



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

**June 2, 2016
2:00 PM - 5:00 PM**

**Clackamas Community College
Wilsonville Training Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville, Oregon,
97070**

Section 1.0

Call to Order

AGENDA

EVIDENCE-BASED GUIDELINES SUBCOMMITTEE (EbGS)

June 2, 2016

2:00pm - 5:00pm

Clackamas Community College
Wilsonville Training Center, Rooms 111-112
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.

#	Time	Item	Presenter
1	2:00 PM	Call to Order	Wiley Chan
2	2:05 PM	Review of April 7, 2016 minutes	Wiley Chan
3	2:10 PM	Staff update	Darren Coffman
4	2:15 PM	Skin substitutes for chronic skin ulcers <ul style="list-style-type: none">Review of public comment and draft coverage guidance	Adam Obley Cat Livingston
5	3:15 PM	Tobacco cessation during pregnancy <ul style="list-style-type: none">Review of public comment and draft coverage guidance	Adam Obley Cat Livingston
6	4:05 PM	Timing of Long Acting Reversible Contraceptives (LARCs) <ul style="list-style-type: none">Approve for public commentReview draft cover letter	Valerie King Cat Livingston
7	4:50 PM	Confirmation of the next meeting, September 1, 2016	Wiley Chan
8	4:55 PM	Next Topics	Cat Livingston
9	5:00 PM	Adjournment	Wiley Chan

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

MINUTES

Evidence-based Guidelines Subcommittee

Clackamas Community College
Wilsonville Training Center, Rooms 111-112
29353 SW Town Center Loop E
Wilsonville, Oregon 97070
April 7, 2016
2:00-5:00pm

Members Present: Wiley Chan, MD, Chair; Eric Stecker, MD, MPH, Vice-Chair (by phone); Beth Westbrook, PsyD; George Waldmann, MD (by phone); Alison Little, MD, MPH; Kim Tippens, ND, MPH.

Members Absent: None

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

Also Attending: Adam Obley, MD, Moira Ray, MD, MPH and Craig Mosbaek (OHSU Center for Evidence-based Policy); Erica Pettigrew, MD (OHSU); Charles Bentz, MD and Duncan Neilson, MD (Legacy Health); Kim Wentz, MD (by phone) and Jessie Little (OHA); Joanne Rogovoy (March of Dimes), Maria Rodriguez (OHSU), Emily Elman (OHA Public Health).

1. CALL TO ORDER

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

2. MINUTES REVIEW

No changes were made to the February 4, 2016 minutes.

Minutes approved 6-0.

3. STAFF REPORT

Coffman welcomed Tippens to the subcommittee. She introduced herself as a naturopath and acupuncturist. She is an assistant professor at the National College of Natural Medicine. She will be serving on HERC as well.

Coffman reported that the HERC has referred the draft coverage guidance on Skin Substitutes for Chronic Skin Ulcers back to EbGS and requested that it be put out for an additional public comment period. This coverage guidance will come back to the subcommittee at its June meeting.

4. DRAFT COVERAGE GUIDANCE: Timing of Long-Acting Reversible Contraceptive (LARC) Placement

Ray reviewed the draft coverage guidance and evidence as presented in the meeting materials. Coffman introduced Maria Rodriguez as appointed expert on the topic. She is an assistant professor at OHSU in the Obstetrics & Gynecology/Generalist Division. Her research has focused on the evaluation and monitoring of family planning programs, including reproductive health outcomes and disparities among the Medicaid Population. She has received research funding from the National Institutes of Health as a Women's Reproductive Health Research Fellow. She has consulted for the World Health Organization. She has been trained as a trainer for Nexplanon insertions.

Livingston also invited Dr. Duncan Neilson to participate as he is familiar with the topic and was already present in preparation for the upcoming discussion of Tobacco Cessation During Pregnancy. Dr. Duncan Neilson is Clinical Vice President, Legacy Health System, Portland. His responsibilities include program development in Women's Services, Quality and Patient Safety measurement and program implementation. He has served in the past as clinical vice president of Legacy's Women's Services and Surgical Services. He has served the commission as an expert on previous obstetric-related topics, including Out-of-Hospital Birth and Elective Induction of Labor.

Chan asked what the comparison was for the observational study which reported higher perforation among women who had delayed insertion and who were breastfeeding. Ray said that the study followed women over time and collected baseline data as well as information about expulsion events, perforation events and other adverse events, then looked retrospectively to find risk factors for the adverse events. Breastfeeding was found to be an independent risk factor for perforation over other factors like nulliparity and recent pregnancy. Chan said that breastfeeding is clearly correlated with time after delivery, but Ray said she believes the association was stronger than one would expect even given that fact.

Waldmann asked why breastfeeding would be associated with a higher risk than immediate postpartum status. Ray explained that it is believed to be related to hormonal changes affecting the uterus after delivery, and that six weeks postpartum is a vulnerable time; Neilson and Rodriguez confirmed this understanding. Rodriguez said it could also be that the placement was guided by ultrasound in the postpartum setting but not in the outpatient setting at 6 weeks. Chan said it may just be time after delivery rather than breastfeeding that is the major risk factor.

Livingston reviewed the resource allocation, values and preferences and other factors influencing the recommendation in the GRADE table. She also explained that despite lack of evidence specific to the timing question, there is CDC guidance saying that it is appropriate to place an implant postpartum or post abortion.

Little asked about the administrative issues surrounding reimbursement for these services. Staff recognized that with this intervention, ensuring appropriate reimbursement is key as the devices are expensive and providers can't be expected to stock them and pay for them if not reimbursed. Neilson shared of his experience at Legacy where they started offering LARC immediately postpartum, but were asked by administrators to stop because it was cost-prohibitive. This is because the global rate for delivery paid to a hospital isn't adjusted as a matter of course if a LARC is placed. He said that there are two separate issues—device manufacturers charging providers hundreds of dollars for a simple device

costing under two dollars to the manufacturer, and insurance companies failing to reimburse providers for their acquisition costs for the devices. Ray said that some states use outpatient billing to pay, while others do a periodic query of their claims data and make an extra payment to reimburse for LARC. Waldmann asked about using a modifier on professional claims. Others stated that there are ways of getting reimbursement for professional services; the issue is paying for the device itself.

Kim Wentz spoke about research she and Oregon Health Plan staff have been doing on reimbursement for LARC devices in the inpatient setting. There are three methods used by 18 states. She believes there are ways for the Oregon Health Plan to pay for these devices, along with their insertion, in all settings, but they need to be implemented. Rodriguez said OHSU has been providing postpartum LARC to uninsured women because of a charitable gift, but that they haven't been available for insured women because of the reimbursement issues. They have not had success getting reimbursement for these devices after discussions with state officials and legislators. The hospital has been donating the physician services, which are fairly minimal in the postpartum setting.

Livingston said that this coverage guidance will advance efforts to get health plans to pay for these devices in all setting. Waldmann said this shouldn't be difficult and that he doesn't understand why we can't solve this problem. Westbrook and Little also expressed support for the coverage guidance. Little requested a separate document to address implementation issues and motivate policymakers to find a solution. Livingston said that Wentz is already beginning some of these discussions now, even though the coverage guidance wouldn't be officially implemented until January for the Oregon Health Plan. The hope is that by January there will be a clear plan.

The subcommittee discussed various options for emphasizing that both the device and insertion should be reimbursed appropriately and bureaucratic barriers addressed. They considered adding language to the recommendation box but decided that this policy aspect should be kept separate from the evidence-based report. Several members and attendees expressed frustration that this issue has not been solved in Oregon despite a lack of philosophical opposition. Livingston directed the subcommittee's attention to sections of the coverage guidances which do address payment and administrative issues.

After discussion the subcommittee requested that staff draft a cover letter to accompany the report, addressing implementation issues and barriers to reimbursement, and describing the administrative issues in the coverage guidance more thoroughly. Waldmann specifically requested that the cover letter address the hospital's discontinuation of postpartum LARC placement as described by Neilson.

Because of an issue with posting sources, the subcommittee deferred voting on the draft coverage guidance until its June meeting.

5. DRAFT COVERAGE GUIDANCE: Tobacco Cessation During Pregnancy

Livingston introduced the report, reminding the subcommittee that this is the first evidence-based report to include multisector interventions (which may occur outside of the clinical setting, and not require any coverage changes from health plans, but nonetheless be effective ways of achieving health outcomes). Staff ran into challenges with the subcommittee's request to separate the document into two separate reports, and so has kept the report together as shown in the meeting materials.

Coffman introduced Dr. Charles Bentz who is the appointed expert on this topic. He is a Medical Director and Professor at the Pacific University College of Health Professions and is in private practice at Fanno Creek Clinic in Portland. In addition to his clinical and academic work, he has published several articles on tobacco-related topics. He has also worked on tobacco-related quality measurement, smoking cessation programs and reimbursement strategies. He has received funding from the National Institutes of Health, the Robert Wood Johnson Foundation, state health organizations, as well as manufacturers of all tobacco cessation products (including nicotine patches, lozenges, gums and sprays as well as bupropion and varenicline).

Coffman also re-introduced Neilson, who has been appointed as an expert for this topic. Neilson declared no conflicts of interest with respect to this topic.

Bentz said other interventions have been studied, such as provider and health system incentives. He asked why they were not included in the review. Bentz said beyond simply covering services, promoting them in the provider community and providing incentives to providers can be important. Obley said that evidence was not found in the evidence review. Bentz also asked about carbon monoxide as feedback. This was not included in the Cochrane review. Livingston asked whether these would have been included in scope. Obley said they may have been grouped under behavioral interventions. This grouping includes everything from the “Five A’s” program advocated by the Centers for Disease Control to more intensive interventions. Bentz said that his practice uses carbon monoxide as feedback and that it is actually helpful. Livingston noted that these interventions could be submitted as public comment. Bentz said some of the studies he is referring to were not conducted in pregnant women, and this may explain why they weren’t included. Livingston said we would need evidence in the pregnant population.

Chan asked whether there is any reason to think that most interventions effective in other populations would have differential effectiveness in pregnant women? Obley said that the Patnode review does divide pregnant women from the general adult population. He assumes this is because pregnant women may have been excluded from general population studies. Bentz said that pregnant women can be particularly motivated to quit. Sometimes they spontaneously quit or suspend smoking during the pregnancy. He agreed that the behavioral interventions would work in pregnant women. But in designing interventions for pregnant women you need to think about special issues including relapse after the birth. Bentz said all behavioral interventions are tailored by type of tobacco use and cultural factors and pregnancy is another similar factor.

Coffman noted that the Commission has already approved a statement on multisector interventions for tobacco. He suggested that when implemented on the prioritized list, a special statement about pregnant women could be added to that section.

Westbrook asked about levels of addiction. Neilson said that interventions would need to be tailored to women based on the number of years they smoked and how much they smoked. For instance, behavioral interventions would more likely be effective in a casual smoker. Both clinicians and researchers are reluctant to do drug research on pregnant patients. Thus the drugs are generally reserved for the most nicotine dependent patients, resulting in a biased population for any research that would be done (that is, the study population would include the most difficult-to-treat patients). However, he also said that more dependent patients generally show a better response to nicotine replacement therapy (NRT), because they have more nicotine receptors. He said that there is a strong dose response for behavioral interventions (more intensive counseling is more effective) and that at any intensity of counseling, NRT doubles the quit rate.

Livingston turned the group's attention to the GRADE table for NRT. Most outcomes showed equivalence, though it showed effectiveness for tobacco abstinence during pregnancy. Ordinarily the staff recommendation might be to recommend noncoverage based on this evidence profile. Federal law, however, requires coverage of medication therapy for tobacco cessation for pregnant women in Medicaid, and the prohibition on prior authorization of tobacco cessation aids in the Affordable Care Act would make it difficult for most commercial insurers to restrict coverage. Based on this, the staff recommendation is for the subcommittee to state that it makes no recommendation for this population.

Bentz said that study designs for tobacco cessation during pregnancy are fatally flawed because of high relapse rates among postpartum women. Most studies weren't designed to include postpartum support. He advocated for coverage because there is no harm and because getting people to quit is the most important thing. Because of the ethical issues around conducting trials in this population, it is unlikely that evidence is likely to change. Neilson agreed.

Chan noted that there is no good evidence that NRT has harms. Obley confirmed this, noting that the studies included the pregnancy outcomes for the purpose of showing that NRT is no more harmful than continued smoking based on these outcomes, not to show a benefit of NRT for these outcomes. Chan asked if a recommendation could be made based on the broader evidence base for NRT in nonpregnant populations. Livingston noted that for the nonpregnant population, the outcomes of interest would be chronic obstructive pulmonary disease, asthma and lung cancer, which is different than the outcomes of interest in the pregnant population. Bentz and Neilson agreed that the population is distinct.

After discussion the subcommittee accepted the lack of recommendation for pharmacologic therapy and changed the recommendation for noncoverage for electronic nicotine delivery devices in pregnant women to a strong recommendation.

The subcommittee affirmed the recommendation for coverage for behavioral interventions with little discussion.

For high feedback ultrasound, the subcommittee discussed the large effect size, balanced by the fact that it is based on a single RCT from 1982 with 129 participants. The subcommittee also discussed that in another context, high feedback ultrasound can be considered coercive, as it is used by abortion opponents to influence women's reproductive choices. Westbrook stated that sometimes this is termed "obstetric violence." Bentz noted that even with carbon monoxide feedback, clinicians need to be careful, or patients can become anxious and not return for care. Livingston noted that concerns about psychological distress appear in the values and preferences column.

After discussion, the subcommittee decided that the context of tobacco smoking is sufficiently different than in the case of counseling about abortion and that in this context, smoking cessation can only improve outcomes for the mother and baby. Obley noted that the GRADE assessment from the Cochrane review was low. Livingston noted that with skin substitutes, low quality evidence was considered sufficient. Bentz noted that the cost would be relatively small cost on top of the existing cost of the ultrasound. After discussion the subcommittee decided to make a weak recommendation for coverage, while noting the age of the study.

The subcommittee accepted staff recommendations for financial incentives, partner support, interventions to reduce secondhand smoke exposure, smoke-free legislation and tobacco excise taxes.

There was discussion about how social supports including partner support are supported by evidence in the general population, but the evidence may not exist in pregnancy. Livingston noted that behavioral interventions are covered in general, it would just be an intervention targeted solely at partner support that would not be recommended.

Bentz suggested adding system-level interventions such as provider and plan incentives, though they are difficult to implement. He said systems interventions may be the most important thing that can be done to increase tobacco cessation. Livingston said we didn't find evidence about these interventions, so evidence that these interventions affect pregnancy-related outcomes would need to be submitted during public comment in order to add statements about them in this document.

The subcommittee discussed options for distinguishing between coverage recommendations and statements on multisector evidence. After discussion the subcommittee agreed to use the current format with different colors to highlight the distinctions between the coverage recommendations and evidence statements on multisector interventions as well as the distinctions between the GRADE tables and evidence tables. Chan requested that staff include an explanation of what a multisector intervention is along with the evidence statement. Staff will also make heading changes to clearly delineate which sections relate to multisector interventions.

After brief additional discussion, the subcommittee decided to remove the description of the effects of the multisector interventions to be consistent with the coverage guidance recommendations.

The subcommittee voted to put the draft coverage guidance (as amended) out for a 30-day public comment period by a vote of 5-0 (Stecker absent).

6. ADJOURNMENT

The meeting was adjourned at 5:00 pm. The next meeting is scheduled for June 2, 2016 from 2:00-5:00 pm at Clackamas Community College, Wilsonville Training Center, Rooms 111-112, 29353 SW Town Center Loop E, Wilsonville, Oregon 97070.

Section 2.0

CG-Skin substitutes for
diabetic foot ulcers and
venous leg ulcers

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: SKIN SUBSTITUTES FOR CHRONIC SKIN ULCERS

DRAFT for EbGS meeting materials 6/2/2016

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. Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
4. For patients with diabetes, Hba1c level is < 12
5. Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
6. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, with continued significant improvement every 6 weeks required for coverage of ongoing applications
7. 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 and Ultra Tri-Layer Matrix)	Recommended	Recommended (OASIS® Wound Matrix only)
EpiFix®	Not recommended	Not recommended
Grafix®	Not recommended	Not recommended
Graftjacket®	Not recommended	Not recommended
Omnigraft®	<u>Not recommended</u>	<u>Not recommended</u>
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) (*weak recommendation*).

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description*.

RATIONALE FOR GUIDANCE DEVELOPMENT

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

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

Coverage guidance development follows 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
Deep soft tissue or bone infection <i>(Critical outcome)</i>	<u>DFU</u> ¹ : osteomyelitis 2.7% vs 10.4% (p = 0.4) ●●○○ (low certainty of no benefit, based on one good quality RCT) DFU (Apligraf® vs TheraSkin®): One amputation due to infection with TheraSkin® vs none for Apligraf® (p-value not reported) ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT) <u>VLU</u> : osteomyelitis 8.1% vs 0% (no statistical analysis)	Incremental cost for adding Apligraf® to a patient’s course of treatment for a small leg ulcer (<25 cm ²) 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 somewhat higher for foot ulcers due to higher physician fees/bundled fees for application. Product is sold in 44 cm ² sheets.

