	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

## OASIS® Wound Matrix

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFUs	1	RCT	Moderate	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
VLU	3	RCT	Low to moderate	Unknown	Direct	Imprecise	Effectiveness varied based on type of usual care	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
VLU	3	RCTs	Low to moderate	Unknown	Direct	Imprecise	Effectiveness varied based on type of usual care	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
VLUs	1	RCT	Low	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect ●○○○
DFUs	1	RCT	Moderate	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

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Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
VLU	1	RCT	Low	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
VLU	1	RCT	Low	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○

Abbreviations: RCT – randomized controlled trial; VLU – venous leg ulcer

## TheraSkin® versus Apligraf®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i> DFUs		RCT	Moderate	Unknown	Indirect	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFUs	1	RCT	Moderate	Unknown	Direct Indirect	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
<i>No evidence identified</i>								

Abbreviations: RCT – randomized controlled trial; DFU – diabetic foot ulcer

## OASIS® versus Dermagraft®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFUs	1	RCT	Moderate	Unknown	Indirect	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
<i>No evidence identified</i>								

Abbreviations: RCT – randomized controlled trial; DFU – diabetic foot ulcer

## APPENDIX C. METHODS

### Scope Statement

#### *Populations*

Adults with chronic skin ulcers

Population scoping notes: *Considered limiting scope to diabetic foot ulcers and venous leg ulcers, sacral decubitus ulcers, but decided on the broader definition above, considered burns and other types of wounds*

#### *Interventions*

Skin substitutes

Intervention exclusions: None

#### *Comparators*

Usual care

#### *Outcomes*

Critical: Deep soft tissue or bone infections, complete wound healing, quality of life

Important: Time to complete wound healing, adverse effects

Considered but not selected for the GRADE table: *Cellulitis, sepsis, death, need for surgical management, ulcer recurrence*

#### *Key Questions*

1. What is comparative effectiveness of different types of skin substitutes compared with wound care alternatives for individuals with chronic skin ulcers? Include consideration of:
  - a. Age
  - b. Body mass index (BMI)
  - c. Comorbidities
  - d. Site of ulcer
  - e. Ulcer etiology (e.g. infectious, pressure or circulatory).
  - f. Wound severity
  - g. Prior need for skin substitute
  - h. Failure of prior therapies
2. What adverse events are associated with skin substitutes?
3. What are contraindications to the use of skin substitutes?

### 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 “wound,” “ulcer,” “skin substitute,” or “bioengineered skin.” Searches of core sources were limited to citations published after 2005.

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

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 (Snyder et al, 2012). The search was limited to publications in English published after 2011 (the end search date for the AHRQ SR). Using the 2012 AHRQ systematic review as the predominant evidence source, a second MEDLINE® (Ovid) search was conducted to identify any randomized controlled trials published after the search dates of the AHRQ review (2011).

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. A MEDLINE® search was conducted for randomized control trials published after the AHRQ systematic review.

The AHRQ systematic review (Snyder, Sullivan and Schoelles, 2012) was selected as the base systematic review for this topic based on its comprehensiveness; thus systematic reviews published prior to the

AHRQ review were excluded. In addition, several systematic reviews published more recently than the AHRQ review were excluded because they did not include any additional studies that were not already summarized by the included systematic reviews. These four systematic reviews were excluded because they included only studies that were in the AHRQ systematic review:

Game , F. L., Hinchliffe, R. J., Apelqvist, J., Armstrong, D. G., Bakker, K., Hartemann, A., ... Jeffcoate, W.J. (2012). A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev*, 28 Suppl 1:119-41. DOI: 10.1002/dmrr.2246.

Greer , N., Foman, N., Dorrian, J., Fitzgerald, P., MacDonald, R., Rutks, I., & Wilt, T. (2012). Advanced wound care therapies for non-healing diabetic, venous, and arterial ulcers: A systematic review. VA-ESP Project #09-009.. Retrieved from <http://link.springer.com/article/10.1007%2Fs40257-014-0081-9>.

Hankin , C. S., Knispel, J., Lopes, M., Bronstone, A., & Maus, E. (2012). Clinical and cost efficacy of advanced wound care matrices for venous ulcers. *Journal of Managed Care Pharmacy*, 18(5), 375-384. Retrieved from <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15289>.

Iorio, M. L., Shuck, J., Attinger, C. E. (2014). Wound healing in the upper and lower extremities – A systematic review on the use of acellular dermal matrices. *Plastic and Reconstructive Surgery*, 130: 5S-2. DOI: 10.1097/PRS.0b013e3182615703.

The following systematic review was excluded because it only include studies found in the AHRQ systematic review or Jones and colleagues (2013):

Valle , M. F., Maruthur, N. M., Wilson, L. M., Malas, M., Qazi, U., Haberl, E., ... Lazarus, G. (2014). Comparative effectiveness of advanced wound dressings for patients with chronic venous leg ulcers: A systematic review. *Wound Repair and Regeneration*, 22(2), 193-204. DOI: 10.1111/wrr.12151.

Finally, the following systematic review was excluded because it did not provide sufficient detail regarding outcomes reported in trials of skin substitutes:

Braun, L. R., Fisk, W. A., Lev-Tov, H., Kirsner, R.S., & Isseroff, R. R. (2014). Diabetic foot ulcer: an evidence-based treatment update. *Am J Clin Dermatol*, 15, 267–281. DOI: 10.1007/s40257-014-0081-9.

## APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
<b>ICD-10 Diagnosis Codes</b>	
E08.621	Diabetes mellitus due to underlying condition with foot ulcer
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer
E10.621	Type I diabetes mellitus with foot ulcer
E11.621	Type II diabetes mellitus with foot ulcer
E13.621	Other diabetes mellitus with foot ulcer
L97-L97.9	Non-pressure chronic ulcer of lower limb
L89-L89.0	Pressure ulcer
L98.4	Non-pressure chronic ulcer of skin
<b>CPT Codes</b>	
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Each additional 25 sq cm wound surface, or part thereof
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Each additional 25 sq cm wound surface, or part thereof
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Each additional 100 sq cm wound surface area or part thereof, or each additional 1% of body area of infants and children or part thereof
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound area, or 1% of body area of infants and children
15278	Each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children or part thereof
<b>HCPCS Level II Codes</b>	
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list

C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of bod
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or
Q4100	Skin substitute, NOS
Q4101	Apligraf
Q4102	OASIS wound matrix
Q4103	OASIS burn matric
Q4104	Integra BMWWD
Q4105	Integra DRT
Q4106	Dermagraft
Q4107	Graftjacket
Q4108	Integra Matrix
Q4110	Primatrix
Q4111	Gammagraft
Q4112	Cymetra injectable
Q4113	Graftjacket Xpress
Q4114	Integra Flowable Wound Matrix
Q4115	Alloskin
Q4116	Alloderm
Q4117	Hyalomatrix
Q4118	Matristem Micromatrix
Q4119	Matristem Wound Matrix
Q4120	Matristem Burn Matrix
Q4121	Theraskin
Q4122	Dermacell
Q4123	Alloskin
Q4124	Oaskis Tri-layer Wound Matrix
Q4125	Arthroflex
Q4126	Memoderm/derma/tranz/integup
Q4127	Taylmed
Q4128	Flexhd/Alopatchhd/matrixhd
Q4129	Unite Biomatrix
Q4131	Epifix
Q4132	Grafix core
Q4133	Grafix prime
Q4134	HMatrix
Q4135	Mediskin
Q4136	EZderm
Q4137	Amnioexcel or Biodmatrix, 1cc
Q4138	DioDfence DryFlex, 1cc
Q4139	Amniomatrix or Biodmatrix, 1cc
Q4140	Biodfence 1cm
Q4141	Alloskin ac, 1 cm
Q4142	Xcm biologic tiss matrix 1cm
Q4143	Repriza, 1cm
Q4145	Epifix, 1mg

Q4146	Tensix, 1 cm
Q4147	Architect ecm px fx 1 sq cm
Q4148	Neox 1k, 1cm
Q4149	Excellagen, 0.1cc
Q4150	Allowrap DS or Dry 1 sq cm
Q4151	AmnioBand, Guardian 1 sq cm
Q4152	Dermapure 1 square cm
Q4153	Dermavest 1 square cm
Q4154	Biovance 1 square cm
Q4155	NeoxFlow or ClarixFlo 1mg
Q4156	Neox 100 1 square cm
Q4157	Revitalon 1 square cm
Q4158	Marigen 1 square cm
Q4159	Affinity 1 square cm
Q4160	NuShield 1 square cm
Q9349	Fortaderm, fortaderm antimic
Q9358	SergiMend, fetal
C9360	SurgiMend, neonatal
C9363	Integra Meshed Bil Wound Mat

ICD-10-PCS (Procedure Codes)						
Section	Body System	Operation	Body Part	Approach	Device	Qualifier
<b>O</b> (Medical and surgical)	<b>H</b> (skin and breast) <b>J</b> (subcutaneous tissue and fascia) <b>R</b> (mouth and throat)	<b>R</b> (replacement) <b>U</b> (supplement) <b>W</b> (revision)	All (0-X) except: Q finger nail R toe nail S hair	<b>O</b> (open) <b>3</b> (percutaneous)	<b>J</b> (synthetic substitute) <b>K</b> (nonautologous tissue substitute)	<b>Z</b> (no qualifier)
CODES	DESCRIPTION					
OHR0	Skin, Scalp					
OHR1	Skin, Face					
OHR2	Skin, Right Ear					
OHR3	Skin, Left Ear					
OHR4	Skin, Neck					
OHR5	Skin, Chest					
OHR6	Skin, Back					
OHR7	Skin, Abdomen					
OHR8	Skin, Buttock					
OHR9	Skin, Perineum					
OHRA	Skin, Genitalia					
OHRB	Skin, Right Upper Arm					
OHRC	Skin, Left Upper Arm					
OHRD	Skin, Right Lower Arm					
OHRE	Skin, Left Lower Arm					
OHRF	Skin, Right Hand					
OHRG	Skin, Left Hand					
OHRH	Skin, Right Upper Leg					
OHRJ	Skin, Left Upper Leg					

OHRK	Skin, Right Lower Leg
OHRL	Skin, Left Lower Leg
OHRM	Skin, Right Foot
OHRN	Skin, Left Foot
OHRQ	Finger Nail
OHRR	Toe Nail
OHRS	Hair
OHRT	Breast, Right
OHRU	Breast, Left
OHRV	Breast, Bilateral
OHRW	Nipple, Right
OHRX	Nipple, Left

Note: Inclusion on this list does not guarantee coverage.

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## Frequency of application and cost of skin substitutes

Product	Proposed maximum covered applications	Rationale	Medicare cost information (National Average Fee For Service, October, 2015*)
Apligraf	3/5	Greater than 5 applications not studied per FDA. Early studies limited to 5 applications, and one later study found wound healing was completed within 3 applications. Cigna limits to 4 applications in 12 weeks. Two Medicare LCD limits to 5 applications.	ASC: \$771x3=\$2,314 HOPD: \$1,495x3=\$4,485 Phys. Off = \$1,518x3 = \$4,554
Derma-graft	4/8	The FDA prescribing information contains a caution that Dermagraft has not been studied in patients receiving greater than 8 device applications. 2003 study showed that 4 applications is equivalent to 8. Cigna limits to 8 applications in 12 weeks. One Medicare LCD limits to 8 applications.	ASC: \$771x4=\$3,085 HOPD: \$1,495x4=\$5,980 Phys. Off = \$1,409x4 = \$5,635
Epifix	5	One study limited to 5 applications. Cigna limits to 4 applications in 12 weeks. Two Medicare LCD limits to 5 applications.	ASC: \$771x5=\$3,856 HOPD: \$1,495x5=\$7,476 Phys. Office: \$535x5 = \$2,674
Grafix	12	Weekly applications up to 84 days in the one study	ASC: \$771x12=\$9,254 HOPD: \$1,495x12=\$17,941 Phys. Off **
Graft-jacket	1	Single application used in both studies. Cigna and one Medicare LCD limits to 1 application.	ASC: \$771 HOPD: \$1,495 Phys. Office: \$1,672
Oasis Wound Matrix	12	One study of DFU showed an average of 10 sheets. One study of VLU reported an average of 8 sheets. Study showed equivalence of 8 sheets of Oasis to 3 sheets of Dermagraft. One Medicare LCD limits to 12 weeks of therapy.	ASC: \$236x12=\$2,828 HOPD: \$518x12=\$6,214 Phys. Office: \$262x12 = \$3,140
Talymed	10	Study used applications every 1-3 weeks over 20 weeks. Found fewer applications ineffective.	ASC: \$771x10=\$7,712 HOPD: \$1,495x10=\$14,951 Phys. Office **
Thera-skin	5	Up to 5 applications received in the study, however, most patients only had 1. Cigna limits to 4 applications in 12 weeks. One Medicare LCD limits to 5 applications.	ASC: \$771x5=\$3,856 HOPD: \$1,495x5=\$7,476 Phys. Office: \$612x5=\$2,447

ASC=ambulatory surgery center; DFU=diabetic foot ulcers; HOPD=hospital outpatient department; LCD=local coverage determination; VLU=venous leg ulcers

\*Costs reported are for the smallest available product and include applicable professional fees for applying the skin substitute to a leg ulcer smaller than 25 cm<sup>2</sup>. Fees are higher for some other body parts or larger applications.

\*\*Physician's office average sales price (ASP) fees cannot be calculated, product not on ASP fee schedule.

**References for pricing information:**

Hospital outpatient bundle costs retrieved from

<https://www.cms.gov/apps/ama/license.asp?file=/hospitaloutpatientpps/downloads/2015-Jan-Addendum-B-File.zip>

Ambulatory surgical center bundled rates retrieved from

<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/Downloads/2015-October-ASC-Addenda.zip>

Physician fees retrieved from

<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/index.html?redirect=/PhysicianFeeSched/>

October 2015 ASP Pricing file (for physician's office product fees) retrieved from:

<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2015ASPFiles.html>

All retrievals made October 29, 2015.