¹ 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
	●○○○ (very low certainty of benefit, based on one good quality RCT)	Up to 3 applications appear to be the maximum necessary based on included studies.
Complete wound healing (Critical outcome)	<p><u>DFU</u>: RR 1.5, 1.96 (p = 0.01, 0.03)</p> <p>●●●○ (moderate certainty of benefit, based on two good quality RCTs)</p> <p>DFU (Apligraf® vs TheraSkin®): 47.1% vs 66.7% (p-value not reported)</p> <p>●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p><u>VLU</u>: RR 2.38 (p < 0.001)</p> <p>●●○○ (low certainty of benefit, based on one good quality RCT)</p> <p><u>Unspecified non-healing ulcers</u>: 100% vs 75% (p < 0.01)</p> <p>●○○○ (very low certainty of benefit, based on one poor quality RCT)</p>	
Quality of life (Critical outcome)	No evidence identified.	
Time to complete wound healing (Important outcome)	<p><u>DFU</u>: No evidence identified.</p> <p><u>VLU</u>: 61 vs 191 days (statistical analysis not provided)</p> <p>●●○○ (low certainty of benefit, based on one good quality RCT)</p> <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>	

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
Adverse effects <i>(Important outcome)</i>	<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>●●○○ <i>(low certainty of no harm, based on four good quality RCT)</i></p> <p><u>VLU</u>: Infection rates of 8.2% vs 7.8% (statistical analysis not reported)</p> <p>●○○○ <i>(very low certainty of no harm, based on one good quality RCT)</i></p>	
<p>Rationale: 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>Recommendation: 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 cm² 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
Deep soft tissue or bone infection <i>(Critical outcome)</i>	<p><u>DFU</u>: Osteomyelitis incidence 8.6% in both intervention and control groups ●○○○ <i>(very low certainty of no benefit, based on one fair quality RCT)</i></p>	<p>Incremental cost for adding Dermagraft® to a patient's course of treatment for a small leg ulcer (<25 cm²) 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. Product is sold in 37.5 cm² sheets.</p>
Complete wound healing <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) ●●○○ <i>(low certainty of benefit, based on three fair quality concordant RCTs and one poor quality discordant RCT)</i></p> <p><u>DFU</u>: (Dermagraft® vs OASIS® Wound Matrix): 84.6% vs 76.9%, p = 0.62 ●○○○ <i>(very low certainty of no comparative benefit, based on one fair quality RCT)</i></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) ●○○○ <i>(very low certainty of no benefit, based on two fair quality RCTs)</i></p>	
Quality of life <i>(Critical outcome)</i>	No evidence identified.	
Time to complete wound healing <i>(Important outcome)</i>	<p><u>DFU</u>: 13 weeks vs 28 weeks (statistical analysis not reported) ●●○○ <i>(low certainty of benefit, based on four poor to fair quality RCTs)</i></p>	

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
	<p><u>DFU</u> (Dermagraft® vs OASIS® Wound Matrix): 40.90 vs 35.67 days, p = 0.73</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>	
Adverse effects (Important outcome)	<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>Rationale: 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>Recommendation:</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 cm² and has a short shelf life, which may lead to waste.</p>		

OASIS® Wound Matrix/Ultra Tri-Layer Matrix

Coverage question: Should OASIS® Wound Matrix/ <u>Ultra Tri-Layer Matrix</u> be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
Deep soft tissue or bone infection <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 ²) 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 ² 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 ² . 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® <u>Wound Matrix</u> to 3 sheets of Dermagraft® for DFU. One Medicare LCD limits to 12 weeks of therapy.
Complete wound healing <i>(Critical outcome)</i>	<p>DFU: 49% vs 28% (p = 0.06) at 12 weeks (<u>OASIS Wound Matrix</u>); 54% vs 32% (p=0.021) at 12 weeks (<u>OASIS® Ultra Tri-Layer Matrix</u>)</p> <p>●●○○ (low certainty of benefit, based on two fair quality RCTs <i>with inconsistency in comparator groups</i>)</p> <p>DFU: (OASIS® <u>Wound Matrix</u> vs Dermagraft®): 76.9% vs 84.6%, p = 0.62</p> <p>●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p>VLU: 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) (<u>OASIS® Wound Matrix</u>)</p> <p>●●○○ (low certainty of benefit, based on three fair to good quality RCTs with inconsistency in comparator groups)</p>	
Quality of life <i>(Critical outcome)</i>	No evidence identified.	
Time to complete wound healing <i>(Important outcome)</i>	<p>DFU: 5.4 vs 8.3 weeks, statistical analysis not reported (<u>OASIS® Wound Matrix</u>); 67 vs 73 days (p = 0.245) (<u>OASIS® Ultra Tri-Layer Matrix</u>)</p> <p>●●○○ (low certainty of no benefit, based on two fair quality RCTs)</p> <p>DFU: (OASIS® <u>Wound Matrix</u> vs Dermagraft®): 35.67 vs 40.90 days, p = 0.73</p> <p>●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p>	

Coverage question: Should OASIS® Wound Matrix/ Ultra Tri-Layer Matrix be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
	<p>VLU: 63% vs 40% expected to heal at 12 weeks, $p = 0.0226$ (OASIS® Wound Matrix)</p> <p>●○○○ (very low certainty of benefit, based on one good quality RCT)</p>	
<p>Adverse effects (Important outcome)</p>	<p>DFU: Approximately equal number of AEs between groups, statistical analysis not reported (OASIS® Wound Matrix)</p> <p>●○○○ (very low certainty of no benefit, based on one fair quality RCT)</p> <p>VLU: Approximately equal number of AEs between groups, statistical analysis not reported (OASIS® Wound Matrix)</p> <p>●○○○ (very low certainty of no benefit, based on one good quality RCT)</p>	
<p>Rationale: 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® Ultra Tri-Layer Matrix and OASIS® Wound matrix is Matrix are recommended for coverage for diabetic foot ulcers based on low certainty evidence of benefit of improved wound healing and low variability in values and preferences.</p>		
<p>Recommendation: OASIS® is recommended for coverage for diabetic foot ulcers (Oasis® Ultra Tri-Layer Matrix and Wound Matrix) and venous leg ulcers (Oasis® Wound Matrix) (weak recommendation), when conditions necessary for wound healing are present.</p>		

Coverage question: Should EpiFix® 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 <i>(Critical outcome)</i>	No evidence identified.
Complete wound healing <i>(Critical outcome)</i>	DFU: 92% versus 8% (p < 0.0001), 95% vs 35% (p = 0.0001) ●○○○ <i>(very low certainty of benefit, based on one RCT two RCTs of fair/poor quality)</i>
Quality of life <i>(Critical outcome)</i>	No evidence identified.
Time to complete wound healing <i>(Important outcome)</i>	No evidence identified. DFU: 2.5 weeks versus 5 weeks (no statistical test), 13 days versus 49 days (p<0.0001) ●○○○ (very low certainty of benefit, based on two RCTs of poor quality)
Adverse effects <i>(Important outcome)</i>	No evidence identified. Adverse events were sparsely reported in both trials and tests for statistically significant differences were not reported
Rationale: EpiFix® is not recommended for coverage due to insufficient evidence of effectiveness and the availability of effective alternatives <i>(weak recommendation)</i> .	
Recommendation: EpiFix® is not recommended for coverage for chronic skin ulcers <i>(weak recommendation)</i> .	

Omnigraft Integra Dermal Regeneration Template®

<u>Coverage question: Should Omnigraft Integra® be recommended for coverage for treatment of chronic skin ulcers?</u>	
<u>Outcomes</u>	<u>Estimate of Effect for Outcome/ Confidence in Estimate</u>
<u>Deep soft tissue or bone infection</u> <i>(Critical outcome)</i>	<u>No evidence identified.</u>
<u>Complete wound healing</u> <i>(Critical outcome)</i>	<u>DFU: 51% versus 32% at 16 weeks (p = 0.001)</u> <u>●○○○ (very low certainty of benefit, based on one RCT of fair quality)</u>
<u>Quality of life</u> <i>(Critical outcome)</i>	<u>DFU: Statistically significant differences in SF-36 Physical Functioning score (p = 0.047) and Bodily Pain score (p = 0.033) in favor of Omnigraft Integra®, but the magnitude of the improvements are not reported</u> <u>●○○○ (very low certainty of benefit, based on one RCT of fair quality)</u>
<u>Time to complete wound healing</u> <i>(Important outcome)</i>	<u>DFU: 43 days versus 78 days (p = 0.001)</u> <u>●○○○ (very low certainty of benefit, based on one RCT of fair quality)</u>
<u>Adverse effects</u> <i>(Important outcome)</i>	<u>Adverse events were similar in both groups (4.5% versus 5.2%)</u> <u>●○○○ (very low certainty of no difference, based on one RCT of fair quality)</u>
<u>Rationale: Omnigraft® is not recommended for coverage due to insufficient evidence of effectiveness and the availability of effective alternatives.</u>	
<u>Recommendation: Omnigraft® is not recommended for coverage (weak recommendation).</u>	

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 fair quality)
Complete wound healing (Critical outcome)	DFU: 62% vs 21%, p < 0.01 ●○○○ (very low certainty of benefit, based on one RCT of poor fair 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 fair quality)
Adverse effects (Important outcome)	DFU: 44% vs 66% (p = 0.031) ●○○○ (very low certainty of benefit, based on one RCT of poor fair quality)
Rationale: Grafix® is not recommended for coverage for chronic skin ulcers due to insufficient evidence of effectiveness and the availability of effective alternatives (<i>weak recommendation</i>).	
Recommendation: 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
Deep soft tissue or bone infection (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)
Complete wound healing (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 poor to fair quality RCTs)
Quality of life (Critical outcome)	No evidence identified.
Time to complete wound healing (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 poor to fair quality RCTs)
Adverse effects (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)
Rationale: 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.	
Recommendation: 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
Deep soft tissue or bone infection (<i>Critical outcome</i>)	No evidence identified.
Complete wound healing (<i>Critical outcome</i>)	<u>VLU</u> : 86% vs 45% (p = 0.0005) ●○○○ (<i>very low certainty of benefit, based on one good quality RCT</i>)
Quality of life (<i>Critical outcome</i>)	No evidence identified.
Time to complete wound healing (<i>Important outcome</i>)	No evidence identified.
Adverse effects (<i>Important outcome</i>)	<u>VLU</u> : No significant treatment-related AEs ●○○○ (<i>very low certainty of no benefit, based on one good quality RCT</i>)
Rationale: 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.	
Recommendation: 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
Deep soft tissue or bone infection <i>(Critical outcome)</i>	DFU: (TheraSkin® vs Apligraf®): One amputation for infection, compared to none with Apligraf® ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
Complete wound healing <i>(Critical outcome)</i>	DFU: (TheraSkin® vs Apligraf®): 66.7% vs 41.3% (p = 0.21) ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
Quality of life <i>(Critical outcome)</i>	No evidence identified.
Time to complete wound healing <i>(Important outcome)</i>	No evidence identified.
Adverse effects <i>(Important outcome)</i>	No evidence identified.
Rationale: TheraSkin® is not recommended for coverage because of insufficient evidence of benefit (limited evidence suggesting it is comparable to another effective product), a lack of strong patient preferences for this, alternatives available, and its cost.	
Recommendation: 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 Integra™ Bilayer Matrix Wound Dressing	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™ 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 OASIS® Ultra Tri-Layer 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 (Tegapore®) 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

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

Systematic Review (Quality) Total N	Population No. and Type of Included Studies	Skin Substitute Category	Outcomes of Interest
	infected): 15 RCTs 1 Cohort 5 SRs	<ul style="list-style-type: none"> • Neonatal fibroblasts and keratinocytes cultured onto bovine collagen matrix (OrCel®) • Cryopreserved split-thickness skin allograft (TheraSkin®) • Allogeneic fetal fibroblasts on polyglactic matrix (Dermagraft®) • Autologous cultured keratinocytes on hyaluronic acid-derived, perforated lamina (Laserskin®) • Decellularized cadaveric dermis (Graftjacket®) • Bovine collagen and chondroitin-6-sulfate scaffold with silicone covering (Synthetic Integra) 	<ul style="list-style-type: none"> • Ulcer recurrence
Jones (2013) (Good) N = 438	Venous leg ulcers: 5 RCTs	<ul style="list-style-type: none"> • Allogenic bilaminar Composite Cultured Skin (OrCel™) • Cultured epidermal allograft (Autoderm™) • Products derived from live human/animal tissue (Apligraf®, Dermagraft®) 	<ul style="list-style-type: none"> • Complete wound healing • Time to complete healing • Rate of change in ulcer area • Pain • Adverse events
Snyder (2012) (Good) N = 1,829	Diabetic foot ulcers: 12 RCTs Vascular leg ulcers:	<ul style="list-style-type: none"> • Products derived from human donor tissue (Graftjacket®) 	<ul style="list-style-type: none"> • Wound infection • Complete wound healing

Systematic Review (Quality)	Population No. and Type of Included Studies	Skin Substitute Category	Outcomes of Interest
Total N	6 RCTs	<ul style="list-style-type: none"> • Products derived from live human/animal tissue (Apligraf®, Dermagraft®) • Acellular animal derived products (OASIS® Wound Matrix) • Biosynthetic products (Talymed®) 	<ul style="list-style-type: none"> • Time to complete wound healing • Adverse events • Quality of life surrogate outcomes (return to baseline activities of daily living and function, pain reduction)

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

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

EVIDENCE SUMMARY

Snyder [AHRQ] (2012)

The AHRQ systematic review by Snyder, Sullivan and Schoelles (2012) included 18 RCTs (12 on DFUs, 6 on VLU). 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 ≥ 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 TESHG and as the optimal dressing and management of TESHG-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 VLU 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® [Wound Matrix](#)

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® [Wound Matrix](#) 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® [Wound Matrix](#) 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® [Wound Matrix](#)

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® [Wound Matrix](#) for DFUs (n = 26). There were no significant differences reported in time to complete wound closure between the two products (Dermagraft® 40.90 ± 32.32 days vs OASIS® [Wound Matrix](#) 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 2.8cm² in the intervention group and 3.4 cm² in the controls. Other inclusion/exclusion criteria were not described and significance of baseline differences were not reported.~~

~~In this~~ This evidence review identified one small, poor quality, open-label RCT of EpiFix® for DFU (Zelen, et al., 2013)). This study was also highlighted in the second public comment period. This trial randomized 25 patients who had incomplete epithelialization received an additional application with DFUs between 1 cm² and 25 cm² present for at least four weeks 2, 4, 6, 8, and 10. The authors state, “Five to receive EpiFix® or standard care. There were several limitations to this trial including:

- This was a very small, single-center study with 13 patients (45%) healed with one dHAM application, one (9.1%) healed with in the treatment group and 12 patients in the control group.
- There is no description of allocation concealment.
- There were baseline differences in wound size between the two applications, one (9.1%) healed groups (2.6 cm² in the EpiFix® group and 3.4 cm² in the standard care group. There were also differences between the groups with three applications, respect to mean body mass index (30 kg/m² in the EpiFix® group and 35.4 kg/m² in the standard care group. Additionally, baseline information on smoking and glycemic control were not provided.
- Dressing changes for the EpiFix® group were performed by clinicians every two (18%) healed weeks, while the daily dressing changes in the standard care group were performed by patients or their caregivers.
- The outcome assessor was unblinded.
- Conclusions about comparative effectiveness for sustained wound healing beyond six weeks cannot be made because all but two of the 12 patients in the standard care group exited the trial at 6 weeks to pursue other treatments.

A second poor quality RCT (Zelen, et al, 2015) of EpiFix® compared to Apligraf or standard care was identified during the second public comment period. This trial randomized 60 patients with four

applications, and one (9.1%) healed after five applications.” This is an average of 2.3 applications. [DFU to EpiFix[®], Apligraf[®], or standard care.](#) There were several limitations to this trial including:

- [There were baseline differences in the three groups with respect to:](#)
 - [Mean wound size \(2.6 cm² in the Apligraf[®] group, 2.7 cm² in the EpiFix[®] group, 3.3 cm² in the standard care group\)](#)
 - [Mean wound duration \(129 days in the Apligraf[®] group, 109 days in the EpiFix[®] group, 113 days in the standard care group\)](#)
 - [Percentage of patients with HbA1c>9 \(30% in the Apligraf[®] group, 10% in the EpiFix[®] group, 25% in the standard care group\)](#)
- [The primary outcome of complete wound closure at 4 and 6 weeks was assessed by an unblinded primary investigator.](#)
- [There are potential differences in the treatments and follow-up between groups. In the Apligraf[®] and EpiFix[®] groups, the products were applied weekly by study investigators. In the standard care group, daily dressing changes were done by the patients. Debridement was carried out in each group “as necessary.”](#)
- [Conclusions about comparative effectiveness for sustained wound healing beyond six weeks cannot be made because more than half \(11/20\) patients in the standard group exited the trial at 6 weeks.](#)

[Both trials were funded by the maker of EpiFix.](#)

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 cm² were treated with EpiFix[®] and 12 patients with an average wound size of 3.4 cm² were treated with moistened gauze and silver; all patients received compression dressings. At four weeks, [Zelen, et al, 2013 reported](#) complete wound healing ~~was 77%~~ at 6 weeks of 92% in the EpiFix[®] group and 08% in the control ~~standard care~~ group ($p < < 0.0001$). ~~By six weeks, rates of complete healing were 92% and 8%, respectively ($p < 0.0001$).~~ [This is Game and colleagues \(2015\) noted in their review that this represents](#) an unexpectedly low rate of healing in the control group.~~

[Zelen, et al, 2015 reported complete wound healing at 6 weeks of 95% in the EpiFix[®] group compared to 45% in the Apligraf[®] group \(\$p = 0.0006\$ \) and 35% in the standard care group \(\$p = 0.0001\$ \).](#)

Critical Outcome: Quality of Life

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

Important Outcome: Time to Complete Wound Healing

~~No SRs or RCTs~~ [Zelen, et al., 2013](#) reported ~~on the effect of EpiFix® on~~ [mean](#) time to complete [healing of 5 weeks in the control group and 2.5 weeks in the EpiFix® group](#). [No test of statistical significance was reported.](#)

[Zelen, et al, 2015](#) reported [median wound healing-- time of 13 days in the EpiFix® group compared to 49 days in both the Apligraf® and standard care groups \(p<0.0001\).](#)

Important Outcome: Adverse Effects

~~No SRs or RCTs reported on the adverse effects of EpiFix®.~~ [Zelen, et al, 2013](#) reported [four adverse events in the standard care group \(2 cases of cellulitis, one gastrointestinal bleed, and one acute pyelonephritis; there was one case of pneumonia in the EpiFix® group. No test of statistical significance was reported.](#)

[Zelen, et al, 2015](#) reported [five adverse events. There was one cellulitis of the study foot in the EpiFix® group \(of note, this patient was withdrawn from the study\). There was one urinary tract infection and one cellulitis of the non-study foot in the Apligraf® group. There were two cases of cellulitis \(one study foot and one non-study foot\) in the standard care group \(of note, both of these patients remained in the study\). No test of statistical significance was reported.](#)

Omnigraft Integra Dermal Regeneration Template®

[Omnigraft Integra Dermal Regeneration Template® \(IDRT\)](#) is an acellular bilayer matrix that was [approved by the FDA for use in DFU in January 2016. This evidence review identified one RCT of fair quality \(Driver, 2015\). This multicenter trial randomized 307 patients with DFU to standard wound care or IDRT after a 14-day run-in period to exclude wounds that were healing well \(>30% epithelialization\) with standard care. There were several limitations to this RCT including:](#)

- [The treatment and control groups were generally similar at baseline, but the median age of ulcers in the control group was greater \(152 days vs 126 days in the Omnigraft® group\) and there were small differences in the location of wounds between the two groups.](#)
- [While computerized planimetry was used for in assessing the time to complete wound closure, the primary endpoint of complete closure was assessed by an unblinded study investigator during the treatment phase.](#)
- [There was both high overall attrition \(39%\), as well as differential attrition between study groups \(32% dropout in the Omnigraft® group compared to 47% dropout in the control group\).](#)

[The trial was funded by the maker of Omnigraft®.](#)

Critical Outcome: Deep Soft Tissue or Bone Infection

[No SRs or RCTs reported on the effect of IDRT on deep soft tissue or bone infection.](#)

Critical Outcome: Complete Wound Healing

[Driver and colleagues \(2015\) reported greater complete wound healing at 16 weeks in patients treated with IDRT \(51%\) compared with standard care \(32%\) \(p = 0.01\). At final follow-up 12 weeks after the](#)

study period there was no statistically significant difference in wound recurrence between the 2 groups (19% IDRT versus 26% control, p = 0.32).