Section 5.0  
Coverage Guidance Rescan  
2015

## Induction of Labor – 2015 Rescanning Summary

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

**Bottom Line:** There is little new evidence related to the benefits or harms of induction of labor (IOL). The studies that were identified would not likely result in a change to the HERC coverage guidance issued in 2013.

### Coverage Recommendation (Box Language)

Induction of labor is recommended for coverage for the following indications (*strong recommendation*):

- Gestational age beyond 41 weeks 0 days
- Prelabor rupture of membranes, term
- Fetal demise
- Preeclampsia, term (severe or mild)
- Eclampsia
- Chorioamnionitis

Induction of labor is recommended for coverage for the following indications (*weak recommendation*):

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

Induction of labor is not recommended for coverage for the following indications (*weak recommendation*):

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

Induction of labor is not recommended for coverage for the following indications (*strong recommendation*):

- Elective purposes <39 weeks (without a medical or obstetrical indication)

### Scope Statement

<b>Population description</b>	Pregnant adolescents and women <i>Population scoping notes: None</i>
<b>Intervention(s)</b>	IOL without medical or obstetrical indications <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	Expectant management
<b>Outcome(s) (up to five)</b>	<b>Critical:</b> Perinatal mortality, maternal mortality, neonatal morbidity <b>Important:</b> Mode of birth (stratified by indication for operative delivery), maternal length of stay <i>Considered but not selected for GRADE table: iatrogenic prematurity, hemorrhage, epidural, patient satisfaction, neonatal length of stay</i>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What are the outcomes of IOL versus expectant management for women without medical or obstetrical indications for induction of labor?</li> <li>2. How do outcomes vary by cervical favorability, gestational age and parity?</li> </ol>
<b>Contextual question</b>	<ol style="list-style-type: none"> <li>1. What are the evidence-based medical or obstetrical indications for induction of labor?</li> </ol>

### Original Evidence Sources

American College of Obstetrics and Gynecology (ACOG). (2009). Induction of labor. ACOG Practice Bulletin No. 107, American College of Obstetricians and Gynecologists.

*Obstetrics & Gynecology*, 114, 386-97. Guideline summary available at:  
<http://www.guidelines.gov/content.aspx?id=14884>

King, V., Pilliod, R., & Little, A. (2010). *Rapid review: Elective induction of labor*. Portland: Center for Evidence-based Policy. Retrieved February 12, 2013, from  
<http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policycenter/med/index.cfm>

Mozurkewich, E., Chilimigras, J., Koepke, E., Keeton, K., & King, V.J. (2009). Indications for induction of labour: a best-evidence review. *British Journal of Obstetrics and Gynecology*, 116, 626-636. doi: 10.1111/j.1471-0528.2008.02065.x

National Institute for Health and Clinical Excellence (NICE), & National Collaborating Centre for Women's and Children's Health. (2008). *Induction of labour*. London: RCOG Press at the Royal College of Obstetricians and Gynaecologists. Retrieved February 12, 2013, from <http://guidance.nice.org.uk/CG70/Guidance/pdf/English>

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

1. Dodd, J. M., Crowther, C. A., Grivell, R. M., & Deussen, A. R. (2014). Elective repeat caesarean section versus induction of labour for women with a previous caesarean birth. *Cochrane Database of Systematic Reviews*, Issue 12. Art. DOI: 10.1002/14651858.CD004906.pub4.

Citation 1 identified no RCTs available to inform management of this population.

2. Dodd, J. M., Deussen, A. R., Grivell, R. M., & Crowther, C. A. (2014). Elective birth at 37 weeks' gestation for women with an uncomplicated twin pregnancy. *Cochrane Database of Systematic Reviews*, Issue 2. Art. DOI: 10.1002/14651858.CD003582.pub2.

Citation 2 identified no new studies since its prior update and had no changes in conclusions. Elective birth at 37 weeks increased the risk of infants being born at less than the third centile of birthweight compared with expectant management, but there were no other significant differences in maternal or fetal/neonatal outcomes. Current HERC guidance provides a weak recommendation for IOL for twin gestations, but does not specify gestational age restrictions.

3. Gülmezoglu, A. M., Crowther, C. A., Middleton, P., & Heatley, E. (2012). Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database of Systematic Reviews*, Issue 6. Art. DOI: 10.1002/14651858.CD004945.pub3.

The findings of Citation 3 do not change the conclusions of the HERC guidance. Perinatal deaths were lower with IOL at >41 weeks of gestation, but were not significantly different at fewer weeks of gestation. There were fewer cases of meconium aspiration syndrome and macrosomia at 41 and >41 weeks with IOL, but no differences in NICU admission or Apgar score <7 at 5 minutes. Cesarean births were lower with IOL at 41 and >41 weeks, but not significantly different at 37 to 40 weeks of gestation. Operative vaginal births (forceps or vacuum) were more frequent at 37 to 39 weeks with IOL, but not at higher gestational ages. This SR/MA found higher rates of Cesarean birth with “unfavorable” (as defined by study authors, but commonly Bishop Score >6) cervical status, but did not simultaneously control for gestational age or other risk factors.

4. Kaimal, A. J., Little, S. E., Odibo, A. O., Stamilio, D. M., Grobman, W. A., Long, E. F., ... Caughey, A. B. (2011). Cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women. *American Journal of Obstetrics and Gynecology*, 204(2), 137.e1-137.e9. doi: <http://dx.doi.org/10.1016/j.ajog.2010.08.012>

Citation 4 is a cost-effectiveness study of eIOL vs. expectant management using a decision-analytic model. Modeling was used rather than a primary economic study done alongside a RCT or other type of study and therefore is subject to the associated usual biases of modeling studies. The analysis found that eIOL at 41 weeks was cost-effective with an incremental cost of \$10,945 per QALY. The authors stated that improved outcomes, including neonatal mortality/morbidity and fewer maternal severe perineal lacerations helped to account for the incremental cost difference.

5. Hussain, A. A., Yakoob, M. Y., Imdad, A., & Bhutta, Z. A. (2011). Elective induction for pregnancies at or beyond 41 weeks of gestation and its impact on stillbirths: a systematic review with meta-analysis. *BMC Public Health*, 11(Supplement 3), S5. doi:10.1186/1471-2458-11-S3-S5

Citation 5 is a SR/MA of eIOL vs. expectant management for pregnancies ≥ 41 weeks of gestation. The SR included 25 studies, of all study designs, and the primary outcome of interest was stillbirth. The authors concluded that eIOL decreases perinatal death overall (RR 0.31, 95% CI 0.11-0.88), but not stillbirth (RR 0.29, 95% CI 0.06-1.38). These findings are in line with evidence considered for the current HERC guidance.

6. Kenny, T. H., Nicodemo, J. M., Fenton, B. W., von Gruenigen, V. E. (2013). Does enhanced “bundling” criteria improve outcomes? A comparative study of elective inductions. *Journal of Reproductive Medicine*, 58(9-10), 402-410. PMID: 24050029

Citation 6 is a single institution interrupted time series study of an intervention that “bundled” a IHI set of eIOL quality criteria (>=39 weeks, normal fetal status; documentation of all Bishop score components including dilation, effacement, station, cervical position and

consistency; and appropriate management of uterine tachysystole during IOL). Adoption of bundling criteria reduced the rate of Cesarean birth (12% vs. 21%), but did not change the rate of NICU admission. However, when the Bishop score was >6 then the rate of Cesarean birth was markedly reduced (4% vs. 19%), as was the rate of NICU admission (1% vs. 10%). The authors concluded that using the IHI eIOL bundle without requiring a specific Bishop score did not achieve optimal results. The current HERC guidance requires a Bishop score of  $\geq 6$  for eIOL. This single study does not provide sufficient information to change that cutoff without the addition of other data.

7. Kolkman, D. G., Verhoeven, C. J., Brinkhorst, S. J., van der Post, J. A., Pajkrt, E., Opmeer, B. C., & Mol, B. J. (2013). The Bishop score as a predictor of labor induction success: a systematic review. *American Journal of Perinatology*, 30(8), 625-630. doi: 10.1055/s-0032-1331024

Citation 7 looked at the ability of Bishop Scores to predict Cesarean delivery among women undergoing IOL at term. The reported sensitivity/specificity of Bishop Scores of 4, 5 and 6, were 47%-75%, 61%-53%, and 78%-44%, respectively.

8. Mishanina, E., Rogozinska, E., Thatthi, T., Uddin-Khan, R., Khan, K. S., & Meads, C. (2014). Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. *CMAJ: Canadian Medical Association Journal*, 186(9), 665-673. doi: 10.1503/cmaj.130925

Citation 8 is a SR/MA of RCTs examining the risk of Cesarean birth with IOL. The review found 157 eligible RCTs. The risk of Cesarean birth was overall lower with IOL than expectant management (RR 0.88, 95%CI 0.84-0.93), but the effect was statistically significant for term (37 to <42 weeks) and post-term (>42 weeks) gestations only. Meta-regression demonstrated that initial cervical score, indication for IOL and method of IOL did not change the main result. The risk of fetal death (0.50, 95% CI 0.25-0.99) and admission to a NICU (0.86, 95% CI 0.79-0.94) were lower with IOL, but there was no impact on maternal mortality. This SR/MA included studies using different methods of IOL, with varying indications for IOL, and including women of different term gestational ages, pregnancy risk status, parity and degree of cervical readiness. This SR does not offer new information to the current HERC guidance.

9. NICE. (2014). *Induction of labour. NICE quality standard 60*. London: NICE. Retrieved August 11, 2015 from <http://www.nice.org.uk/guidance/qs60/resources/guidance-induction-of-labour-pdf>

Background: NICE. (2014). *Clinical guideline: CG70: Induction of labour. Surveillance report*. London: NICE. Retrieved September 25, 2015 from

<http://www.nice.org.uk/guidance/cg70/documents/cg70-induction-of-labour-surveillance-review-decision-may-20142>

Background: NICE. (2013). *Induction of labour. Evidence update July 2013. A summary of selected new evidence relevant to NICE clinical guideline 70 'Induction of labor' (2008)*. London: NICE. Retrieved September 25, 2015 from <http://www.nice.org.uk/guidance/cg70/evidence/cg70-induction-of-labour-evidence-update2>

The resources listed above in Citation 9 relate to a core source used for the 2013 coverage guidance. NICE conducted surveillance of studies published through December 2013 to determine whether the 2008 IOL guideline should be updated. No new evidence that would impact the guideline was located. The next guideline review is scheduled for 2016.

The second resource represents the quality standards developed by NICE for use in quality of care monitoring and improvement for the NHS. The three quality standards statements relate to: 1) giving personalized information about the benefits and risks of IOL for a woman and her baby when IOL is offered; 2) not conducting outpatient IOL unless safety, support and audit procedures are in place; and 3) providing access to appropriate pain relief for women who are having IOL.

10. Nicholson, J. M., Kellar, L. C., Henning, G. F., Waheed, A., Colon-Gonzalez, M., & Ural, S. (2015). The association between the regular use of preventive labour induction and improved term birth outcomes: findings of a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, 122(6), 773-84. doi: 10.1111/1471-0528.13301

Citation 10 is a SR/MA re-analysis of four previously published studies of the AMOR-IPAT program of "preventive" IOL at  $\geq 38$  weeks for women with moderate risk factors such as gestational diabetes, chronic hypertension, etc. These studies were considered in the prior review for the current HERC guidance and this article does not add new information to consideration of guidance update.

11. Rossi, A. C., & Prefumo, F. (2015). Pregnancy outcomes of induced labor in women with previous cesarean section: a systematic review and meta-analysis. *Archives of Gynecology & Obstetrics*, 291(2), 273-80. doi: 10.1007/s00404-014-3444-9

Citation 11 is a SR/MA of eight retrospective and one prospective cohort studies of IOL vs. spontaneous labor among women with a history of prior Cesarean birth. This review found that IOL increases the risk of uterine rupture and Cesarean birth, but given the largely retrospective nature of the studies and lack of expectant management control groups this data is of very poor quality and does not add new information to the prior HERC guidance.

12. Teixeira, C., Lunet, N., Rodrigues, T., & Barros, H. (2012). The Bishop Score as a determinant of labour induction success: a systematic review and meta-analysis. *Archives of Gynecology and Obstetrics*, 286(3), 739-753. doi: 10.1007/s00404-012-2341-3

Citation 12 was a SR/MA examining the odds of achieving a vaginal birth after IOL. Higher Bishop scores were associated with both vaginal birth and shorter induction to delivery time intervals. For each unit increase in Bishop Score the odds of vaginal birth was increased by 1.33 (95% CI 1.13-1.56), although there was fair heterogeneity among included studies.

13. Vijgen, S. M., Boers, K. E., Opmeer, B. C., Bijlenga, D., Bekedam, D. J., Bloemenkamp, K. W., ... Scherjon, S. A. (2013). Economic analysis comparing induction of labour and expectant management for intrauterine growth restriction at term (DIGITAT trial). *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 170(2), 358-363. doi: 10.1016/j.ejogrb.2013.07.017

Citation 13 is an alongside economic evaluation conducted with a Dutch RCT of IOL vs. expectant management for suspected IUGR beyond 36 completed weeks of gestation. Both strategies generated comparable costs (7106 euros for IOL vs. 6995 euros for expectant monitoring), although the distribution of antepartum and intrapartum costs differed. Costs were also lower in the expectant management group prior to 38 weeks and in the IOL group after that point. The authors concluded that, given the clinical and economic results of the RCT, that expectant management prior to 38 weeks is a reasonable strategy.

14. Vijgen, S. M., Koopmans, C. M., Opmeer, B. C., Groen, H., Bijlenga, D., Aarnoudse, J. G., ... van Pampus, M. G. (2010). An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial). *BJOG. An International Journal of Obstetrics and Gynaecology*, 117(13), 1577-1585. doi: 10.1111/j.1471-0528.2010.02710.x

Citation 14 is an economic study done in conjunction with a Dutch RCT of IOL vs. expectant management of women with gestational hypertension or pre-eclampsia between 36w + 0d and 41w + 0d of gestation. More costs were generated with expectant monitoring compared to IOL (7908 euros vs 7077 euros). This 11% difference was primarily due to costs originating in the antepartum period. During delivery, more costs were generated by women in the IOL group. There were essentially no differences for costs in the postpartum period. Given the differences in the systems of care between the Netherlands and the U.S., any direct comparability of costs is not possible.