Critical Outcome: Quality of Life

Driver and colleagues (2015) reported statistically significant differences in SF-36 Physical Functioning score (p = 0.047) and Bodily Pain score (p = 0.033) in favor of IDRT, but the magnitude of the improvements were not reported.

Important Outcome: Time to Complete Wound Healing

Driver and colleagues (2015) reported a statistically significant improvement in time to complete wound healing of 43 days in the IDRT group versus 78 days in the control group (p = 0.001).

Important Outcome: Adverse Effects

Adverse events attributed to the study treatments were similar in both groups (4.5% versus 5.2%).

Grafix®

Grafix® 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~~ fair quality. Patients in this trial had wounds of four to 52 weeks’ duration, and of ~~one~~ 1 cm² to 15 cm² in area. Patients were excluded for A1c ≥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). There were several limitations to this RCT including:

- Insufficient information to determine the appropriateness of the randomization scheme. The use of a central third party in treatment assignment likely satisfies the need for concealment of allocation.
- There are potentially important baseline differences between the two groups, specifically, larger average ulcer size in the standard treatment group (3.93 cm² vs 3.41 cm² in the Grafix® group), and the presence of twice as many dorsal foot ulcers in the Grafix® group (8 vs 4 in the standard care group).
- The trial permitted the use of custom off-loading devices at the discretion of the investigator, raising the possibility that this additional intervention was not equally applied in the treatment and control groups.
- The overall rate of attrition in the trial exceeds 15% with 19 of 97 participants withdrawing prior to study completion. There were more dropouts in the control group (23%) compared with the Grafix® group (16%).
- There is a discrepancy in the reported outcome of complete wound healing which was originally stated as occurring in 31 of 50 patients in the Grafix® group, but in later reporting on wound recurrence after the 12 week treatment phase the authors state that ulcers remained closed in 23 of 28 patients in the Grafix® group.

- [Although the study states that “wound closure was independently confirmed via a central wound core laboratory” the initial determination of the primary outcome \(complete wound closure\) was made by an unblinded site investigator.](#)

[The trial was funded by the maker of Grafix®.](#)

Critical Outcome: Deep Soft Tissue or Bone Infection

No SRs or RCTs reported on the effect of Grafix® on deep soft tissue or bone infection. The RCT by Lavery and colleagues (2014) did report that patients randomized to Grafix® 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® versus standard wound care for DFUs. ~~Patient groups were similar at baseline.~~ Complete wound healing occurred in 62% of patients treated with Grafix® 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® on validated quality of life indicators or surrogate measures.

Important Outcome: Time to Complete Wound Healing

In the ~~poor~~fair quality RCT by Lavery and colleagues (2014), time to complete healing was a secondary outcome. Patients treated with Grafix® 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 Grafix® 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 (3.6cm² in the treatment subjects versus 5.1cm² 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/~~Ultra Tri-Layer~~ 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® [Wound Matrix](#). 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® [Wound Matrix](#) for DFU, the product was re-applied as deemed clinically necessary. One RCT (Niezgodna, 2005) reported an average use of 10 sheets of OASIS [Wound Matrix](#) per patient. A trial of OASIS [Wound Matrix](#) compared to Dermagraft® (Landsman, 2008) reported that up to eight applications of OASIS [Wound Matrix](#) was similarly effective to up to three applications of Dermagraft®. The third trial (Romanelli, 2010) reported an average of 5.2 days between dressing changes for OASIS patients.

Two RCTs reported on OASIS® [Wound Matrix](#) 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® 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® Wound Matrix with Regranex Gel (contains platelet-derived growth factor) and found greater wound closure of plantar ulcers at 12 weeks in the OASIS® group (49% vs 28%, p=0.06).

A ~~second~~ fair quality RCT comparing OASIS® ~~Wound~~[Ultra Tri-Layer](#) Matrix with standard care was identified after the initial search and draft coverage guidance was completed. Cazzell and colleagues (2015) published results of an open-label RCT of 82 patients comparing OASIS® [Ultra Tri-Layer](#) to standard care for treatment of DFU. In the intervention group, OASIS® [Ultra Tri-Layer](#) was applied once each week. Patients in the control group were also seen weekly and the standard care intervention was selected by the investigator (standard care included silver dressing, Hydrogel, wet-to-dry, alginate, Manuka honey, or triple antibiotic dressing). Ulcer measurement was standardized by use of a digital image capture and wound measurement device. At 12 weeks, wound healing was greater in the OASIS® group (54%) compared with the standard care group (32%) (p=0.021). Smith and Nephew funded the study and employs three of the authors. Aside from the conflicts of interest and open-label design, the study otherwise appears to be at low risk of bias. This fair quality RCT demonstrates improved DFU wound healing at 12 weeks for patients treated with OASIS® [Ultra Tri-Layer](#) compared to standard care.

Snyder and colleagues (2012) included three RCTs of patients with VLUs that evaluated the effectiveness of OASIS® 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® 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® Wound Matrix vs Dermagraft®

The AHRQ SR (Snyder, Sullivan and Schoelles, 2012) included one RCT that compared OASIS® Wound Matrix with Dermagraft® for individuals with DFUs ($n = 26$). The study found no significant difference in complete wound closure between the two products (Dermagraft® 84.6% vs OASIS® [Wound Matrix](#) 76.9%, $p = 0.62$).

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of OASIS® [Wound Matrix](#) on validated quality of life indicators. One RCT identified in the AHRQ review reported fewer wound dressings with OASIS® [Wound Matrix](#) (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® 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® 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 ± 41.47 days in the OASIS® arm vs 40.90 ± 32.32 days in the control (not significant). The third RCT reported average time of 67 days with OASIS® [Wound Matrix](#) and 73 days with control ($p = 0.245$). All three RCTs were of fair quality.

One RCT of OASIS® [Wound Matrix](#) 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, Sullivan and Schoelles, 2012).

Important Outcome: Adverse Effects

The AHRQ SR included one RCT that compared OASIS® [Wound Matrix](#) 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® [Wound Matrix](#) 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~~ [A single](#) application was equivalent to control (45%, n = 9 of 20) [for complete wound healing](#). 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. Information about costs for a course of treatment in the GRADE-informed framework and in Appendix E reflects a certain number of applications, based on FDA approval criteria, other payers’ coverage criteria or averages from studies.

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/ authorization
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.

REFERENCES

Evidence Sources

- Felder, J. M., Goyal, S. S., Attinger, C. E. (2012). A systematic review of skin substitutes for foot ulcers. *Plastic and Reconstructive Surgery*, 130(1):145-64. DOI: 10.1097/PRS.0b013e318254b1ea.
- Game, F. L., Apelqvist, J., Attinger, C., Hartemann, A., Hinchliffe, R. J., Londahl, M., ... Jeffcoate, W.J., on behalf of the International Working Group on the Diabetic Foot (IWGDF). (2015). Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: A systematic review. *Diabetes / Metabolism Research and Reviews*, accepted manuscript online. doi: 10.1002/dmrr.2707
- Jones, J. E., Nelson, E. A., & Al-Hity, A. (2013). Skin grafting for venous leg ulcers. *Cochrane Database of Systematic Reviews*, 1. DOI: 10.1002/14651858.CD001737.pub4.
- Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., . . . Nadarajah, J. (2014). The efficacy and safety of Grafix((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J*, 11(5), 554-560. DOI:10.1111/iwj.12329.
- Snyder, D. L., Sullivan, N., & Schoelles, K. M. (2012). *Skin substitutes for treating chronic wounds*. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ). Retrieved from http://www.ahrq.gov/research/findings/ta/skinsubs/HCPRO610_skinsubstfinal.pdf.

Other Citations

- Aetna. (2015). *Wound care*. Hartford, CT: Aetna. Retrieved from http://www.aetna.com/cpb/medical/data/200_299/0244.html.
- Association for the Advancement of Wound Care (AAWC). (2010). Association for the Advancement of Wound Care venous ulcer guideline. Malvern, PA: AAWC. Retrieved from <http://aawconline.org/professional-resources/resources/>.
- The Australian Wound Management Association Inc. and the New Zealand Wound Care Society Inc. (2011). Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers. Retrieved from http://www.awma.com.au/publications/2011_awma_vlug.pdf.
- Braun, L., Kim, P. J., Margolis, D., Peters, E. J. & Lavery, L. A. (2014). What's new in the literature: An update of new research since the original WHS diabetic foot ulcer guidelines in 2006. *Wound Repair and Regeneration*, 22, 594–604. DOI: 10.1111/wrr.12220.
- Cahaba Government Benefit Administrators®, LLC. (2015). Local coverage determination (LCD): Surgery: Bioengineered skin substitutes (BSS) for the treatment of diabetic and venous stasis ulcers of the lower extremities (L34285). Washington, DC: CMS. Retrieved from <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34285&ContrlId=213&ver=12&ContrVer=1&CoverageSelection=Both&ArticleTy>

[pe=All&PolicyType=Final&s=All&Keyword=skin&KeywordLookUp=Title&KeywordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=139&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Keyword=skin&KeywordLookUp=Title&KeywordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&).

- Cazzell, S. M., Lange, D. L., Dickerson, J. E. Jr., Slade, H. B. (2015). The Management of diabetic foot ulcers with porcine small intestine submucosa tri-layer matrix: A randomized controlled trial. *Advances in Wound Care*, 4, 1-8. DOI: 10.1089/wound.2015.0645.
- Centers for Medicare and Medicaid Services. (unknown). National coverage determination (NCD) for porcine skin and gradient pressure dressings (270.5). Washington, DC: CMS. Retrieved from <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=139&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Keyword=skin&KeywordLookUp=Title&KeywordSearchType=And&articleId=52974&ver=3&ContrId=370&ContrVer=1&bc=gAAAABAAAAAAAA%3d%3d&>.
- Centers for Medicare and Medicaid Services. (2015). October 2015 ASC HCPCS codes and payment rates. Washington, DC: CMS. Retrieved from <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/Downloads/2015-October-ASC-Addenda.zip>.
- Cigna. (2015). *Cigna medical coverage policy: tissue-engineered skin substitutes*. Bloomfield, CT: Cigna. Retrieved from https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0068_coveragepositioncriteria_woundhealing.pdf.
- First Coast Service Options, Inc. (2015). Local coverage determination (LCD): Application of skin substitute grafts for treatment of DFU and VLU of lower extremities (L36377). Washington, DC: CMS. Retrieved from <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36377&ContrId=368&ver=2&ContrVer=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Keyword=skin&KeywordLookUp=Title&KeywordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&>.
- Institute for Clinical Systems Improvement (ICSI). (2012). Pressure ulcer prevention and treatment protocol: Health care protocol. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI). Retrieved from https://www.icsi.org/_asset/6t7kxy/PressureUlcer.pdf.
- Margolis, D. J., Malay, D. S., Hoffstad, O. J., Leonard, C. E., MaCurdy, T., Nava, K. L., ... Siegel, K. L. (2011). *Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008: Data Points #2*. Rockville (MD): Agency for Healthcare Research and Quality. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK65149/>.
- National Institute for Health and Clinical Excellence (NICE). (2011). Diabetic foot problems: prevention and management. London: NICE. Retrieved from <http://www.nice.org.uk/guidance/ng19/resources/diabetic-foot-problems-prevention-and-management-1837279828933>.
- Novitas Solutions, Inc. (2015). Local coverage determination (LCD): Application of bioengineered skin substitutes to lower extremity chronic non-healing wounds (L35041). Washington, DC: CMS. Retrieved from <https://www.cms.gov/medicare-coverage-database/details/lcd->

[details.aspx?LCDId=35041&ContrId=314&ver=22&ContrVer=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Keyword=skin&KeywordLookUp=Title&KeywordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&](https://pubmed.ncbi.nlm.nih.gov/22741465/)

O'Meara, S., Al-Kurdi, D., & Ovington, L. G. (2008). Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database of Systematic Reviews*, Issue 1. DOI: 10.1002/14651858.CD003557.pub2

Oregon Heart Disease and Stroke and Diabetes Prevention Programs. (2013). *Heart disease, stroke and diabetes in Oregon: 2013*. Portland, OR: Oregon Health Authority, Public Health Division. Retrieved September 9, 2015 from https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Documents/OHA8582_AllVolumes.pdf.

Park-Lee, E., & Caffrey, C. (2009). *Pressure ulcers among nursing home residents: United States, 2004*. Atlanta, GA: National Center for Health Statistics. Retrieved September 29, 2015 from <http://www.cdc.gov/nchs/data/databriefs/db14.htm>.

Registered Nurses' Association of Ontario (RNAO). (2013). Assessment and management of foot ulcers for people with diabetes. Toronto (ON): Registered Nurses' Association of Ontario (RNAO). Retrieved from [http://rnao.ca/sites/rnao-ca/files/Assessment and Management of Foot Ulcers for People with Diabetes Second Edition1.pdf](http://rnao.ca/sites/rnao-ca/files/Assessment_and_Management_of_Foot_Ulcers_for_People_with_Diabetes_Second_Edition1.pdf).

Scottish Intercollegiate Guidelines Network (SIGN). (2010). Management of chronic venous leg ulcers. Edinburgh: SIGN. Retrieved from <http://www.sign.ac.uk/guidelines/fulltext/120/index.html>.

Smith & Nephew, Inc. (2015). OASIS® Wound Matrix: Frequently asked questions. Retrieved from <http://www.oasiswoundmatrix.com/faq>

Washington State Healthcare Authority. (2015). Physician-related services/health care professional services provider guide. Olympia, WA: Washington State Healthcare Authority. Retrieved from http://www.hca.wa.gov/medicaid/billing/Documents/guides/physician-related_services_mpg.pdf.

Wisconsin Physicians Service Insurance Corporation (2015). Local coverage determination (LCD): Application of bioengineered skin substitutes (L34593). Washington, DC: CMS. Retrieved from <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34593&ContrId=143&ver=11&ContrVer=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&Keyword=skin&KeywordLookUp=Title&KeywordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&>.

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

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

APPENDIX A. GRADE INFORMED FRAMEWORK – ELEMENT

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.

DESCRIPTIONS

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/outcome²

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.

² 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.

APPENDIX B. GRADE EVIDENCE PROFILE³

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	
Deep Soft Tissue or Bone Infection								
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 ●○○○
Complete Wound Healing								
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 ●○○○
Quality of Life								
<i>No evidence identified</i>								

³ 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	
Time to Complete Wound Healing								
VLUs	1	RCT	Low	Unknown	Direct	Precise	<i>None</i>	Low confidence in estimate of effect ●●○○
Nonhealing foot ulcers – undefined	1	RCT	High	Unknown	Indirect	Precise	<i>None</i>	Very low confidence in estimate of effect ●○○○
Adverse Effects								
DFUs	1	RCT	Low	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect ●○○○
VLUs	1	RCT	Low	Unknown	Direct	Unknown	<i>None</i>	Very low confidence in estimate of effect ●○○○

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

Derma graft®

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

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

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

Omnigraft Integra Dermal Regeneration Template®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<u>Deep Soft Tissue or Bone Infection</u>								
<i>No evidence identified</i>								
<u>Complete Wound Healing</u>								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
<u>Quality of Life</u>								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
<u>Time to Complete Wound Healing</u>								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
<u>Adverse Effects</u>								
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	
Deep Soft Tissue or Bone Infection								
DFUs	1	RCT	Moderate High	Unknown	Direct	Precise	“Wound-related infection” not defined	Very low confidence in estimate of effect ●○○○
Complete Wound Healing								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
Quality of Life								
<i>No evidence identified</i>								
Time to Complete Wound Healing								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
Adverse Effects								
DFU	1	RCT	HighModerate	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)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
<i>No evidence identified</i>								
Complete Wound Healing								
DFUs	2	RCT	Moderate to high	Consistent	Unknown	Precise	None	Very low confidence in estimate of effect ●○○○
Quality of Life								
<i>No evidence identified</i>								
Time to Complete Wound Healing								
DFUs	2	RCTs	Moderate to high	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○
Adverse Effects								
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/Ultra Trilayer Matrix

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
<i>No evidence identified</i>								
Complete Wound Healing								
DFUs	1 2	RCT	Moderate Low to moderate	Unknown Consistent	Direct	Imp precise	None	Very low Low confidence in estimate of effect 
VLUs	3	RCT	Low to moderate	Unknown Consistent	Direct	Imp precise	Effectiveness varied based on type of usual care	Very low Low confidence in estimate of effect 
Quality of Life								
<i>No evidence identified</i>								
Time to Complete Wound Healing								
DFUs	2	RCT	Low to moderate	Consistent	Direct	Precise	None	Low confidence in estimate of effect 
VLUs	3 1	RCTs	Low to moderate	Unknown	Direct	Imprecise	Effectiveness varied based on type of usual care None	Very low confidence in estimate of effect 
Adverse Effects								

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
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

Talymed®

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

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

OASIS® Wound Matrix versus Dermagraft®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
<i>No evidence identified</i>								
Complete Wound Healing								
DFUs	1	RCT	Moderate	Unknown	Indirect	Unknown	None	Very low confidence in estimate of effect ●○○○
Quality of Life								
<i>No evidence identified</i>								
Time to Complete Wound Healing								
<i>No evidence identified</i>								
Adverse Effects								
<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 included 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
ICD-10 Diagnosis Codes	
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
CPT Codes	
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
HCPCS Level II Codes	
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 matrix
Q4104	Integra BMWD
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	Oasis 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	NuSheild 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
O (Medical and surgical)	H (skin and breast) J (subcutaneous tissue and fascia) R (mouth and throat)	R (replacement) U (supplement) W (revision)	All (0-X) except: Q finger nail R toe nail S hair	O (open) 3 (percutaneous)	J (synthetic substitute) K (nonautologous tissue substitute)	Z (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.