15. Wood, S., Cooper, S., & Ross, S. (2014). Does induction of labour increase the risk of caesarean section? A systematic review and meta-analysis of trials in women with

intact membranes. *BJOG. An International Journal of Obstetrics and Gynaecology*, 121(6), 674-685. doi: 10.1111/1471-0528.12328

Citation 15 is a SR/MA of RCTs studying IOL vs. expectant management among women with intact amniotic membranes. Of 37 included studies, 27 included women with uncomplicated pregnancies at 37 to 42 weeks of gestation and the remaining 10 included women with medical and obstetric complications (suspected macrosomia, twins, oligohydramnios, IUGR, hypertension and high risk score for Cesarean birth). The authors concluded that a policy of eIOL reduces the risk of Cesarean birth among women beyond their due dates (OR 0.85, 95% CI 0.76-0.95) and among women with obstetric and medical complications (OR 0.81, 95% CI 0.69-0.95). The odds were similar among both groups when only high quality trials were included, but the CI for the group with complications was no longer statistically significant. The authors noted that only one RCT in the complicated pregnancy group was actually designed to assess the outcome of Cesarean birth and that the effects observed across the included RCTs could, therefore, be due to non-treatment effects and that conclusions based on these data may be premature.

16. World Health Organization (WHO). (2011). *Induction of labour*. Geneva, Switzerland: WHO. Retrieved on August 11, 2015 from [http://apps.who.int/iris/bitstream/10665/44531/1/9789241501156\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/44531/1/9789241501156_eng.pdf)

Citation 16 is largely in alignment with current HERC guidance. The only strong recommendation in the WHO guideline is for IOL among women with prelabor rupture of membrane. There is a weak recommendation for IOL for women at or beyond 41 weeks (41 w. + 0 d.) of gestation. There are weak recommendations against IOL for: 1). women with uncomplicated pregnancy who are less than 41 weeks, 2). including those for whom gestational diabetes is the only abnormality; and 3). women with suspected fetal macrosomia. The WHO panel found insufficient evidence to guide management of women with uncomplicated twin gestation at or near term and so no recommendation was made.

### **Summary:**

This rescan for the HERC's IOL guidance found evidence that largely comported with and supported existing coverage guidance. Little contradictory or newer evidence was identified that would be likely to change the current coverage recommendations or the strength of those recommendations. The exception is the WHO recommendation against induction without a specific indication for women at fewer than 41 weeks of gestation. The current coverage guidance is silent on the subject of gestational age and IOL for twin pregnancy or pregnancy complicated by gestational hypertension or suspected IUGR. The rescan may have identified studies that could help to identify a target gestational age for expectant monitoring vs. IOL. However, the HERC guidance currently has weak recommendations for these conditions and so largely leaves the decision up to clinical

judgement. The rescan identified data confirming that outcomes for eIOL are improved with higher Bishop Score and no need for cervical ripening prior to IOL. The guidance currently recommends a minimum Bishop score of  $\geq 6$ , although some newer evidence indicates that setting a cutoff higher ( $>6$ ) may improve both maternal and neonatal outcomes. These would not likely be substantial changes to the guidance at present, but the HERC could consider a targeted search relative to each potential indication and modifying factor (such as Bishop Score) at the next rescan. Three economic studies found positive economic results for IOL in the case of gestations over 41 weeks, maternal hypertensive disease and suspected IUGR.

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## 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 “induction of labor [or labour],” “elective induction,” and “labor induce.” Searches of core sources were limited to citations published after 2009 (the last search dates of the 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 2009 (the last search dates of the initial evidence sources).

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
- 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

# Management of Recurrent Acute Otitis Media in Children – 2015 Rescanning Summary

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

**Bottom Line:** The evidence for adenoidectomy and/or tympanostomy tubes for recurrent acute otitis media (AOM) is mixed with several new publications since the initial coverage guidance was issued. There appears to be no new summary evidence on the effectiveness of prophylactic antibiotics for recurrent AOM, though it should be noted that AAP guidelines recommend against it.

## Coverage Recommendation (Box Language)

Prophylactic antibiotics should be covered for recurrent acute otitis media.\*

Tympanostomy tubes may be covered for acute otitis media only for recurrent acute otitis media.

Adenoidectomy or adenotonsillectomy should not be covered for the treatment of recurrent acute otitis media.

*\*Recurrent acute otitis media is defined here as three or more episodes in six months or four or more episodes in one year.*

*Note: Coverage guidance for chronic otitis media with effusion is addressed in a separate document.*

## Scope Statement

<b>Population(s)</b>	Children with recurrent acute otitis media (AOM)
<b>Intervention(s)</b>	Prophylactic or suppressive antibiotics, tympanostomy tubes (grommets), tonsillectomy and/or adenoidectomy (note that these interventions may be used alone, serially or in combination)
<b>Comparator(s)</b>	Usual care, episodic treatment of AOM

<p><b>Outcome(s) (up to five)</b></p>	<p><i>Critical:</i> Severe infection (e.g. systemic infection, sepsis, meningitis, locally invasive infection), clinically significant hearing loss, speech delay</p> <p><i>Important:</i> Treatment harms, acute otitis media episodes</p> <p><i>Outcomes considered but not selected for GRADE table:</i> Missed school days, school performance/academic achievement</p>
<p><b>Key questions</b></p>	<p>KQ1: What is the comparative effectiveness of interventions (alone, serially, or in combination) for recurrent acute otitis media?</p> <p style="padding-left: 40px;">a. Are there subpopulations of children with recurrent acute otitis media who are more likely to benefit from prophylactic interventions?</p> <p>KQ2: What are the harms of interventions for recurrent acute otitis media?</p>

### Original Evidence Sources

Leach, A.J., & Morris, P.S. (2006). Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database of Systematic Reviews*, 4(CD004401), 1-70. [Assessed as up-to-date: 5 AUG 2010]. Retrieved September 27, 2012, from <http://summaries.cochrane.org/CD004401/antibiotics-to-prevent-acute-earinfections-in-children>

McDonald, S., Langton Hewer, C.D., & Nunez, D.A. (2008). Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database of Systematic Reviews*, 4(CD 004741), 1-14. [Assessed as up-to-date: 10 JAN 2011]. Retrieved September 27, 2012, from <http://summaries.cochrane.org/CD004741/grommets-ventilation-tubes-for-recurrentacute-otitis-media-in-children>

Shekelle PG, Takata G, Newberry SJ, Coker T, Limbos M, Chan LS, et al. (2010). *Management of Acute Otitis Media: Update*. Evidence Report/Technology Assessment No. 198. (Prepared by the RAND Evidence-Based Practice Center under Contract No. 290 2007 10056 I). Rockville, MD: Agency for Healthcare Research and Quality. Retrieved September 26, 2012, from <http://www.ncbi.nlm.nih.gov/books/NBK56132/>

## Scanning Results

1. Boonacker, C. W., Rovers, M. M., Browning, G. G., Hoes, A. W., Schilder, A. G., & Burton, M. J. (2014). Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. *Health Technology Assessment, 18*(5), 1-117.