APPENDIX E: FREQUENCY OF APPLICATION AND COST OF SKIN SUBSTITUTES

Product	Proposed maximum covered applications	Rationale	Medicare cost information per application (National Average Fee For Service, October, 2015*)
Apligraf®	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: \$771 HOPD: \$1,495 Phys. Off = \$1,518
Derma-graft®	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: \$771 HOPD: \$1,495 Phys. Off = \$1,409
EpiFix®	5	One study limited to 5 applications. Cigna limits to 4 applications in 12 weeks. Two Medicare LCD limits to 5 applications.	ASC: \$771 HOPD: \$1,495 Phys. Office: \$535
Grafix®	12	Weekly applications up to 84 days in the one study	ASC: \$771 HOPD: \$1,495 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®	ASC: \$236 HOPD: \$518

		Wound Matrix to 3 sheets of Dermagraft. One Medicare LCD limits to 12 weeks of therapy.	Phys. Office: \$262
Talymed®	10	Study used applications every 1-3 weeks over 20 weeks. Found fewer applications ineffective.	ASC: \$771 HOPD: \$1,495 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: \$771 HOPD: \$1,495 Phys. Office: \$612

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 cm². 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.

Cost information in this applications table did not affect the coverage guidance recommendations. Costs represent a single application; the appropriate number of applications for a patient may differ by product.

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

Table of Contents

Commenters.....	1
Public Comments	1
References Provided by Commenters	17

Commenters

Identification	Stakeholder
A	Integra [Submitted February 1, 2016]
B	Lacey Loveland, DPM [Submitted March 23, 2016]
C	Lisa Nakadate, Executive Director, Oregon Podiatric Medical Association [Submitted March 24, 2016]
D	Chris Seufferling, DPM [Submitted March 26, 2016]
E	Smith & Nephew [Submitted March 31, 2016]
F	John T. Callahan, D.P.M., F.A.C.F.A.S., Santiam Foot Clinic, PC [Submitted April 1, 2016]
G	Alliqua Biomedical [Submitted April 3, 2016]
H	Osiris Therapeutics [Submitted April 3, 2016]

Public Comments

ID/#	Comment	Disposition
A1	<p>Integra LifeSciences requests that Skin Substitutes for Chronic Skin Ulcers be revised to include coverage of IDRT and Omnigraft™ for the treatment of diabetic foot ulcers. Specific coverage language could be taken from the indications for use tab within the attached payer packet.</p> <p>IDRT is an advanced, acellular, bilayer matrix specifically engineered for dermal regeneration. On the market since 1996, it is the only FDA-approved product indicated</p>	<p><i>Thank you for your comments and for your submission of the FOUNDER study which was published after the initial search. This was added to the evidence section. See new GRADE-informed framework.</i></p> <p><i>For EbGS discussion.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>for the treatment of third degree burns and the reconstruction of scar contracture with a dermal regeneration claim.</p> <p>On January 7, 2016, FDA added an additional indication for use via PMA Supplement to IDRT based on the clinical results of a large multi-center, randomized, controlled clinical trial (the Foot Ulcer New Dermal Replacement Study (FOUNDER) Study). This study evaluated the safety and efficacy of IDRT for the treatment of non-healing chronic diabetic foot ulcers.</p> <p>The FOUNDER study is unmatched in the wound care area in terms of the strength of its study design, and the study results are both direct and conclusive. Key aspects of the FOUNDER study’s design include the following:</p> <ul style="list-style-type: none"> • <i>Large, Multi-Center RCT.</i> The FOUNDER study, published in the <i>Wound Healing and Tissue Regeneration</i> Journal, which served as the clinical basis for FDA approval, is the largest multi-center, randomized controlled clinical trial of its kind designed to evaluate the safety and effectiveness of a cellular and/or tissue-based product for the treatment of diabetic foot ulcers. It included 32 sites from across the United States, and it involved 307 subjects with Type II diabetes and at least one diabetic foot ulcer. • <i>14-Day Run-In Period.</i> In contrast to some previous trials of diabetic foot ulcer treatments that had no run-in period or a run-in period of 7 days, eligible patients were first required to complete a 14-day run-in period during which time they were treated with the standard of care regimen. This ensured that the study evaluated the most difficult to heal diabetic foot ulcers. • <i>Computerized Planimetry.</i> Third party computerized planimetry was used as an independent assessment method to confirm wound closure and wound size. • <i>Generalizability.</i> Despite strict inclusion and exclusion criteria, any bias against generalizability was minimized by enrolling and randomizing subjects from 32 academic and private practice sites across the US to ensure that study 	

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>participants represent patients with chronic diabetic foot ulcers from a heterogeneous population. Further, a full range of age groups were represented in the study, including the Medicare-age population (e.g., 31 of 153 patients in the control group were age 65 or older [20.3%], and 20 of the 154 patients in the treatment arm [18.2%] were age 65 or older).</p> <p>Key outcomes of the FOUNDER study include the following:</p> <ul style="list-style-type: none"> • <i>Higher Relative Wound Closure.</i> Diabetic foot ulcers treated with IDRT/Omnigraft™ achieved a 125% relative improvement in closure compared to standard of care at 12 weeks • <i>Faster Time to Healing.</i> Patients treated with IDRT/Omnigraft™ healed 5 weeks faster than patients in the control group who received standard of care. • <i>Rapid Wound Closure Rate.</i> Patients who received IDRT/Omnigraft™ experienced a 50% faster wound size reduction compared to the control group. • <i>Single Application.</i> Of the wounds that healed, 96% of those treated with IDRT, Omnigraft™ healed with three or less applications with 72% healing in one application. In contrast, studies of cell-based products and minimally processed human tissue allografts required an average of 4-6 applications. • <i>Improved Quality of Life.</i> Patients treated with IDRT/Omnigraft™ experienced a significant improvement in Physical Functioning and a decrease in Bodily Pain over standard of care (as defined by SF-36). <p>We hope that you find these materials sufficient to act favorably on our request to add IDRT and Omnigraft™ as covered for the treatment of diabetic foot ulcers in Skin Substitutes for Chronic Skin Ulcers.</p>	
B1	<p>I am a board certified podiatrist practicing in Eugene, Oregon. I have used many skin substitutes on the market over the past years and also do wound care studies for the FDA as an investigator for the Center for Clinical Research based in San Francisco,</p>	<p><i>Thank you for your comments and for providing your clinical experience and the perspective on the greater ease of use for Epifix in clinical practice. Cost differences depend heavily on</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>California. By far the most utilized skin substitute in my office is Epifix, for both financial and medical reasons.</p> <p>Epifix is approved by Medicare, and comes in multiple sizes, so there is no waste compared to apligraf and other amniotic products. This is an important factor in financial based decision making, and I feel that it is an economically sound modality to utilize in all stalled wounds. In fact, the use of skin substitutes ultimately saves money by healing this at risk patient population sooner, which eliminates the cost of continued wound care modalities, infections, debridements and amputations. There is an actual financial cost as well as a human cost in the form of continued disability due to chronic open wounds.</p> <p>I feel that Medicare exemplifies the very most basic standard of care that should be available to all patients. It is my sincere hope that your program follows Medicare’s example and allows me to use this limb saving modality on all my patients.</p> <p>Epifix is by far the most easy to use and in my opinion, effective, skin substitute on the market. The shelf life of the product is five years, and it does not require refrigeration or other special storage circumstances. There is sound research supporting its efficacy in a variety of wounds, and I have attached references demonstrating this.</p> <p>Please feel free to contact me at any time if you have any questions or need additional information. Thanking you in advance for considering this important limb saving product for my patients who do not have it currently available to them.</p>	<p><i>wound characteristics and plan contracting, so EbGS’s coverage recommendations include all products with adequate evidence of effectiveness for each type of wounds, acknowledging that each plan will develop its own purchasing strategies. We did not identify any direct evidence from economic analyses to suggest that the use of skin substitutes is cost-saving.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
C1	<p>I am writing on behalf of the Oregon Podiatric Medical Association (OPMA) regarding the draft guidance for skin substitutes for chronic skin ulcers. Although OPMA does not advocate one skin substitute product over another, we do believe skin substitutes, in general, play a critical role in healing chronic wounds. Therefore, OPMA recommends HERC exercise caution before labeling a product as "not recommended."</p>	<p><i>Some products examined in this coverage guidance are recommended for coverage based on comparative evidence showing their effectiveness for given indications. The subcommittee's recommendations not to cover products with insufficient evidence of effectiveness could change as additional evidence becomes available. The subcommittee does not find a rationale for covering products not shown to be effective when there are effective alternatives.</i></p>
D1	<p>I would ask to please reconsider Epifix as Recommended. I have had excellent results in outpatient setting. I can obtain evidence data for you if necessary.</p> <p>[Submitted bibliography, including articles by Zelen and colleagues (2015), Serena and colleagues (2014), and Zelen and colleagues (2013), among others.]</p>	<p><i>Thank you for your comments. The commenter submitted two randomized controlled studies that would have met screening inclusion criteria had they been indexed in Medline at the time of the initial search (Zelen, et al., 2015; Serena, et al., 2014). A third randomized controlled study was included in the original evidence review (Zelen, et al., 2013). The potential concerns regarding the validity of each of these trials are discussed below. The remaining trials submitted (Zelen, 2013; Sheikh, 2013) are non-comparative trials and would not meet inclusion criteria. The final submitted document reviews various local coverage determinations (LCDs) as well as an explanation of the process by which Medicare contractors reach such decisions; relevant LCDs had already been noted and discussed in the original draft coverage guidance.</i></p> <p><i>Concerns regarding Zelen, et al., 2015:</i></p> <ul style="list-style-type: none"> • <i>There were baseline differences in the three groups with respect to:</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<ul style="list-style-type: none"> ○ Mean wound size (2.6 cm² in the Apligraf group, 2.7 cm² in the EpiFix group, 3.3 cm² in the standard care group) ○ Mean wound duration (129 days in the Apligraf group, 109 days in the EpiFix group, 113 days in the standard care group) ○ Percentage of patients with HbA1c>9 (30% in the Apligraf group, 10% in the EpiFix group, 25% in the standard care group) <ul style="list-style-type: none"> ● The primary outcome of complete wound closure at 4 and 6 weeks was assessed by an unblinded primary investigator. ● There are potential differences in the treatments and follow-up between groups. In the Apligraf and EpiFix groups, the products were applied weekly by study investigators. In the standard care group, daily dressing changes were done by the patients. Debridement was carried out in each group “as necessary.” ● Conclusions about comparative effectiveness for sustained wound healing beyond six weeks cannot be made because more than half (11/20) patients in the standard group exited the trial at 6 weeks. <p>Concerns regarding Serena, et al., 2014:</p> <ul style="list-style-type: none"> ● The primary limitation of this study is its use of a surrogate measure (proportion of wounds achieving

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<p>40% reduction in size at 4 weeks) as the primary outcome. The trial does not report on complete wound healing, or any of the other critical or important outcomes pre-specified by HERC.</p> <ul style="list-style-type: none"> • Additional concerns are the use of an unblinded study investigator as the outcomes assessor and the absence of information on salient baseline characteristics including smoking and diabetes. <p>Zelen, et al., 2013 was included in the original evidence review. Concerns regarding this trial include:</p> <ul style="list-style-type: none"> • This is a very small, single-center study with 13 patients in the treatment group and 12 patients in the control group. • There is no description of allocation concealment. • There were baseline differences in wound size between the two groups (2.6 cm² in the EpiFix group and 3.4 cm² in the standard care group. There were also differences between the groups with respect to mean body mass index (30 kg/m² in the EpiFix group and 35.4 kg/m² in the standard care group. Additionally, baseline information on smoking and glycemic control were not provided. • Dressing changes for the EpiFix group were performed by clinicians every two weeks, while the daily dressing changes in the standard care group were performed by patients or their caregivers. • The outcome assessor was unblinded.

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<ul style="list-style-type: none"> <i>Conclusions about comparative effectiveness for sustained wound healing beyond six weeks cannot be made because all but two of the 12 patients in the standard care group exited the trial at 6 weeks to pursue other treatments.</i> <p><i>Overall, these studies are at moderate to high risk of bias.</i></p>
E1	<p>In the latest draft guidance, the Commission recommends (with a weak recommendation) coverage of OASIS Wound Matrix for venous leg ulcers (“VLU”) and diabetic foot ulcers (“DFU”). We appreciate the Commission’s thoughtful review of the clinical evidence and comments from stakeholders to date. We support the recent changes in the draft coverage guidance, recommending for coverage of OASIS not only for VLU but also DFU, and we thank the Commission for its position.</p> <p>OASIS comprises OASIS® Wound Matrix and OASIS® Ultra Tri-Layer Matrix.</p> <p>Under the draft guidance, the Commission recommends coverage specifically for OASIS Wound Matrix for VLU and DFU. The OASIS product is currently sold as OASIS Wound Matrix (single layer) and OASIS Ultra Tri-layer Matrix (three layer) with OASIS Burn Matrix no longer commercially available. From a regulatory perspective, OASIS is a single product. Both OASIS Wound Matrix and OASIS Ultra Tri-Layer Matrix fall under the same 510(k), varying only in thickness (single (0.1 mm) versus tri-layer (0.3 mm)). OASIS Wound Matrix and OASIS Ultra Tri-Layer Matrix are both available in different size sheets allowing physicians to select the specific form most appropriate for their patients’ needs.</p> <p>The Commission has approved OASIS Wound Matrix for coverage based on the current clinical evidence. In our prior comment letter, we presented clinical evidence from multiple studies including a 2015 randomized controlled trial. We were pleased that as</p>	<p><i>Thank you for your comments providing clarification regarding the range of available OASIS products. Both OASIS Wound Matrix and OASIS Ultra Tri-layer Matrix have been studied for DFU in RCTs. The included RCTs for VLU used OASIS Wound Matrix. We have revised our recommendations to recommend OASIS Wound Matrix and OASIS Ultra Tri-layer Matrix for DFUs and OASIS Wound Matrix for VLUs. We also deleted Q4103 as you requested.</i></p> <p><i>For EbGS discussion</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>the Commission reviewed this evidence and other clinical evidence, the Commission decided to expand its coverage of OASIS Wound Matrix to include DFU. We would like to draw your attention to the fact that the 2015 randomized controlled trial evidence that we provided used the <u>OASIS Ultra Trilayer Matrix</u> versus standard care. In this trial, the results of which were published in 2015 in <i>Advances in Wound Care</i> 82 qualified patients were randomly assigned to 12 weeks’ treatment with OASIS or standard care. The trial found that a greater proportion of the DFUs were closed by the end of the treatment period (week 12) for the OASIS group than for the standard care group (54% vs. 32%; p = 0.021). More ulcers were closed at each weekly study visit in the OASIS group than the standard care group beginning at week 3 (first visit showing ulcers closed). The overall treatment effect on proportion of ulcers closed over the 12 weeks and the interaction of treatment by week were found to be statistically significant in favor of the OASIS group. This study supports the effectiveness of the 3-layer product (Ultra Tri-layer) consistent with the evidence supporting single layer (Wound Matrix) product.</p> <p>Given that OASIS Wound Matrix and OASIS Ultra Tri-Layer Matrix represent different thicknesses of the same product, we request that the Commission recommend coverage for both, identified by HCPCS codes Q4102 and Q4124 respectively. In addition, we suggest that the Commission delete reference to OASIS Burn Matrix, identified by HCPCS Q4103, as it is no longer commercially available.</p>	

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition								
F1	I write this letter in support of Oregon Health Plans, DMAP, ATRIO, etc. covering and approving the use of EPIFIX on ulcers. I have used this product over the past year and have saved many feet and toes from amputation, months of antibiotic use for the patient, hospitalizations etc. When insurances have chosen not to cover EPIFIX for some of my patients, the patient has endured months to almost years of debridements, hospitalizations, months of antibiotics and amputation of forefoot, foot or toe. I hope that you see the benefit to approving this product and appreciate your time in hearing from providers to have a better understanding of this product.	<i>Thank you for your comments and for providing your clinical experience. However, no randomized controlled trials of EpiFix have demonstrated reductions in amputations or need for hospitalization. Alternative products are recommended for coverage for both indications.</i>								
G1	Alliqua BioMedical respectfully requests Biovance be included in this coverage guidance for Skin Substitutes For Chronic Skin Ulcers as we believe the evidence demonstrates net health outcome benefits compared to standard of care (SOC).	<i>Thank you for your comments.</i>								
G2	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Populations</th> <th style="width: 25%;">Interventions</th> <th style="width: 25%;">Outcomes</th> <th style="width: 25%;">References</th> </tr> </thead> <tbody> <tr> <td>Diabetic Foot Ulcers</td> <td>During 12 week trial each patient received up to 3 applications</td> <td>14 diabetic foot ulcer patients with 9 (55%) subjects showing complete wound closure within the 12 weeks of the study period.</td> <td>Publication: Letendre, S., et al., Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. Adv Skin Wound Care, 2009. 22(4): p. 161-6.</td> </tr> </tbody> </table>	Populations	Interventions	Outcomes	References	Diabetic Foot Ulcers	During 12 week trial each patient received up to 3 applications	14 diabetic foot ulcer patients with 9 (55%) subjects showing complete wound closure within the 12 weeks of the study period.	Publication: Letendre, S., et al., Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. Adv Skin Wound Care, 2009. 22(4): p. 161-6.	<i>None of the submitted references meet inclusion criteria. Letendre, et al., 2009 is a non-comparative case series of 14 patients.</i>
Populations	Interventions	Outcomes	References							
Diabetic Foot Ulcers	During 12 week trial each patient received up to 3 applications	14 diabetic foot ulcer patients with 9 (55%) subjects showing complete wound closure within the 12 weeks of the study period.	Publication: Letendre, S., et al., Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. Adv Skin Wound Care, 2009. 22(4): p. 161-6.							
G3	<table border="1" style="width: 100%; border-collapse: collapse;"> <tbody> <tr> <td style="width: 25%;">Venous Leg Ulcers</td> <td style="width: 25%;">Biovance placed initially and then at physician discretion (average 2.4 applications)</td> <td style="width: 25%;">Ulcers of venous stasis etiology comprised the largest subset within the chronic wound group with 85 wounds in 78 intent-to-treat (ITT) subjects. This</td> <td style="width: 25%;">“Key Factors Influencing Outcomes of Dehydrated, Decellularized Human</td> </tr> </tbody> </table>	Venous Leg Ulcers	Biovance placed initially and then at physician discretion (average 2.4 applications)	Ulcers of venous stasis etiology comprised the largest subset within the chronic wound group with 85 wounds in 78 intent-to-treat (ITT) subjects. This	“Key Factors Influencing Outcomes of Dehydrated, Decellularized Human	<i>None of the submitted references meet inclusion criteria.</i>				
Venous Leg Ulcers	Biovance placed initially and then at physician discretion (average 2.4 applications)	Ulcers of venous stasis etiology comprised the largest subset within the chronic wound group with 85 wounds in 78 intent-to-treat (ITT) subjects. This	“Key Factors Influencing Outcomes of Dehydrated, Decellularized Human							

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment				Disposition
			<p>analysis demonstrated clinical benefits in a real world, heterogeneous venous stasis ulcer population showing:</p> <ul style="list-style-type: none"> • 53% of the subjects in the Good Wound Care (GWC) Group completely closed in an average observation period of about 6 weeks. The impact of good wound care, as defined in this study, resulted in a 26% increase in the incidence of closure for the GWC Group, compared to the ITT population. • At an average of 8 weeks, the GWC Group’s venous stasis ulcers reduced in size by nearly 68%. • None of the venous stasis ulcers in the GWC Group that completely closed had reported infection prior to or during treatment while about one-third of those that did not close reported at least one episode of clinically suspected wound infection. 	<p>Amniotic Membrane Allograft (DDHAM) Treated Venous Ulcers in a Real World Experience Study,” presented at Fall SAWC 2015, Las Vegas, NV.</p>	
G4	Chronic Wounds (venous leg ulcers, diabetic foot ulcers)	Bioavance placed initially and then at physician discretion	The wound closure rate for Bioavance® is notable given the eight-week observation time point, when many	Smiell JM, Treadwell T, Hahn HD, Hermans MH.	<i>Smiell, et al., 2015 is a non-comparative study in which “any subject with a chronic wound who, in the investigator’s opinion, would benefit from treatment with DDHAM” was enrolled in a registry to track treatment outcomes .Thus, this is essentially a</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>(Average application 2.3)</p> <p>chronic wound studies evaluate closure rate at 12 and/or 20 week endpoints; and the broad inclusion criteria for the patient and wound population. The typical wound size in the Use Registry Study was also almost double the size of the Margolis article (1.6 cm² vs. 3.1cm² in the Use Registry Study).</p> <p><u>Failure of prior therapies</u> Thirty-two subjects with a variety of chronic ulcer types (venous, n = 14 [13 wounds]; diabetic foot, n = 10; pressure, n = 1; arterial [ischemic], n = 7 [4 wounds]) had failed previous courses of therapy with 1 or more advanced biologic therapies (ie, Apligraf, Organogenesis, Canton, MA; Dermagraft, Organogenesis, Canton, MA; Oasis, Smith and Nephew, Hull, UK; or Regranex, Smith and Nephew, Hull, UK). After a course of therapy that included the DDHAM allograft, nearly half (48.4%) of these ulcers closed despite previous</p>	<p>Real World Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. Wounds. 2015;27(6):158-169.</p> <p><i>non-consecutive case series and does not meet inclusion criteria.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>biologic therapy failures. Those that did not close during a mean observation time of 10.3 weeks reduced in size from baseline by 50% (Table 8).</p>	
G5	<p>Improvements over currently available treatments include (1) a more rapid resolution of chronic non-healing wounds, as measured by time to closure and wound area reduction; (2) ability to treat a patient population unresponsive to currently available treatments; (3) reduced rate of device-related complications; and (4) decreased rate of subsequent therapeutic interventions.</p> <p>A prospective, multi-center registry was conducted, inclusive of all patients with any type of partial or full-thickness wound that would benefit from having a human amniotic membrane allograft as part of good wound care treatment (the “Use Registry Study”). The only requirement was that wounds were free of infection. The broad inclusion criteria resulted in a number of patients that were otherwise likely to be excluded from an RCT, either due to co-morbidities, age, wound size, or another factor</p> <p>A total of 19 sites across the U.S. enrolled 230 patients with a total of 246 wounds. Ultimately, the “intent to treat” (ITT) group (defined as any individual that was observed for greater than 3 days and had a documented wound start measurement and end measurement) consisted of 59 acute (traumatic and burn wounds) and 155 chronic wound patients (including diabetic, venous, arterial, pressure, and collagen vascular disease ulcers). The Good Wound Care (GWC) Group represents a large subset of the IIT population. Good wound care was described as compliance with the use of off-loading (DFU) or compression dressings/wraps (venous ulcers), maintenance of applied allograft, and without the concomitant use of enzymatic debriders.</p> <p>In the Use Registry Study, the chronic wound population demonstrated a closure rate of 50% at approximately 8 weeks. In contrast, Mostow demonstrated that 34% (20/58) of</p>	<p><i>As noted above there is no direct comparative evidence from randomized controlled trials demonstrating the effectiveness of Biovance.</i></p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>the control (standard care) arm in a venous leg ulcer study closed at 12 weeks with compression dressings and debridement as a SOC, and in the Apligraf® pivotal venous ulcer study, the control arm (n=100) achieved an incidence of complete closure in approximately 24% of the ulcers at 12 weeks.</p> <p>The wound closure rate for Biovance® is notable given the eight-week observation time point, when many chronic wound studies evaluate closure rate at 12 and/or 20 week endpoints; and the broad inclusion criteria for the patient and wound population. The typical wound size in the Use Registry Study was also almost double the size of the Margolis article (1.6 cm² vs. 3.1cm² in the Use Registry Study). This improvement in wound closure rates was most likely related to the use of Biovance® in combination with the SOC. The registry provides a persuasive demonstration of effectiveness for Biovance® in a broad “real world” population of all wound types. In addition, there were no serious or unexpected adverse effects related to the use of Biovance® reported and subject and investigator opinions were generally positive.</p>	
G6	<p>Citations to suggested commercial and Medicare coverage and guidance materials:</p> <ul style="list-style-type: none"> • Blue Cross Blue Shield Association - February 2016 Evidence Review – Bio-Engineered Skin and Soft Tissue Substitutes (submitted with this document) • Medicare Administrative Contractors References Attached- <ul style="list-style-type: none"> ○ Novitas Local Coverage Determination (LCD) - Application of Bioengineered Skin Substitutes to Lower Extremity Chronic Non-Healing Wounds (L35041) ○ First Coast LCD Application of Skin Substitute Grafts for Treatment of DFU and VLU of Lower Extremities (L36377) ○ WPS LCD (Retired 03/01/2016) - Application of Bioengineered Skin Substitutes (L34593) ○ Palmetto Future (effective date 05 17 2016) LCD – Application of Skin Substitutes (L36466) 	<p><i>The BCBS review bases their conclusion on the Smiell, et al., 2015 trial which does not meet criteria for inclusion in the HERC review.</i></p> <p><i>Thank you for submission of various coverage policies. We would note that coverage of Biovance is variable and that many insurers regard the product as investigational or experimental.</i></p>
H1	Osiris Therapeutics kindly requests a reconsideration review for the recommended	<i>Thank you for your comments and for providing clarification on</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>coverage of Grafix® in this indication based on the following clarifications:</p> <ul style="list-style-type: none"> • Explanation of the biological characteristics of placental membranes, important and favorable properties for wound closure • Additional details of a randomized controlled trial (RCT) comparing Grafix to standard of care for the treatment of chronic diabetic foot ulcers, reported by Lavery et al in 2014. <ul style="list-style-type: none"> ○ Detailed description of subject characteristics ○ Clarification of study results ○ Randomization methodology ○ Maintaining the blind ○ Clarification of adverse event relationships to study product ○ Characteristics of the study support the fact that this is a high-quality RCT ○ Review and assessment of Lavery et al by the National Institute for Health and Care Excellence (NICE) in the UK <p>In view of the independent evidence assessments indicating that the Lavery study is high quality and the meta-analysis indicating a larger strength of effect than other studies on advanced dermal substitutes, Osiris therapeutics requests that you reconsider your decision based on the enclosed information, and cover Grafix at Oregon Medicaid.</p>	<p><i>several aspects of the Lavery, et al., 2014 study. However, several concerns about the internal validity of the Lavery study persist:</i></p> <ul style="list-style-type: none"> • <i>There is still insufficient information to determine the appropriateness of the randomization scheme. The use of a central third party in treatment assignment likely satisfies the need for concealment of allocation.</i> • <i>There are potentially important baseline differences between the two groups, specifically, larger average ulcer size in the standard treatment group (3.93 cm² vs 3.41 cm² in the Grafix group), and the presence of twice as many dorsal foot ulcers in the Grafix group (8 vs 4 in the standard care group).</i> • <i>The trial permitted the use of custom off-loading devices at the discretion of the investigator raising the possibility that this additional treatment was not equally applied in the treatment and control groups.</i> • <i>The overall rate of attrition in the trial exceeds 15% with 19 of 97 participants withdrawing prior to study completion. There were more dropouts in the control group (23%) compared with the Grafix group (16%).</i> • <i>There is a discrepancy in the reported outcome of complete wound healing which was originally stated as occurring in 31 of 50 patients in the Grafix group, but in later reporting on wound recurrence after the 12 week treatment phase the authors state that ulcers remained closed in 23 of 28 patients in the Grafix</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
		<p>group.</p> <ul style="list-style-type: none"> • Reporting the odds ratio for complete healing overstates the relative benefits of the treatment; it would be more appropriate to report a risk ratio (which in this case would be 2.91, 95% CI 1.61 to 5.26, as reported in the NICE appendix I submitted by the commenter). • Although the study states that “wound closure was independently confirmed via a central wound core laboratory” the initial determination of the primary outcome (complete wound closure) was made by an unblinded site investigator. <p>Thus, the Lavery study is at least at moderate risk of bias.</p> <p>We find the assessment of High GRADE quality in the NICE appendix to be perplexing in light of the potential risk of bias in this single trial. Furthermore, the final NICE recommendations for diabetic foot ulcers state that skin substitutes be considered an adjunct to standard care but do not recommend specific products.</p> <p>The Reguski, et al., 2013 study (a retrospective non-consecutive case series) and the studies by Duan-Arnold, et al., 2015 (all in vitro studies of the biologic properties of human amniotic membrane) do not meet inclusion criteria.</p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

References Provided by Commenters

ID/#	References
A1	Driver, V. R., Lavery, L. A., Reyzelman, A. M., Dutra, T. G., Dove, C. R., Kotsis, S. V., ... Chung, K. C. (2015). A clinical trial of Integra Template for diabetic foot ulcer treatment. <i>Wound Repair Regen</i> , 23(6), 891-900. DOI: 10.1111/wrr.12357.
D1	Zelen, C. M., Gould, L., Serena, T. E., Carter, M. J., Keller, J., & Li, W. W. (2015). A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. <i>Int Wound J</i> , 12(6), 724-732. DOI: 10.1111/iwj.12395.
D1	Serena, T. E., Carter, M. J., Le, L. T., Sabo, M. J., & DiMarco, D. T. (2014). A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. <i>Wound Repair Regen</i> , 22(6), 688-693. DOI: 10.1111/wrr.12227.
D1	Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. <i>Int Wound J</i> , 10(5), 502-507. DOI: 10.1111/iwj.12097.
G2	Letendre, S., LaPorta, G., O'Donnell, E., Dempsey, J., & Leonard, K. (2009). Pilot trial of Biovance collagen-based wound covering for diabetic ulcers. <i>Adv Skin Wound Care</i> , 22(4), 161-166. DOI: 10.1097/01.asw.0000305463.32800.32.
G3	Hahn, H. D., & Smiell, J. M. (2015). Key factors influencing outcomes of dehydrated, decellularized human amniotic membrane allograft (DDHAM) treated venous ulcers in a real world experience study. Presented at Symposium on Advanced Wound Care Fall meeting. Retrieved from http://alliqua.com/biovance-venous-ulcers-poster/
G4	Smiell, J. M., Treadwell, T., Hahn, H. D., & Hermans, M. H. (2015). Real-world experience with a decellularized dehydrated human amniotic membrane allograft. <i>Wounds</i> , 27(6), 158-169. Retrieved from http://www.woundsresearch.com/article/real-world-experience-decellularized-dehydrated-human-amniotic-membrane-allograft
H1	Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., ... Nadarajah, J. (2014). The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: Results of a multi-centre, controlled, randomised, blinded, clinical trial. <i>Int Wound J</i> , 11(5), 554-560. DOI: 10.1111/iwj.12329.
H1	Duan-Arnold, Y., Uveges, T. E., Gyurdieva, A., Johnson, A., & Danilkovitch, A. (2015). Angiogenic potential of cryopreserved amniotic membrane is enhanced through retention of all tissue components in their native state. <i>Adv Wound Care (New Rochelle)</i> , 4(9), 513-522. DOI: 10.1089/wound.2015.0638.
H1	Duan-Arnold, Y., Gyurdieva, A., Johnson, A., Jacobstein, D. A., & Danilkovitch, A. (2015). Soluble factors released by endogenous viable cells enhance the antioxidant and chemoattractive activities of cryopreserved amniotic membrane. <i>Advances in Wound Care</i> , 4(6), 329–338. DOI: 10.1089/wound.2015.0637

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

Table of Contents

Commenters.....	1
Public Comments	2
References Provided by Commenters	8

Commenters

Identification	Stakeholder
A	Soluble Systems <i>[Submitted December 7, 2015]</i>
B	Smith & Nephew Advance Wound Management <i>[Submitted December 15, 2015]</i>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