Citation 1 is a health technology assessment by the NHS and includes a meta-analysis of 10 trials of adenoidectomy with or without grommets. In the meta-analysis, adenoidectomy with or without grommets had a failure rate (defined as >4 episodes of AOM over 12 months) of 32% compared with 45% in the group that did not undergo adenoidectomy. The benefit of adenoidectomy for recurrent AOM appeared to be greatest in children under the age of 2 years.

2. Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Tympanostomy tube insertion system for children with otitis media*. Ottawa: CADTH. Retrieved August 12, 2015 from [https://www.cadth.ca/sites/default/files/pdf/EH0018\\_TympanostomyTubeInsertionDelivery\\_e.pdf](https://www.cadth.ca/sites/default/files/pdf/EH0018_TympanostomyTubeInsertionDelivery_e.pdf)

Citation 2 is a CADTH brief summary on the TULA system for placing tympanostomy tubes in the outpatient setting using local anesthesia only. Based on three single-arm, open-label, prospective trials the TULA system appears to be safe and cost-effective. It should be noted that there are competing technologies under development.

3. Cheong, K. H., & Hussain, S. S. (2012). Management of recurrent acute otitis media in children: systematic review of the effect of different interventions on otitis media recurrence, recurrence frequency and total recurrence time. *Journal of Laryngology & Otology, 126*(9), 874-85.

Citation 3 is a systematic review that includes seven studies examining various interventions for recurrent AOM. The authors conclude that prophylactic antibiotics and adenoidectomy both reduce recurrence of AOM, but tympanostomy tubes do not.

4. Courter, J. D., Baker, W. L., Nowak, K. S., Smogowicz, L. A., Desjardins, L. L., Coleman, C. I., & Giroto, J. E. (2010). Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. *Annals of Pharmacotherapy, 44*(3), 471-478.

Citation 4 is a meta-analysis of studies comparing macrolides to beta-lactam antibiotics for AOM. It is out of scope.

5. Gaboury, I., Coyle, K., Coyle, D., & Le Saux, N. (2010). Treatment cost effectiveness in acute otitis media: a watch-and-wait approach versus amoxicillin. *Paediatrics and Child Health, 15*(7), e14-e18.

Citation 5 is a Canadian cost-effectiveness study comparing watchful-waiting to amoxicillin treatment for AOM. It is out of scope.

6. Gisselsson-Solen, M. (2014). The importance of being specific – a meta-analysis evaluating the effect of antibiotics in acute otitis media. *International Journal of Pediatric Otorhinolaryngology, 78*(8), 1221-1227.

Citation 6 is meta-analysis that addresses methodologic issues in the selection of outcomes for trials of antibiotic treatment of AOM. It is out of scope.

7. Hellstrom, S., Groth, A., Jorgensen, F., Pettersson, A., Ryding, M., Uhlen, I., & Bostrom, K. B. (2011). Ventilation tube treatment: a systematic review of the literature. *Otolaryngology – Health & Neck Surgery, 145*(3), 383-95.

Citation 7 is a systematic review of 63 studies of “secretory otitis media.” The authors conclude that tympanostomy tubes are associated with improve QoL but there is insufficient evidence of an effect on recurrent AOM.

8. Kozyrskyj, A. L., Klassen, T. P., Moffatt, M., & Harvey, K. (2010). Short-course antibiotics for acute otitis media. *Cochrane Database of Systematic Reviews*, Issue 9. DOI: 10.1002/14651858.CD001095.pub2.

Citation 8 is a Cochrane review of short-course antibiotic treatment of AOM. It is out of scope.

9. Lieberthal, A. S., Carroll, A. E., Chonmaitree, T., Ganiats, T. G., Hoberman, A., Jackson, M. A., ... Tunkel, D. E. (2013). The diagnosis and management of acute otitis media. *Pediatrics, 131*(3), e964-99.

Citation 9 is a CPG from the American Academy of Pediatrics. The guidelines state that prophylactic antibiotics should not be prescribed for the treatment of recurrent AOM (evidence level: B, strength: recommendation). Tympanostomy tubes can be offered for recurrent AOM (evidence level: B, strength: option).

10. Lous, J., Ryborg, C. T., & Thomsen, J. L. (2011). A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media. *International Journal of Pediatric Otorhinolaryngology*, 75(9), 1058-61.

Citation 10 is a systematic review of tympanostomy tubes for recurrent AOM. The authors conclude that 2 to 5 children need to receive tympanostomy tubes in order to prevent one episode of recurrent AOM over 6 months. The authors note that this appears to be similar to the effects of six months of prophylactic antibiotic treatment.

11. Mikals, S. J., & Brigger, M. T. (2014). Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. *JAMA Otolaryngology - Head and Neck Surgery*, 140(2), 95-101.

Citation 11 is a SR and MA of 15 trials of adenoidectomy in addition to tympanostomy tube placement for treatment of recurrent AOM, otitis media with effusion, or otorrhea. The study results were mixed and heterogeneous, but in the meta-analysis addition of adenoidectomy reduced the need for repeated tympanostomy tubes, although the effects appeared to be attenuated in children under the age of 4 years.

12. Rosenfeld, R. M., Schwartz, S. R., Pynnonen, M. A., Tunkel, D. E., Hussey, H. M., Fichera, J. S., ... Schellhase, K. G. (2013). Clinical practice guideline: tympanostomy tubes in children. *Otolaryngology - Head and Neck Surgery*, 149(1 Suppl):S1-35.

Citation 12 is a CPG from the American Academy of Otolaryngology – Head and Neck Surgery. The guidelines recommend that tympanostomy tubes should not be offered for treatment of recurrent AOM unless a middle ear effusion is present at the time of evaluation for tubes.

13. Subcommittee of Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children (Japan Otological Society, Japan Society for Pediatric Otorhinolaryngology, Japan Society for Infectious Diseases in Otolaryngology). (2012). Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan. *Auris, Nasus, Larynx*, 39(1), 1-8.

Citation 13 is multi-society CPG from several ENT societies in Japan pertaining to treatment of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

14. Thanaviratnanich, S., Laopaiboon, M., & Vatanasapt, P. (2013). Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database of Systematic Reviews*, Issue 12. DOI: 10.1002/14651858.CD004975.pub3.

Citation 14 is a Cochrane review comparing the effectiveness of various dosing regimens for the treatment of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

15. Thorton, K., Parrish, F., & Swords, C. (2011). Topical vs. systematic treatments for acute otitis media. *Pediatric Nursing*, 37(5), 263-7.

Citation 15 is a narrative review of treatment strategies for AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

16. Toll, E. C., & Nunez, D. A. (2012). Diagnosis and treatment of acute otitis media: review. *Journal of Laryngology & Otology*, 126(10), 976-83.