Public Comments

ID/#	Comment	Disposition
A1	<p>“We would like to request that Oregon Medicaid reconsider the current non-coverage recommendation of Theraskin based on the following conclusions obtained from previously submitted clinical data. Upon review of the included references, Theraskin is as effective and at least equivalent to products currently recommended for coverage by Oregon Medicaid (Apligraf and Dermagraft).”</p>	<p>Thank you for your comment. We will address each of these studies individually below.</p>
A2	<p>“The 2011 Landman’s study concluded that Theraskin healed (closed) 60% of previously non-progressing diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) at 12 weeks and 74% at 20 weeks.”</p>	<p>Because this is a non-comparative retrospective case series, it does not meet individual inclusion criteria for the evidence review.</p>
A3	<p>“DiDomenico’s 2011 study concluded that TheraSkin had a greater rate of wound healing than Apligraf, both at 12 weeks (66.7% vs. 41.3%) and 20 weeks (66.7% vs. 47.1%).”</p>	<p>This study is included in the systematic review by Snyder, Sullivan, & Schoelles (2014), and has thus already been included in the evidence review for the draft coverage guidance. DiDomenico and colleagues did not report a test of statistical significance of the difference observed in the trial; the authors of the AHRQ report found that the difference was not statistically significant (p=0.21).</p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
A4	<p>“Sanders 2014 clinical study showed wounds treated with TheraSkin are <u>twice</u> as likely to close by week 12, with half the number of grafts, versus wounds treated with Dermagraft.”</p>	<p>This manuscript is not indexed in Medline and therefore was not included in the evidence review. Furthermore, this small (n=23) RCT is of poor quality because of uncertainty about allocation concealment; baseline differences in study population (particularly with respect to number of diabetes medications, peripheral arterial disease, tobacco use and wound duration before treatment); differences in the number of office visits in each treatment group and use of offloading techniques; and inadequate blinding of participants, personnel, and outcomes assessors. Additionally, two authors are paid consultants of Soluble Systems and the research was funded by Soluble Systems.</p>
A5	<p>“Snyder, Sullivan and Schoelles 2012 (AHRQ Review included on page 26 of Oregon’s Draft Policy) evaluated the effectiveness of Apligraf and TheraSkin for DFUs with average wound sizes. The study also concluded that there were no significant differences reported in complete wound closure between the two products Apligraf 41% vs. Theraskin 67%, p=0.21.”</p>	<p>The AHRQ systematic review concluded that there is insufficient evidence to draw conclusions about the comparative effectiveness of Theraskin and Apligraf. The single trial that informed this comparison (DiDomenico, 2011) was a small (n=28) and imprecise trial deemed to be at moderate risk of bias by the authors of the AHRQ review.</p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
A6	<p>“We respectfully recommend Oregon Medicaid to take into consideration that Theraskin is broadly and long accepted by the medical community and insurance carriers as medically and reasonably necessary therapy for the treatment of a broad range of chronic wound indications.</p> <ul style="list-style-type: none"> ○ All A/B <u>Medicare Administrative Contractors (MACs)</u> across the U.S., including Oregon, cover Theraskin. ○ 41 <u>Medicaid</u> plans throughout the country, including many states surrounding Oregon, also provide Theraskin coverage. ○ Many large <u>Private Health Plans</u> cover Theraskin including Regence, Kaiser, Cigna, Blue Cross Independence, HCSC (BCBS IL/NM/OK/TX), Amerihealth, BCBS Highmark, United Health Care, Tricare, UPMC Health Plan, etc.” 	<p>Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that Theraskin is commonly, but not uniformly, covered.</p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
A7	<p>“Oregon Medicaid proposes a recommendation of non-coverage for Theraskin due to ‘product cost being moderate compared to alternative treatment options.’</p> <p>Listed within the Oregon Medicaid draft policy under ‘Frequency of application and cost of skin substitute’ Apligraf and Dermagraft product costs were based upon clinical studies while Theraskin’s product cost was based upon Medicare LCD limits. Thus, causing Theraskin associated cost-savings to appear modest when compared to alternative treatments.</p> <p>We respectfully recommend that Oregon Medicaid reevaluate Theraskin’s product cost in a similar manner as Apligraf and Dermagraft or adults <u>all</u> product cost using Medicare’s’ LCFD maximum limits.”</p>	<p>The right-hand column of the frequency of application document presented to EbGS was based on the maximum number of applications from the study, while lower limits were used for other products. The rationale column does note that most patients in the study only required a single application.</p> <p>At its November 3, 2015 meeting, the subcommittee recognized that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level. Therefore we have removed a specific number of applications for each product from the right column of the applications table and added information on application frequency used in the studies for those products recommended for coverage.</p> <p>However, the subcommittee still finds insufficient evidence of effectiveness to recommend this product for coverage.</p>
B1	<p>“In the draft guidance, the Commission recommends (with a weak recommendation) coverage of OASIS Wound Matrix for venous leg ulcers (‘VLU’). We support the recommendation for coverage of OASIS for VLU, and we thank the Commission for its position.”</p>	<p>Thank you for your comment.</p>
B2	<p>“By contrast, the Commission recommends against coverage of OASIS Wound Matrix for the treatment of diabetic foot ulcers (‘DFU’) concluding that there is ‘inadequate evidence of benefit, other alternatives available, and its costliness.’ We respectfully disagree with this recommendation for the reasons summarized below.</p>	<p>The study by Cazzell and colleagues was not indexed in Medline at the time of the search; it has subsequently been indexed. The previous RCTs of Oasis for DFU were included in the AHRQ review. Landsman, et al (2008) found no statistically significant difference between OASIS and Dermagraft for DFU wound healing at 12 weeks. Niezgoda, et al (2005) compared OASIS to Regranex Gel and found a</p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>There is new evidence, published after the 2012 Agency for Healthcare Research & Quality ('AHRQ') systematic review from supporting the use of OASIS in the treatment of diabetic foot ulcers. This evidence was not considered by the Commission.</p> <p>The findings from a prospective, randomized controlled trial of OASIS Ultra Trilayer Matrix versus standard care were published in 2015 in <i>Advances in Wound Care</i>. In this 16 week trial, 82 qualified patients were randomly assigned to 12 weeks' treatment with OASIS or standard care. The trial demonstrated that a greater proportion of the DFUs were closed by the end of the treatment period (week 12) for the OASIS group than for the standard care group (54% vs. 32%; $p = 0.021$). More ulcers were closed at each weekly study visit in the OASIS group than the standard care group beginning at week 3 (first visit showing ulcers closed). The overall treatment effect on proportion of ulcers closed over the 12 weeks and the interaction of treatment by week were found to be statistically significant ($p = 0.047$) in favor of the OASIS group.</p> <p>In the draft coverage guidance, the Commission defined five outcomes considered in its evaluation:</p> <ul style="list-style-type: none"> ▪ Critical Outcomes <ul style="list-style-type: none"> – Deep soft tissue or bone infection – Complete wound healing ▪ Important Outcomes <ul style="list-style-type: none"> – Quality of life – Time to complete wound healing – Adverse effects <p>The randomized, controlled study above included three of these outcomes and supports the use of OASIS compared to the standard care with statistically significant results.”</p>	<p>difference in healing at 12 weeks that approached statistical significance (49% vs 28% respectively, $p=0.06$).</p> <p>Cazzell is an open-label RCT of 82 patients comparing OASIS to standard care for treatment of DFU. In the intervention group, OASIS was applied once each week. Patients in the control group were also seen weekly and the standard care intervention was selected by the investigator (standard care included sliver dressing, Hydrogel, wet-to-dry, alginate, Manuka honey, or triple antibiotic dressing). Ulcer measurement was standardized by use of a digital image capture and wound measurement device. At 12 weeks, wound healing was greater in the OASIS group (54%) compared with the standard care group (32%) ($p=0.021$). Smith and Nephew funded the study and employs three of the authors. Aside from the conflicts of interest and inadequate blinding, the study otherwise appears to be at low risk of bias. This fair quality RCT demonstrates improved DFU wound healing at 12 weeks for patients treated with OASIS compared to standard care.</p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
B3	<p>“OASIS has the same level of general acceptance by the medical community as Apligraf.</p> <p>While not a consideration for coverage, the Commission does review the policy landscape and payer coverage policies. Under Medicare, with respect to local coverage determinations, the policy must be based on published authoritative evidence derived from definitive RCTs or other definitive studies, and general acceptance by the medical community (standard of practice), as supported by sound medical evidence. Use of OASIS in the treatment of DFU is well established in the payer community:</p> <ul style="list-style-type: none"> ▪ All of the MACs cover OASIS for VLU and DFU ▪ OASIS has positive coverage based on medical necessity from 760 private payers” 	<p>Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that OASIS is commonly, but not uniformly, covered.</p>
B4	<p>“OASIS is the least costly product per application compared with Apligraf and Dermagraft.</p> <p>The Commission’s recommendation against coverage for OASIS for DFUs is based, in part, on the Commission’s conclusion that the product is costly. In fact, as is shown below, OASIS has a lower cost per application compared with Apligraf and Dermagraft—two other products recommended for coverage for diabetic foot ulcers.” <i>See chart in submitted comments.</i></p>	<p>OASIS does have a lower unit cost than Apligraf and Dermagraft. However, as noted in the cost comparison chart, studies which showed effectiveness of OASIS used 8 to 10 applications of this product per patient versus smaller quantities used in the studies showing effectiveness for Dermagraft and Apligraf.</p> <p>The subcommittee does recognize that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level.</p>
B5	<p>“The Commission stated in the draft guidance that OASIS ‘is not recommended for coverage for diabetic foot ulcers based on inadequate evidence of benefit, other alternatives available, and its costliness.’ We believe that this new evidence, together with the position taken by private and public payers as well as the relative low cost of OASIS compared to Apligraf and Dermagraft, support coverage for OASIS for the treatment of diabetic foot ulcers.”</p>	<p>Thank you for your comment.</p>

HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

References Provided by Commenters

ID/#	References
A2	Landsman A. S., Cook J., Cook E., Landsman A. R., Garrett P., Yoon J., Kirkwood A., Desman E. (2011). A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin®) on the treatment of diabetic foot ulcers and venous leg ulcers. <i>Foot Ankle Spec.</i> 4(1):29-41. DOI: 0.1177/1938640010387417.
A3	DiDomenico, L., Landsman, A. R., Emch, K. J., Landsman, A. (2011). A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. <i>Wounds</i> , 23(7):184-9.
A4	Sanders, L., Landsman, A. S., Landsman, A., Keller, N., Cook, J., Cook, E., Hopson, M. (2014). A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. <i>Ostomy Wound Manage</i> , 60(9):26-38
B2	Cazzell, S. M., Lange, D. L., Dickerson, J. E. Jr., Slade, H. B. (2015). The Management of diabetic foot ulcers with porcine small intestine submucosa tri-layer matrix: A randomized controlled trial. <i>Adv Wound Care</i> , 4:1-8. DOI: 10.1089/wound.2015.0645.

Section 3.0
CG - Tobacco Cessation
During Pregnancy

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE AND MULTISECTOR INTERVENTION REPORT: TOBACCO CESSATION DURING PREGNANCY

For EbGS Meeting materials 6/2/2016

HERC Coverage Guidance

For women who use tobacco during pregnancy, the following interventions to aid in [smokingtobacco](#) cessation are recommended for coverage:

- Behavioral interventions (*strong recommendation*)
- Financial incentives (contingent) (*weak recommendation*)
- Prenatal ultrasound with high feedback around smoking impacts on the fetus (*weak recommendation*)

The following interventions are not recommended for coverage:

- Electronic nicotine delivery systems (*weakstrong recommendation*)
- Counseling-based interventions to reduce secondhand smoke exposure (*weak recommendation*)
- Partner support for smoking cessation (*weak recommendation*)

No recommendation is being made regarding the coverage of pharmacotherapy:

Federal law requires coverage of tobacco cessation services, including FDA-approved pharmacotherapy to be covered by some plans (including Medicaid). Even so, based on the evidence, the Commission cannot make a coverage recommendation in favor of pharmacotherapy for smoking cessation for pregnant women.

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description*.

Multisector Interventions

To reduce the use of tobacco during pregnancy and improve associated outcomes, the evidence supports the following interventions:

- Financial incentives (contingent most effective)
- Smoke-free legislation
- Tobacco excise taxes

No or insufficient evidence is available for:

- Internet or text messaging based interventions
- Mass media campaigns specific to pregnant women

RATIONALE FOR ~~GUIDANCE~~-DEVELOPMENT OF COVERAGE GUIDANCES AND MULTISECTOR INTERVENTION REPORTS

~~The~~ Coverage guidances and multisector intervention reports are developed to inform coverage recommendations and strategies for public and private health plans in Oregon as they seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of the Affordable Care Act and health system transformation, reaching these goals requires a focus on population-based health interventions from a variety of sectors as well as individually-focused clinical care.

HERC selects topics for ~~guideline development or technology assessment~~ its reports to guide public and private payers 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~~ implementation or practice
- 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.~~

Our reports are based on a review of the relevant research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be cost-effective ways to prevent, treat or manage disease at a population level. For some conditions, the HERC has reviewed evidence and identified effective interventions, but has not made recommendations, as many of these policies are implemented in settings beyond traditional healthcare delivery systems.

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.

Coverage question: Should pharmacotherapy or electronic nicotine delivery systems be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
Pregnancy complications (Critical outcome)	<p>Miscarriage and spontaneous abortion: 7/923 (0.7%) in NRT groups vs. 4/859 (0.4%) in control groups RR 1.47 (95% CI 0.45 to 4.77) ●●●○ (Moderate certainty of equivalence confidence, based on 4 RCTs, N=1782)</p> <p>Preterm birth (<37 weeks) 101/1053 (9.5%) in NRT groups vs. 104/995 (10.4%) in control groups RR 0.87 (95% CI 0.67 to 1.14) ●●●● (High certainty of equivalence) ●●●○ (Moderate confidence, based on 6 RCTs, N=2048)</p>	<p>The costs of medications for smoking cessation are moderate, but there are no projected savings given the lack of proven effectiveness and lack of impact on health outcomes.</p>	<p>Pregnancy can be a motivating time for many women who wish to quit using cigarettes. However, they pregnant women may be concerned about the use of medications which have not been proven safe, or effective during pregnancy. There is likely significant</p>	<p>The only pharmacotherapies for which studies were found were nicotine replacement therapies. Bupropion is considered relatively low risk in pregnancy (pregnancy class B), varenicline has some potential level of risk and it is</p>

Coverage question: Should pharmacotherapy or electronic nicotine delivery systems be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
Low birth weight (Critical outcome)	<p><2500 grams: 107/1043 (1.0%) in NRT groups 112/994 (1.1%) in control groups RR 0.74 (95% CI 0.41 to 1.34) ●●●● (High certainty of equivalence) ●●●○ (Moderate confidence, based on 6 RCTs, N=2037)</p>		variability in women's interest in using medications to assist smoking cessation.	unclear if risk outweighs benefit (pregnancy class C), and nicotine and nortriptyline have evidence of risk (pregnancy class D).
Perinatal/infant death (Critical outcome)	<p>Stillbirth: 14/920 (1.5%) in NRT groups vs. 10/857 (1.1%) in control groups RR 1.24 (95% CI 0.54 to 2.84) ●●●○ (Moderate certainty of equivalence) confidence, based on 4 RCTs, N=1777</p> <p>Neonatal death: 4/898 (0.4%) in NRT groups vs. 5/848 (0.5%) in control groups RR 0.66 (95% CI 0.17 to 2.62) ●●●○ (Moderate certainty of equivalence) confidence, based on 4 RCTs, N=1746</p>			
Tobacco abstinence during pregnancy (Important outcome)	<p>All trials: 143/1133 (12.6%) in NRT groups vs. 91/1066 (8.5%) in control groups ARD 4.1% (95% CI 0.25% to 8%) NNT=25 (95% CI 400 to 12.5) (RR 1.41, 95% CI 1.03 to 1.93)</p>			

Coverage question: Should pharmacotherapy or electronic nicotine delivery systems be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
	<p>●●●● (High certainty that NRT is better than no treatment or placebo confidence, based on 8 RCTs, N=2199)</p> <p>Placebo controlled trials: 118/965 (12.2%) in NRT groups vs. 90/961 (9.3%) in control groups (RR 1.28, 95% CI 0.99 to 1.66)</p> <p>●●●● (High certainty that NRT is equivalent to or better than placebo) ●●●○ (Moderate confidence, based on 5 RCTs, N=1926)</p>			
Tobacco abstinence after pregnancy (Important outcome)	<p>At 3 to 6 months post-partum: 61/346 (17.6%) in the NRT groups vs. 40/279 (14.3%) in the control groups RR 1.22 (95% CI 0.84 to 1.77)</p> <p>●●●● (High certainty of equivalence) ●●●○ (Moderate confidence, based on 3 RCTs, N=625)</p>			
<p>Balance of benefits and harms: There was no definite evidence of benefit from NRT in the highest quality trials, but also no evidence that NRT was harmful. Looking at all randomized trials of NRT (including those without a placebo control arm), there appears to be a benefit of NRT for tobacco abstinence during pregnancy. Inadequate evidence is available to address the relative benefits and harms of other types of pharmacotherapy, or electronic cigarettes.</p>				
<p>Rationale: Pharmacotherapy with NRT appears to be ineffective at reducing maternal and fetal harms. Nicotine replacement therapy may improve tobacco abstinence during pregnancy, however, this does not appear to translate to improved health outcomes. In comparison, with behavioral interventions, there is an improvement in abstinence and an improvement in preterm birth and low birth weight. Given a lack of proven benefit, an effective alternative (behavioral counseling), a possibility of harm, associated costs, and mixed values and preferences, a recommendation against coverage would be considered. Federal law requires some payers (including Medicaid) to cover pharmacotherapy for pregnant women who smoke tobacco.</p>				

Coverage question: Should pharmacotherapy or electronic nicotine delivery systems be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
There are no studies on electronic nicotine delivery systems in pregnant women. Given the lack of proven benefit, unknown harms, and costs, they are recommended for noncoverage.				
Recommendation: No recommendation about pharmacotherapy given federal law requiring coverage . Electronic nicotine delivery systems are not recommended for coverage (<i>strong recommendation</i>).				

Note: GRADE framework elements are described in Appendix A. A GRADE Evidence Profile is provided in Appendix B.

Coverage question: Should behavioral interventions be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
Pregnancy complications (Critical outcome)	Preterm birth (<37 weeks) 251/3992 (6.3%) in intervention groups vs. 307/3860 (7.9%) in control groups ARD 1.6% (95% CI 0.3% to 2.4%) NNT=62 (95% CI 333 to 42) RR 0.82 (95% CI 0.70 to 0.96) ●●●○ (Moderate <i>certainty that behavioral interventions are better than usual care</i> confidence, based on 14 RCTs and cluster-randomized trials, N=7852)	The cost for behavioral interventions is likely moderate. The benefits of decreased low birth weight and preterm labor could result in substantially lower costs.	Many women who are motivated to quit smoking during pregnancy would likely be interested in behavioral interventions to quit smoking. There may be some groups of women or some particular types of behavioral interventions that drive women to	Behavioral interventions can encompass a wide range of types and intensity of interventions. The 5As approach is widely endorsed.
Low birth weight (Critical outcome)	<2500 grams: 304/4298 (7.1%) in intervention groups vs. 381/4264 (8.9%) in control groups ARD 1.8% (95% CI 0.5% to 2.6%)			

Coverage question: Should behavioral interventions be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
	<p>NNT=55 (95% CI 200 to 38) RR 0.82 (95% CI 0.71 to 0.94) ●●●○ (Moderate <i>certainty that behavioral interventions are better than usual care</i>confidence, based on 14 RCTs and cluster-randomized trials, N=8562)</p>		smoke more, and these should be better understood.	
Perinatal/infant death <i>(Critical outcome)</i>	<p>Stillbirth: 38/2676 (1.4%) in intervention groups vs. 31/2738 (1.1%) in control groups RR 1.22 (95% CI 0.76 to 1.95) ●●○○ (Low <i>certainty of equivalence</i>confidence, based on 7 RCTs and cluster-randomized trials, N=5414)</p> <p>Neonatal death: 8/1014 (0.8%) in intervention groups vs. 4/1081 (0.4%) in control groups RR 2.06 (95% CI 0.61 to 6.92) ●●○○ (Low <i>certainty of equivalence</i>)confidence, based on 4 RCTs and cluster-randomized trials, N=2095)</p>			
Tobacco abstinence during pregnancy <i>(Important outcome)</i>	<p>All trials: 743/5896 (12.6%)1691/11111 (15.2%) in intervention groups vs. 546/6083 (8.9%)1213/10837 (11.2%) in control groups ARD 4% (95% CI 3% to 7.2%)</p>			

Coverage question: Should behavioral interventions be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
	<p>NNT=25 (95% CI 33 to 14) RR 1.44⁴⁵ (95% CI 1.19²⁷ to 1.75⁶⁴) ●●●○ (Moderate <i>certainty that behavioral interventions are better than usual care</i>confidence, based on 70 RCTs and cluster-randomized trials, N=21,948)</p> <p>TrialsCounseling trials with biochemical validation: 453/4478 (10.1%) in intervention groups vs. 402/4772 (8.4%) in control groups ARD 1.7% (95% CI 0.15% to 4.2%) NNT=59 (95% CI 667 to 23) RR 1.25 (95% CI 1.03 to 1.50) ●●●○ (Moderate <i>certainty that behavioral interventions are better than usual care</i>confidence, based on 18 RCTs and cluster-randomized trials, N=9250)</p>			
Tobacco abstinence after pregnancy (Important outcome)	<p>At 12 to 17 months post-partum: 56/298 (18.8%) in the intervention groups vs. 12/133 (9.0%) in the control groups ARD 9.8% (95% CI 2% to 27%) NNT=10 (95% CI 50 to 4) RR 2.2 (95% CI 1.23 to 3.96) ●●●○ (Moderate <i>certainty that behavioral interventions are better than usual care</i>confidence, based on 2 RCTs and cluster-randomized trials, N=431)</p>			

Coverage question: Should behavioral interventions be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ <i>Confidence in Estimate</i>	Resource allocation	Values and Preferences	Other considerations
	<p>At >18 months post-partum: 21/466 (4.5%) in the intervention groups vs. 17/468 (3.6%) in the control groups RR 1.25 (95% CI 0.57 to 2.73) ●●●○ (Moderate <i>certainty</i> of <i>equivalence</i>) <u>confidence, based on 2 RCTs, N=934</u>)</p>			
<p>Balance of benefits and harms: Evidence demonstrates that behavioral interventions are effective for reducing preterm labor and low birth weight and also in improving tobacco cessation during, and for a short time after, pregnancy. There was no definite evidence of harms related to behavioral interventions reported in the trials, though a possible paradoxical effect of increased smoking resulting from resistance to anti-smoking messages was observed in 4 trials.</p>				
<p>Rationale: There is moderate <i>certainty</i> <u>confidence</u> that behavioral interventions increase tobacco abstinence during pregnancy and up to 17 months postpartum. The benefit does not persist beyond 18 months. Behavioral interventions are effective at reducing the incidence of low birth weight and preterm birth. A potential harm is a paradoxical increase in smoking that occurred in four of the seventy studies, but otherwise the intervention carries little risk. The strength of the recommendation is based on evidence demonstrating the significant impact on morbidity, few harms, moderate cost, and some pregnant women who would have a strong interest in the intervention.</p>				
<p>Recommendation: Behavioral interventions are recommended for coverage (<i>strong recommendation</i>).</p>				

Coverage question: Should ultrasound with high feedback be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ <i>Confidence in Estimate</i>	Resource allocation	Values and Preferences	Other considerations
<p>Pregnancy complications (Critical outcome)</p>	No data	This would involve an increase in reimbursement for	Many women would want to have additional detailed	

Coverage question: Should ultrasound with high feedback be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
Low birth weight (Critical outcome)	No data	additional physician counseling during a prenatal ultrasound and would likely have minimal to modest costs associated with it.	information provided by physicians at the time of an ultrasound, however, the clinical significance of variable findings may be difficult to interpret. However, if specific harms to their fetus about the impact of tobacco were shown to the pregnant woman it is possible this could create psychological distress.	
Perinatal/infant death (Critical outcome)	No data			
Tobacco abstinence during pregnancy (Important outcome)	Absolute rate (of cessation): 28.4% in ultrasound with high feedback group vs. 8.1% in controls group ARD 20.3% (95% CI 2% to 55%) NNT=5 (95% CI 50 to 2) RR 2.93 (95% CI 1.25 to 6.86) ●●○○ (Low certainty that ultrasound with high feedback is better than low or no feedback) ●●○○ (Low confidence, based on 1 RCT, N=129)			
Tobacco abstinence after pregnancy (Important outcome)	No data			
<p>Balance of benefits and harms: The evidence suggests there is a benefit to high feedback ultrasound for tobacco abstinence during pregnancy, but other pregnancy related outcomes have not been studied. The potential harms of this intervention are not well established by this single trial, but since the ultrasound is being performed regardless of the level of feedback, any harms would have to be attributable to the enhanced feedback itself.</p>				

Coverage question: Should ultrasound with high feedback be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ <i>Confidence in Estimate</i>	Resource allocation	Values and Preferences	Other considerations
<p>Rationale: There is no evidence available on any of the critical outcomes and on only one of the important outcomes. While the increase in absolute rate of cessation was noteworthy (and higher than any other intervention), it is a single, small RCT with a moderate risk of bias and there is low certainty of the benefit. Additionally, this study was published in 1982 and apparently has not been replicated (or published) which may undermine our confidence in these findings. However, the cost of this may be quite modest. A recommendation for coverage is made at this time; it is a weak recommendation because there is potential for this to change, particularly if additional studies confirm the large increase in tobacco abstinence and if associated health benefits or if harms to the mother were demonstrated.</p>				
<p>Recommendation: Ultrasound with high feedback is recommended for coverage (<i>weak recommendation</i>).</p>				

DRAFT

Coverage question: Should financial incentives be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
Pregnancy complications <i>(Critical outcome)</i>	No data	<p>There is a direct, somewhat predictable financial expenditure for the financial incentives. The amounts of incentives used in studies were modest in nature. Performing a contingent model of incentives would lower the overall costs based on individual efficacy (a woman would stop receiving incentives if the intervention failed).</p>	<p>Financial incentives may be quite appealing to many women. One could argue that incentivizing those in poverty raises some ethical concerns, but the clear potential benefit to the woman and the fetus of smoking cessation, with a lack of harm, mitigates those concerns.</p>	
Low birth weight <i>(Critical outcome)</i>	No data			
Perinatal/infant death <i>(Critical outcome)</i>	No data			
Tobacco abstinence during pregnancy <i>(Important outcome)</i>	<p>180/675 (26.6%) in the incentive groups vs. 56/622 (9.0%) in the control groups</p> <p>ARD 17.6%, NNT=6</p> <p>OR 3.79 (95% CI 2.74 to 5.25)</p> <p>●●●○ (Moderate <i>certainty that financial incentives are better than usual care</i> confidence, based on 8 RCTs, N=1297)</p>			
Tobacco abstinence after pregnancy <i>(Important outcome)</i>	<p>Absolute rate (at 10-24 weeks post-partum): 15.4% in the incentive groups vs. 4.8% in the control groups</p> <p>ARD 10.6%, NNT=9</p> <p>OR 3.60 (95% CI 2.39 to 5.43)</p> <p>●●●○ (Moderate <i>certainty that financial incentives are better than usual care</i> confidence, based on 8 RCTs, N=1295)</p>			

Coverage question: Should financial incentives be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
<p>Balance of benefits and harms: The evidence demonstrates that financial incentives are effective for tobacco abstinence during pregnancy and postpartum, but other pregnancy related outcomes have not been studied. The potential harms of financial incentives have not been well described, but there is the possibility that participants could 'game' the system to earn unmerited financial rewards.</p>				
<p>Rationale: Moderate certainty The evidence supports financial incentives to improveing tobacco abstinence during and after pregnancy. The costs of this are relatively modest, and many women would be interested in participating in this model if motivated to quit for additional financial gain. Contingent financial incentives appear to be the most effective. Therefore, this is recommended for coverage. It is a weak recommendation because of the lack of evidence on critical outcomes.</p>				
<p>Recommendation: Financial incentives (especially those contingent on demonstrated tobacco abstinence) are recommended for coverage (<i>weak recommendation</i>).</p> <p><i>As financial incentives are provided in clinical settings, but not typically billed as clinical services, this recommendation is listed both in the Coverage Guidance box and in the multisector recommendations box.</i></p>				

DRAFT

Coverage question: Should partner support be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
Pregnancy complications <i>(Critical outcome)</i>	No data	Cost would likely be incremental above the cost of behavioral interventions provided to the pregnant woman.	Most patients interested in tobacco cessation would likely desire support from their partners. Partner participation would be variable.	
Low birth weight <i>(Critical outcome)</i>	No data			
Perinatal/infant death <i>(Critical outcome)</i>	No data			
Tobacco abstinence during pregnancy <i>(Important outcome)</i>	Three of four studies found equivalence in maternal smoking cessation. The fourth study found increased quit attempts and smoking cessation, but only at 1 week follow-up. ●●○○ (Low <u>certainty confidence, based on a mix of equivalence experimental and observational evidence</u>)			
Tobacco abstinence after pregnancy <i>(Important outcome)</i>	No data			
Balance of benefits and harms: <u>The information from the available studies is insufficient to weigh benefits and harms.</u>				
Rationale: Due to the very limited evidence base and insufficient and mixed evidence of benefit, partner support is not recommended for coverage. The recommendation is weak because more evidence could change the conclusion.				
Recommendation: Partner support for smoking cessation is not recommended for coverage (<i>weak recommendation</i>)				

Coverage question: Should clinical interventions to reduce secondhand smoke exposure be recommended for coverage for tobacco cessation in pregnancy?				
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation	Values and Preferences	Other considerations
Pregnancy complications (Critical outcome)	Preterm birth: OR 1.24 (95% CI 0.70 to 2.10) ●○○○ (Very low <i>certainty of equivalence confidence, based on 1 RCT, N=1,025</i>)	Cost would likely be incremental on top of behavioral counseling or regular clinical visits provided to the tobacco user.	Most patients interested in tobacco cessation would likely desire reduced exposure to secondhand smoke. Preferences of nearby smokers would be highly variable.	These studies looked at self-report of exposure to second hand smoke.
Low birth weight (Critical outcome)	OR 1.31 (95% CI 0.77 to 2.24) ●○○○ (Very low <i>certainty of equivalence confidence, based on 1 RCT, N=1,025</i>)			
Perinatal/infant death (Critical outcome)	No data			
Tobacco abstinence during pregnancy (Important outcome)	No data			
Tobacco abstinence after pregnancy (Important outcome)	No data			
Balance of benefits and harms: Interventions to reduce secondhand smoke appear to be effective for reducing self-reported secondhand smoke exposure, but do not reduce preterm births or low birthweight. There is insufficient information on the harms of interventions to reduce secondhand smoke exposure.				
Rationale: Clinical interventions to reduce secondhand smoke exposure have very limited quality evidence showing inconclusive results. Therefore, these interventions are not recommended for coverage. The recommendation is weak because additional research may show a benefit.				
Recommendation: Counseling-based interventions to reduce secondhand smoke exposure are not recommended for coverage (<i>weak recommendation</i>)				

EVIDENCE TABLES FOR MULTISECTOR INTERVENTIONS

Intervention: Smoke-free legislation				
Setting/sector: Local, state and federal governments				
Outcomes	Estimate of Population Health Effect	Resource Impact	Public Values and Preferences	Other considerations
Pregnancy Complications <i>(Critical outcome)</i>	Smoke-free legislation is associated with an approximately 10% risk reduction for preterm birth (95% CI -18.80 to -2.00) Evidence type: Systematic review of interrupted time series	Limited direct public resource impact to implement legislation; legislation would likely reduce tobacco-related health care and disability-related costs but reduce state tobacco tax revenue due to reduced tobacco use.	Oregon has an existing smoke-free workplace law, including bars and restaurants. Smoke-free legislation has often faced opposition from those with a financial interest in tobacco sales.	
Low birth weight <i>(Critical Outcome)</i>	Smoke-free legislation is associated with a -1.70% risk reduction of low birth rate, but the result is not statistically significant (95% CI -5.10 to 1.60) Evidence type: Systematic review of interrupted time series			

Intervention: Tobacco excise taxes				
Setting/sector: Local, state and federal governments				
Outcomes	Estimate of Population Health Effect	Resource Impact	Public Values and Preferences	Other considerations
Pregnancy Outcomes <i>(Critical outcome)</i> Preterm birth	Each \$1 increase in tobacco taxes is associated with small reduction (0.07% to 0.08%) in the rate of preterm births Evidence type: Quasi-experimental analysis of US natality files	Increases to tobacco taxes generate revenues to the jurisdiction imposing them and reduce health care costs because of reduced tobacco consumption. Oftentimes, tobacco tax revenue is used to help fund addiction and other health services. Tobacco taxes would reduce tobacco-related healthcare costs to the extent they reduce tobacco use.	Tobacco taxes are common in the United States at the state level, though increases in tobacco taxes face opposition from businesses that generate revenue from tobacco sales. Nonsmokers are generally more in favor of tobacco control policies than smokers. Some argue that tobacco taxes are regressive because low-income and less well-educated populations have higher rates of smoking. Counter arguments are that low-income populations show greater decreases in tobacco use after tax increases, and new tobacco tax revenues can be used to fund tobacco control programs and other health and social services.	
Low birth weight <i>(Critical Outcome)</i>	Each \$1 increase in tobacco taxes is associated with a small reduction (0.08% to 0.12%) in the rate of low birth weight Evidence type: Quasi-experimental analysis of US natality files			
Perinatal/infant Death <i>(Critical Outcome)</i>	Each \$1 increase in tobacco taxes is associated with a small reduction (0.19 per 1000) in infant death rate Evidence type: Time series modeling			

Intervention: Tobacco excise taxes				
Setting/sector: Local, state and federal governments				
Outcomes	Estimate of Population Health Effect	Resource Impact	Public Values and Preferences	Other considerations
Tobacco abstinence during pregnancy <i>(Important Outcome)</i>	Each \$1 increase in tobacco taxes is associated with a 2% to 5% reduction in smoking during pregnancy Evidence type: Quasi-experimental and cross-sectional ecological study			
Tobacco abstinence after pregnancy <i>(Important outcome)</i>	Each \$1 increase in tobacco taxes is associated with a 4% reduction in smoking at 4 months post-partum Evidence type: Cross-sectional ecological study			

EVIDENCE OVERVIEW

Clinical background

In 2014, the rate of smoking at any time during pregnancy was estimated at 8.4% based on the National Vital Statistics Report (Curtin, et al., 2016). While this rate represents a substantial improvement over prior decades, smoking during pregnancy remains a major public health problem. Smoking during pregnancy is more common among women aged 20-24 (13%), unmarried women (15%), American Indians or Alaska Natives (18%), Women Infants and Children nutrition assistance recipients (13%), and Medicaid beneficiaries (14%). There is also significant geographic variation in the rate of smoking during pregnancy, ranging from 1.8% in California to 27.1% in West Virginia. In Oregon, the rate of smoking during pregnancy is slightly higher than the overall national average at 10.3%. Among women who smoke in the first or second trimester, only 1 in 5 will successfully quit smoking by the third trimester.

Indications

In addition to the well-established risks of smoking for individual health, smoking in pregnancy entails risks to the fetus, including miscarriage and stillbirth, preterm birth, growth restriction, placental abnormalities and abruption, and premature rupture of membranes (Siu, 2015; American Congress of Obstetricians and Gynecologists (ACOG, 2010). Smoking in the postpartum period is associated with a heightened risk of sudden infant death syndrome and childhood respiratory illnesses (ACOG, 2010). Older data from 2006 suggests that the costs of smoking during pregnancy are substantial and that interventions to promote smoking cessation during pregnancy may be not only cost-effective but cost-saving (ACOG, 2010).

Exposure to secondhand smoke also increases health risks for individuals and can impact pregnancy outcomes. For example, maternal exposure to secondhand smoke increases the risk of having a low birth weight baby and exposure to secondhand smoke increases the risk of sudden infant death syndrome (U.S. Department of Health and Human Services, 2006).

Technology description

Clinical services to aid in tobacco cessation include pharmacological treatments and behavioral interventions. Nicotine (pregnancy category D) is the addictive drug found in tobacco, and nicotine replacement therapy (NRT) can be used to reduce cravings during a quit attempt. NRT is available as transdermal patches, gum, lozenges, sprays, and inhalers. Varenicline (pregnancy category C) is a partial agonist to nicotinic receptors, and it reduces cravings and decreases the pleasurable effects of nicotine. Anti-depressants, such as bupropion (pregnancy category B) and nortriptyline (pregnancy category D) are also used to aid in tobacco cessation.

Behavioral interventions to aid tobacco cessation can be delivered using a variety of methods and in a variety of settings, as summarized by Patnode and colleagues (2015):

Specific behavioral interventions include, but are not limited to: self-help materials (e.g., written materials, videos, audiotapes, computer), phone-based interventions, quitlines, brief provider-delivered interventions (e.g., advice from a physician or nurse), intensive counseling delivered on an individual basis or in a group including motivational interviewing, mobile phone and text messaging interventions, biomedical risk assessment, and combinations of these approaches (p. 5).

A relatively straightforward behavioral intervention known as the “5As approach” is commonly endorsed by professional societies. The 5As direct providers to ask about tobacco use, advise cessation, assess readiness for change, assist with development of a quit plan, and arrange follow-up. An older systematic review (Melvin, et al., 2000) concluded that the use of the 5As approach was associated with a relative risk of 1.7 for smoking cessation (95% CI 1.3 to 2.2).

Financial incentives have been used to increase motivation to quit. These interventions can be implemented in a clinic or in other settings. A behavioral intervention specifically targeting pregnant women is high feedback ultrasounds, where women can see the monitor screen and receive detailed visual and verbal explanations of the ultrasound.

Behavioral interventions can also target a woman’s partner or other family members who use tobacco. For women who do not use tobacco, a partner or family member quitting can reduce exposure to secondhand smoke. Interventions that ban smoking in public places, such as smoke-free workplace laws, can also lead to reduced maternal exposure to secondhand smoke.

Increasing the price of tobacco leads to reductions in use, including increasing successful quit attempts. Jurisdictions have increased the price of tobacco by raising tobacco taxes at the local, state, and federal levels.

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 C.

1. What interventions are most effective and most cost-effective to:
 - a. Reduce tobacco-related perinatal/infant morbidity and mortality?
 - b. Reduce tobacco use in pregnant women?
 - c. Sustain tobacco abstinence among women who quit tobacco use during pregnancy?
2. Does effectiveness vary by socioeconomic factors such as race, ethnicity, income, and educational attainment?
3. What models of care would allow these interventions to be implemented most effectively and cost-effectively?

Critical outcomes selected for inclusion in the GRADE table are pregnancy complications, low birth weight, and perinatal/infant death. Important outcomes selected for inclusion in the GRADE table are abstinence from tobacco during pregnancy and long-term tobacco abstinence.