Citation 16 is a narrative review of the diagnosis and treatment of AOM. It does not specifically address the treatment of recurrent AOM except to briefly note that tympanostomy tubes reduce recurrent AOM.

17. van den Aardweg, M. T. A., Schilder, A. G. M., Herkert, E., Boonacker, C. W. B., & Rovers, M. M. (2010). Adenoidectomy for otitis media in children. *Cochrane Database of Systematic Reviews*, Issue 1. Art. DOI: 10.1002/14651858.CD007810.pub2.

Citation 17 is a Cochrane review of adenoidectomy compared with tympanostomy tubes or non-surgical management in children with otitis media with effusion. The authors conclude that the studies of adenoidectomy did not demonstrate a significant benefit in reducing episodes of AOM.

18. Venekamp, R. P., Sanders, S. L., Glasziou, P. P., Del Mar, C. B., & Rovers, M. M. (2015). Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews*, Issue 6. DOI: 10.1002/14651858.CD000219.pub4.

Citation 18 is a Cochrane review of antibiotic treatment for AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

19. Venekamp, R. P., Damoiseaux, R. A. M. J. & Schilder, A. G. M. (2014). Acute otitis media in children. *BMJ Clinical Evidence*, 09, 301-322.

Citation 19 is a BMJ Clinical Evidence brief on the diagnosis and management of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

20. Washington Health Technology Assessment (WA HTA). (2015). *Tympanostomy tubes in children – draft evidence report*. Olympia, WA: WA HTA. Retrieved August 12, 2015 from [http://www.hca.wa.gov/hta/Documents/tympan\\_tubes\\_draft\\_report\\_073115.pdf](http://www.hca.wa.gov/hta/Documents/tympan_tubes_draft_report_073115.pdf)

Citation 20 is a draft WA HTA report on the use of tympanostomy tubes in children. The report only briefly addresses the population of children with recurrent AOM but notes that there is little evidence of efficacy or only small short-term benefits for tubes in the management of recurrent AOM. It also notes that current guidelines recommend against prescribing prophylactic antibiotics for recurrent AOM.

## 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 “otitis media,” “tonsillectomy,” “adenoidectomy,” and “tympanostomy tube.” Searches of core sources were limited to citations published after 2009.

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 2009.

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
- 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.

# Neuroimaging for Headache – 2015 Rescanning Summary

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

**Bottom Line:** There continues to be very limited good-quality evidence on the utility of neuroimaging for headache. In general, the sources reviewed below recommend that neuroimaging should not be obtained in the evaluation of primary headache disorders without red-flags. There is some minor variability in the definition of red-flag features, and in most cases these determinations are made on the basis of expert opinion. Most of the red-flag features proposed in other guidelines are captured in the current HERC coverage guidance.

## Coverage Recommendation (Box Language)

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

Neuroimaging is recommended for coverage with headache when a red flag\* is present.

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

- new onset or change in headache in patients who are aged over 50
- thunderclap headache: rapid time to peak headache intensity (seconds to 5 min)
- focal neurologic symptoms (e.g. limb weakness, lack of coordination, numbness or tingling)
- non-focal neurological symptoms (e.g. altered mental status, dizziness)
- abnormal neurological examination
- headache that changes with posture
- headache waking the patient up (Note: migraine is the most frequent cause of morning headache)
- headache precipitated by physical exertion or Valsalva maneuver (e.g. coughing, laughing, straining)
- patients with risk factors for cerebral venous sinus thrombosis
- jaw claudication
- nuchal rigidity
- new onset headache in a patient with a history of human immunodeficiency virus (HIV) infection
- new onset headache in a patient with a history of cancer

- cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), or short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA)

### Scope Statement

<b>Population description</b>	Adults and children with non-traumatic, acute or chronic headache
<b>Intervention(s)</b>	MRI or CT head/brain, with or without contrast enhancement <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	Usual care, no neuroimaging
<b>Outcome(s) (up to five)</b>	<b>Critical:</b> Morbidity from significant intracranial abnormalities <b>Important:</b> Headache-free days, quality of life, harms from radiation exposure, harms from incidental findings <i>Outcomes considered but not selected for GRADE table: None</i>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What is the comparative effectiveness of neuroimaging for headache in improving patient outcomes or detecting significant intracranial abnormalities?             <ol style="list-style-type: none"> <li>a. Does the effectiveness of neuroimaging for headache vary based on acuity?</li> </ol> </li> <li>2. What are the evidence-supported red-flag features which are indications for neuroimaging for headache?             <ol style="list-style-type: none"> <li>a. Do the evidence-supported red-flag features which indicate neuroimaging vary based on acuity?</li> </ol> </li> <li>3. What are the harms of neuroimaging for headache?</li> </ol>

### Original Evidence Sources

Clark, E.E., Little, A., & King, V. (2010). *Red flags and imaging in headache*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

*Key Sources Cited in MED Report:*

Detsky, M.E., McDonald, D.R., Baerlocher, M.O., Tomlinson, G.A., McCrory, D.C., & Booth, C.M. (2006). Does this patient with headache have a migraine or need neuroimaging? *JAMA*, 296(10), 1274-1283.

Frishberg, B.M., Rosenberg, J.H., Matchar, D.B., McCrory, D.C., Pietrzak, M.P., Rozen, T.D., et al. (2000). Evidence-based guidelines in the primary care setting: Neuroimaging in patients with nonacute headache. US Headache Consortium. Minneapolis, MN: American Academy of Neurology. Retrieved from <http://www.aan.com/professionals/practice/pdfs/gl0088.pdf>

McCormack, R.F., & Hutson, A. (2010). Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan?. *Academic Emergency Medicine*, 17(4), 444-451.

Scottish Intercollegiate Guidelines Network. (2008). *Diagnosis and Management of Headaches in Adults*. A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guidelines Network. Retrieved from <http://www.sign.ac.uk/pdf/qrg107.pdf>

## Scanning Results

1. Alexiou, G. A. & Argyropoulou, M. I. (2013) Neuroimaging in childhood headache: A systematic review. *Pediatric Radiology*, 43(7):777-784.

Citation 1 is a systematic review of seventeen studies examining the utility of neuroimaging for children with headaches. Of 3,260 children who had undergone neuroimaging for headache, only 82 (2.5%) had imaging findings that led to a change in management and among these patients only 4 had normal neurologic exams. The overall conclusion is that neuroimaging for headache in children is generally low yield and should be limited to those with “a suspicious clinical history, abnormal neurologic findings or other physical signs suggestive of intracranial pathology.”

2. Beithon, J., Gallenberg, M., Johnson, K., Kildahl, P., Krenik, J., Liebow, M., ... Swanson, J. (2013). Diagnosis and treatment of headache. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jan. Retrieved from <http://bit.ly/Headache0113>.

Citation 2 is a guideline from the Institute for Clinical Systems Improvement (ICSI). It is focused mainly on the diagnosis and management of primary headache disorders, for

which neuroimaging is not needed for the diagnosis. The guideline offers the following causes for concern:

- Subacute and/or progressive headaches that worsen over time (months)
- A new or different headache or a statement by a headache patient that "this is the worst headache ever"
- Any headache of maximum severity at onset
- Headaches of new onset after the age of 50 years old
- Persistent headache precipitated by a Valsalva maneuver such as cough, sneeze, bending or with exertion (physical or sexual)
- Evidence such as fever, hypertension, myalgias, weight loss or scalp tenderness suggesting a systemic disorder
- Neurological signs that may suggest a secondary cause. For example: meningismus, confusion, altered levels of consciousness, changes or impairment of memory, papilledema, visual field defect, cranial nerve asymmetry, extremity drifts or weaknesses, clear sensory deficits, reflex asymmetry, extensor plantar response, or gait disturbances
- Seizures

According to the ICSI algorithm, any of the above signs should prompt consideration of secondary headache disorders and additional diagnostic testing (including neuroimaging) or referral for specialty consultation is warranted.

3. Douglas, A. C., Wippold, F. J. II, Broderick, D. F., Aiken, A. H., Amin-Hanjani, S., Brown, D. C., ... Zipfel G. J. (2013). ACR Appropriateness Criteria® headache. [online publication]. Reston (VA): American College of Radiology (ACR).

Citation 3 is the American College of Radiology Appropriateness Criteria for headaches in adults. In general, imaging is usually not appropriate for chronic headaches without new features or abnormalities on neurologic exam. Some form of neuroimaging (MRI, CT, angiography) may be appropriate or is usually appropriate in the following scenarios:

- Chronic headache with new feature or neurologic deficit
- Sudden onset of severe headache
- Sudden onset of unilateral headache or suspected carotid or vertebral dissection
- Headache of trigeminal autonomic origin
- Headache of skull base, orbital, or periorbital origin
- Headache with suspected intracranial complication of sinusitis and/or mastoiditis
- Headache of oromaxillofacial origin
- New headache in elderly patients, ESR>55, temporal tenderness

- New headache in a cancer patient or immunocompromised individual
- New headache with suspected meningitis/encephalitis
- New headache in a pregnant woman
- New headache with focal neurologic deficit or papilledema
- Positional headache
- Headache associated with cough, exertion, or sexual activity
- Post-traumatic headache

4. Hayes, L. L., Coley, B. D., Karmazyn, B., Dempsey-Robertson, M. E., Dillman, J. R., Dory, C. E., ... Wootton-Gorges, S. L. (2012). ACR Appropriateness Criteria® headache - child. [online publication]. Reston (VA): American College of Radiology (ACR).

Citation 4 is the American College of Radiology Appropriateness Criteria for headaches in children. In general, imaging is usually not appropriate for primary headache disorders (chronic or recurrent headache including migraine without permanent neurologic signs or signs of increased intracranial pressure). Some form of neuroimaging (MRI, CT, angiography) may be appropriate or is usually appropriate in the following scenarios:

- Headache with signs of increased intracranial pressure or positive neurologic signs
- High-intensity headache of abrupt onset

5. Medical Advisory Secretariat. (2010). Neuroimaging for the evaluation of chronic headaches: an evidence-based analysis. Ontario Health Technology Assessment Service. 2010]; 10(26) 1-57. Available from: [http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev\\_Headache\\_20101222.pdf](http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_Headache_20101222.pdf)

Citation 5 is a health technology assessment and economic analysis from the Medical Advisory Secretariat of the Ontario Ministry of Health and Long-Term Care. Its focus is on the use of neuroimaging in people with chronic headache with a normal neurologic exam. Of note, the GRADE quality of evidence reported for this review was low to very low. The overall pretest probability of intracranial abnormalities in people with chronic headaches without neurologic findings is 0.9%. Summary likelihood ratios for detecting significant intracranial abnormalities were statistically significant for the following findings/ characteristics:

- Abnormal neurologic exam (+LR 5.3, -LR 0.71)
- Undefined headache (+LR 3.8, -LR 0.66)
- Headache aggravated by exertion or Valsalva (+LR 2.3, -LR 0.70)

- Headache with vomiting (+LR 1.8, -LR 0.47)
- Cluster-type headache (+LR 11, -LR 0.95 [NS])
- Headache with aura (+LR 3.2, -LR 0.51 [NS])

The review did not find evidence that neuroimaging reduced anxiety at 1 year.

6. National Clinical Guideline Centre. (2012). Headaches: diagnosis and management of headaches in young people and adults. London (UK): National Institute for Health and Clinical Excellence (NICE).

Citation 6 is a NICE guideline on headache in young people and adults. NICE recommends that people with tension-type or migraine headache should not be referred for imaging if they do not have signs or symptoms of secondary headache. Signs and symptoms of secondary headache are

- Worsening headache with fever
- Sudden-onset headache reaching maximum intensity within 5 minutes
- New-onset neurologic deficit
- New-onset cognitive dysfunction
- Change in personality
- Impaired level of consciousness
- Recent head trauma (typically within the past 3 months)
- Headache triggered by cough, valsalva, or sneeze
- Headache triggered by exercise
- Orthostatic headache
- Symptoms suggestive of giant cell arteritis
- Symptoms and signs of acute narrow-angle glaucoma
- Substantial change in the characteristics of their headache

NICE guidance also states that further investigation or referral may be warranted for people with new-onset headache and:

- Compromised immunity
- Age under 20 years and a history of malignancy
- A history of malignancy known to metastasize to the brain
- Vomiting without other obvious cause

Note: The NICE guidance is currently being reviewed and updated.

7. Toward Optimized Practice. (2012). Guideline for primary care management of headache in adults. Edmonton (AB): Toward Optimized Practice.

Citation 7 is a guideline from Toward Optimized Practice and the Institute of Health Economics in Alberta. According to these guidelines neuroimaging should not be obtained for common primary headache disorders or to reassure patients. They state that neuroimaging should be obtained:

- Emergently for:
  - Thunderclap headache
  - Headache with meningismus
  - Papilloedema with altered level of consciousness or focal signs
  - Acute angle-closure glaucoma
- Urgently for:
  - Signs of systemic illness in a patient with new onset headache
  - New headache in people over age 50 with other symptoms suggestive of temporal arteritis
  - Papilloedema without focal signs
  - Elderly patients with new headache and subacute cognitive change
- In the outpatient setting for:
  - Atypical headaches and change in headache pattern
  - Unexplained focal signs
  - Unusual headache precipitants
  - Unusual aura symptoms
  - Cluster headache and other uncommon primary headache syndromes
  - Late onset headache (after age 50)

8. vanRavesteijn, H., vanDijk, I., Darmon, D., vandeLaar, F., Lucassen, P., Hartman, T. O., vanWeel, C. & Speckens, A. (2012). The reassuring value of diagnostic tests: a systematic review. *Patient Education and Counseling*, 86(1), 3-8.

Citation 8 is a SR and narrative synthesis of studies pertaining to reassurance provided by diagnostic tests. They include one RCT of MRI brain to provide reassurance for patients with chronic headaches which concluded that while anxiety levels improve at 3 months that there is no difference at 1 year.

## **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 “headache” and “imaging” or “neuroimaging.” Searches of core sources were limited to citations published since 2010.

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 since 2010.

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
- 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.

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