Evidence review

Pharmacologic Treatments

The core sources search identified a Cochrane systematic review of randomized controlled trials (RCTs) of pharmacologic treatments for smoking cessation in pregnancy that was published in December 2015 (Coleman, 2015). The Medline search did not identify any new RCTs published after the search dates of the systematic review, but did identify an economic analysis (Essex, et al., 2015) derived from data from one of the included studies in the Cochrane review.

Coleman and colleagues identified nine RCTs for inclusion. Eight of these trials studied nicotine replacement therapy (NRT) using various doses and delivery systems. Five of the trials compared NRT to a placebo control, while three of the trials compared NRT with behavioral support to behavioral support alone. The ninth trial was a small (n=11) RCT of bupropion compared to placebo that reported limited follow-up at nine weeks. There were no trials of other pharmacologic treatments (such as varenicline and nortriptyline) or the use of electronic nicotine delivery systems. Four of the nine trials were conducted in the United States; the remaining trials were conducted in Australia, Canada, or Western Europe. The authors concluded that the risk of bias in the included trials was generally low, notwithstanding concerns over blinding in the three NRT studies that did not use a placebo control. All of the included trials used biochemical validation to ascertain smoking cessation during pregnancy, although the thresholds for positive testing varied.

In the meta-analysis of the eight trials of NRT spanning nearly 2,200 participants, NRT demonstrated a statistically significant improvement in smoking cessation during pregnancy (RR 1.43, 95% CI 1.03 to 1.93). However, when only the five placebo controlled trials of NRT were included, the effect failed to reach statistical significance (RR 1.28, 95% CI 0.99 to 1.68). In the trials that reported continued abstinence from tobacco after pregnancy, NRT did not demonstrate a statistically significant benefit at 6 months (RR 1.15, 95% CI 0.75 to 1.77), nor at 12 or 24 month follow-up.

Four trials of NRT reported on rates of miscarriage or spontaneous abortion; in the meta-analysis, there was no statistically significant effect of NRT on these outcomes (RR 1.47, 95% CI 0.45 to 4.77). Similarly, in the four studies that reported on stillbirth, there was no statistically significant difference between the NRT and control groups (RR 1.24, 95% CI 0.54 to 2.84).

Among six studies reporting birth weights, NRT did not have a statistically significant effect on birth weight (mean difference 100.54 grams, 95% CI -20.84 to 221.91). Similarly, while the incidence of low birth weight was lower in the NRT group, the effect was not statistically significant (RR 0.74, 95% CI 0.41 to 1.34). It should be noted that both analyses found substantial heterogeneity in the studies.

Six studies reported on preterm birth; in the meta-analysis NRT did not have a statistically significant effect on preterm delivery (RR 0.87, 95% CI 0.67 to 1.14). Similarly, meta-analytic results of studies reporting on neonatal intensive care unit admissions (four studies, RR 0.90, 95% CI 0.64 to 1.27) and

neonatal deaths (four studies, RR 0.66, 95% CI 0.17 to 2.62) did not demonstrate a statistically significant effect of NRT.

Earlier systematic reviews had raised concerns that NRT could be associated with a greater risk of Cesarean birth. However, meta-analysis of data from approximately 1,400 women in two studies included in the Coleman review showed no statistically significant difference in the rate of Cesarean section (RR 1.18, 95% CI 0.83 to 1.69). Two of the included studies reported detailed information on serious harms including maternal hypertension, 5 minute Apgar score, arterial cord blood pH, intraventricular hemorrhage, neonatal convulsions, necrotizing enterocolitis, assisted vaginal delivery, and maternal death. With the exception of one study that showed a small (8 mmHg) but statistically significant increase in maternal diastolic blood pressure, there were no other statistically significant differences in serious harms. Non-serious harms were reported in five studies and included headache, dizziness, fatigue, heartburn, nausea, vomiting, and skin irritation. Non-serious harms were not meta-analyzed but generally occurred in less than 10-15% of patients in most studies.

Overall, the authors conclude that there is high quality evidence of “borderline significance suggesting that nicotine replacement used with behavioural support by pregnant women for smoking cessation may increase smoking abstinence in late pregnancy...” The authors caution that the actual efficacy of NRT for smoking cessation in pregnancy may be closer to the non-statistically significant effect observed in the placebo controlled trials. NRT did not have apparent effects on sustained smoking abstinence after pregnancy, nor on birth outcomes. There was extremely limited evidence on bupropion and no evidence on other pharmacologic treatments such as varenicline and nortriptyline, nor on electronic nicotine delivery systems.

One study identified in the Medline search conducted an economic analysis based on the results of the Smoking, Nicotine, and Pregnancy (SNAP) trial. This economic analysis was done from the perspective of the British National Health Service with a time horizon of up to 7 months. In the SNAP trial (which used nicotine patches as the intervention), the biochemically validated rate of smoking cessation was slightly higher in the NRT group (9.4%) compared to the placebo group (7.6%), though the difference was not statistically significant (RR 1.26, 95% CI 0.82 to 1.96). The authors estimated the incremental cost-effectiveness ratio of NRT to be about £5,000 per quitter (95% CI £-114,128 to £126,747) but also noted the wide confidence interval and the high level of statistical uncertainty.

Behavioral Interventions

The core sources search identified a review of systematic reviews of behavioral interventions for smoking cessation during pregnancy that was prepared by the Agency for Health Research and Quality (AHRQ) in September 2015 (Patnode, et al., 2015). The authors of the AHRQ review relied on a good quality Cochrane systematic review of behavioral interventions published by Chamberlain and colleagues in 2013. The Medline search identified one additional RCT published after the search dates of the AHRQ review. The additional trial examined the effectiveness of a physical activity intervention in addition to behavioral support for smoking cessation during pregnancy (Ussher, et al., 2015).

The Chamberlain review included 86 RCTs of behavioral interventions for smoking cessation in pregnancy. The included RCTs enrolled healthy pregnant women older than age 16 and most of the studies included women of low socioeconomic status. The interventions in the trials were varied. Among the 77 studies that were included for meta-analysis, 48 examined behavioral counseling interventions, 7 examined clinician feedback, 7 examined health education, 4 examined incentives, and 10 examined social support. Forty-four of the trials compared the behavioral interventions to usual care (information and advice to quit), while in 31 trials the comparator was a less intensive or alternative behavioral intervention. There was no evidence on internet- or text messaging-based interventions in pregnant women, but trials are underway.

The meta-analysis of the effect of behavioral interventions on smoking cessation in late pregnancy included 60 RCTs and 10 cluster-randomized trials spanning nearly 22,000 patients. In the pooled analysis of all behavioral interventions, there was a statistically significant improvement in smoking cessation in late pregnancy (RR 1.45, 95% CI 1.27 to 1.64), albeit with moderate heterogeneity. In the exploratory analysis, a statistical test for sub-group differences found no difference by the type of intervention. When only trials of behavioral counseling interventions were included, the results were similar (RR 1.37, 95% CI 1.17 to 1.59). In the restricted analyses of other intervention types (social support, financial incentives, and feedback), the results were uniformly in the positive direction, but did not achieve statistical significance. It is important to note that not all trials of behavioral interventions used biochemical validation of smoking cessation, but the authors did not find evidence of significant between-group heterogeneity based on the presence or absence of biochemical validation. Indeed, in the subset of behavioral counseling trials that used biochemical validation, the results were attenuated but still statistically significant (RR 1.25, 95% CI 1.03 to 1.50). The AHRQ review did not summarize information on the effects of behavioral interventions on smoking abstinence after pregnancy, though outcomes at 12 to 17 months and >18 months post-partum are reported in the Chamberlain review.

Seven of the trials included in the review reported on stillbirth. The stillbirth event rates in both arms of the study group were very low, and while there was a numerically greater number of stillbirths in the behavioral intervention groups (38/2676 vs. 31/2738 in the control groups), there was no statistically significant difference between the groups (RR 1.22, 95% CI 0.76 to 1.95).

Fourteen trials contributed to the meta-analysis of low-birth weight outcomes (defined as <2500 grams). Behavioral interventions were effective in reducing the incidence of low birth weight (RR 0.82, 95% CI 0.71 to 0.94).

Fourteen trials contributed to the meta-analysis of preterm birth (<37 weeks gestation). Behavioral interventions were effective in reducing the incidence of preterm birth (RR 0.82, 95% CI 0.70 to 0.96).

In the trials of behavioral interventions, there were too few neonatal deaths to draw valid conclusions.

The authors note that reporting of adverse events in trials of behavioral interventions was limited and sporadic. They note that four studies include the possibility of a paradoxical effect of increased smoking (the range of possible effects could include escalation of tobacco use) after a behavioral intervention.

Other speculative harms include nicotine withdrawal and the social costs imposed by the loss of partner support, but no trials reported on these potential adverse events.

Overall, the authors of the AHRQ review conclude that there is evidence that behavioral interventions result in statistically significant improvements in smoking cessation during pregnancy as well as some birth outcomes.

As noted, the Medline search identified an additional RCT of a physical activity intervention for smoking cessation in pregnancy (Ussher, et al., 2015). The London Exercise and Pregnancy smoking (LEAP) trial, randomized 789 pregnant smokers to behavioral support with a supervised physical activity intervention or to behavioral support alone. The primary outcome was biochemically validated abstinence from smoking during pregnancy. A secondary outcome was self-reported abstinence at 6 months after pregnancy. In the intention-to-treat analysis, there was no statistically significant difference in smoking abstinence at the end of pregnancy (8% in the physical activity group vs. 6% in the control group; OR 1.21, 95% CI 0.70 to 2.10). Similarly, at six months after pregnancy the smoking abstinence rate was 6% in the physical activity group compared to 4% in the control group (OR 1.55, 95% CI 0.81 to 2.97). Thus, the authors conclude that the addition of a structured, supervised physical activity intervention to behavioral support does not improve smoking cessation in pregnancy.

Prenatal Ultrasound with High Feedback

The core sources search identified one Cochrane systematic review of high feedback versus low feedback prenatal ultrasound during pregnancy that included a smoking cessation outcome (Nabhan & Aflaifel, 2015). The CEBP Medline search did not identify any new RCTs published after the search dates of the Cochrane systematic review.

In high feedback ultrasound, “women can see the screen and receive detailed explanations of the images.” The authors of the review identified a single RCT of 129 women that demonstrated that high feedback ultrasound led to a statistically significant improvement in smoking cessation during pregnancy (RR 2.93, 95% CI 1.25 to 6.86). The authors assessed the GRADE quality of this evidence to be low.

Financial Incentives

The core sources search identified a Cochrane systematic review of randomized controlled trials and controlled before-and-after studies of financial incentives for smoking cessation during pregnancy (Cahill, et al., 2015). The Medline search did not identify any new RCTs published after the search dates of the systematic review.

The Cochrane review included nine studies of financial incentives spanning almost 1,800 pregnant smokers. Eight of the nine studies were conducted in the United States, mostly in clinical settings. The financial incentives in these studies were vouchers for goods or services, not cash payments. The value of the financial awards was up to \$250. Four of the trials used incremental awards in which the vouchers reset to baseline values after relapse or missed visits, but could be restored to the previous value when abstinence was re-established. All of the trials also offered standard cessation support to all participants

in addition to routine care. All of the studies examined smoking cessation at the end of pregnancy and six of the studies followed participants after pregnancy. Financial incentives for smoking cessation can be included as part of insurance benefit design, but are also provided as direct benefits from employers or other groups.

In the meta-analysis, financial incentives showed statistically significant improvements over controls for smoking cessation at end of pregnancy (OR 3.79, 95% CI 2.74 to 5.25) and at longer follow-up of up to 6 months post-partum (OR 3.60, 95% CI 2.39 to 5.43). In the overall meta-analysis for the primary outcome of smoking cessation at longest follow-up, the likelihood of smoking cessation in the control group was 4.8% compared with 15.4% in the financial incentive group. For all adults, long-term smoking cessation (6-24 months) was 8.4% in the control group and 11.2% in the incentives group.

The authors gave a GRADE quality assessment of moderate for this outcome. The effects on fetal, neonatal, and pregnancy outcomes were not reported.

The authors of the Cochrane review address several operational questions about the use of financial incentives, but these conclusions should be interpreted with caution as they are based on the results of smaller numbers of studies. The authors were unable to draw firm conclusions about the effect of reward size. In four studies, contingent rewards (i.e. incentives that increase with prolonged abstinence) appeared to be more effective than fixed payments (OR 6.26, 95% CI 2.35 to 16.68). In one study, front-loading the reward schedule did not improve the odds of quitting (OR 1.17, 95% CI 0.35 to 3.84). Similarly, there was no statistically significant difference between programs that used participant-initiated verification of abstinence compared with researcher-initiated verification (OR 1.70, 95% CI 0.60 to 4.82).

The authors of the Cochrane review note a paucity of economic analysis of financial incentives. One study cited a report from the National Institute for Health and Clinical Evidence (NICE) that concluded that financial incentives produced a net cost-benefit of £2,261. A second study reported short-term incremental cost per quitter of £1,127 and longer-term cost per quality-adjusted life year of £482 based on projected improvements in maternal outcomes.

None of the pregnancy trials included in the Cochrane review reported on harms or adverse events.

Overall, the authors of the Cochrane review conclude that contingent financial incentives improve smoking abstinence in late pregnancy and into the post-partum period.

A separate study (Lopez, et al., 2015) was conducted to explore characteristics associated with successful cessation in three of the trials included in the Cochrane review. The authors of this study conclude that contingent incentives, lower-baseline smoking rate, and a history of quit attempts before pregnancy all predicted successful cessation during pregnancy, but no characteristics were associated with sustained post-partum cessation.

Partner Support for Smoking Cessation

The core sources search identified one narrative systematic review of partner support for smoking cessation during pregnancy (Hemsing, et al., 2012). The Medline search did not identify any new RCTs published after the search dates of the systematic review, though there is an ongoing RCT with a published protocol (Meghea, et al., 2015).

Hemsing and colleagues identified nine studies of partner support that met inclusion criteria. Five studies were RCTs and four studies used before-and-after designs. Overall, in this narrative review, three of the four studies that examined the effects of partner support interventions on smoking cessation for pregnant women found no effect. The fourth study, a cluster-randomized trial of an intervention that offered partners an educational booklet, found a statistically significant increase in quit attempts and 7-day abstinence for the pregnant women. Among the nine studies that examined the effect of partner support on partner smoking cessation, seven found no effect of the intervention.

Overall, the authors of the review conclude that “evidence examining partner support...is sparse, and few intervention studies actually demonstrated significant results in either encouraging partners to support smoking cessation during pregnancy and postpartum or in improving the partner’s smoking cessation.”

Interventions to Reduce Secondhand Smoke Exposure

The core sources search identified one narrative systematic review of interventions to reduce non-smoking pregnant women’s exposure to secondhand smoke (SHS) (Tong, et al., 2014). The Medline search did not identify any new RCTs published after the search dates of the systematic review.

The narrative review included five RCTs. Four examined psychosocial interventions of varying intensity, while one combined psychosocial interventions with NRT for partners of pregnant women. The psychosocial interventions ranged from brief clinical interventions performed by obstetricians to eight sessions spanning pregnancy and the post-partum period that focused on cognitive behavioral strategies delivered by trained counselors. Only one of the studies was done in the United States. The primary outcome was secondhand smoke exposure. Three of the five studies relied on patient reported outcomes rather than biochemical validation of secondhand smoke exposure. Birth outcomes were only reported in one study. Overall, results for secondhand smoke exposure were mixed in the five studies, but the single US-based study (which tested the intensive behavioral counseling intervention detailed above), found a statistically significant reductions in self-reported secondhand smoke exposure (OR 0.57, 95% CI 0.38 to 0.84). The US study was also the only to report birth outcomes; there were no statistically significant differences in the incidence of low birth weight or preterm delivery (<37 weeks).

The overall conclusion offered by the authors is that intervention to reduce SHS exposure during pregnancy may be effective, but firm conclusions are limited by weaknesses in the studies.

Multisector Interventions

Smoke-free legislation

The core sources search identified one systematic review and meta-analysis of the effects of smoke-free legislation on perinatal and child health (Been, et al., 2014). The Medline search did not identify any new studies published after the search dates of the systematic review.

Been and colleagues included eleven interrupted time series examining the effects of smoke-free legislation in various countries (five studies in North America and six in Europe). The analysis of perinatal outcomes includes more than 2.5 million births. Most studies were deemed to be at low or moderate risk of bias; only one was felt to be at high risk of bias.

Meta-analytic results were available for two outcomes of interest. Smoke-free legislation was associated with a statistically significant reduction in the risk of preterm birth (risk change -10.4%, 95% CI -18.80 to -2.00) and a non-statistically significant reduction the risk of low birth weight (-1.70%, 95% CI -5.10 to 1.60).

Overall, the authors conclude that there is clear evidence that smoke-free legislation is associated with a reduction in preterm births. The authors further contend that smoke-free legislation is cost-effective because there are no established adverse economic effects of smoking bans, but also note that formal cost-effectiveness studies are lacking.

Tobacco excise taxes

The core sources search did not identify relevant systematic reviews of tobacco taxes and their effects on smoking during pregnancy or birth outcomes. The Medline search identified three observational studies of the effects of tobacco taxes on smoking during pregnancy and perinatal outcomes.

Patrick and colleagues (2015) created a time series model based on data from all fifty states between 1999 and 2010. Based on their multivariate regression model, they concluded there was a statistically significant effect of tobacco taxes such that every \$1 increase in the per pack cigarette tax was associated with a reduction in infant deaths (before one year of age) of 0.19 per 1000 live births (95% CI -0.33 to -0.05). The estimated effect was greater for African American infants with a reduction of 0.46 infant death per 1000 live births (95% CI -0.90 to -0.01) for each \$1 increase in the per pack tax.

Hawkins and colleagues (2014) performed a quasi-experimental analysis using US natality files of over 16 million singleton births in 28 states between 2000 and 2010 to explore the association of tobacco control policies with birth outcomes. The statistical analysis was done using two models and the results were analyzed by race and educational attainment. In the first model, each \$1 increase in the tobacco tax was associated with a reduction in the rate of smoking during pregnancy of 2.4% for white mothers with 0-11 years of education and 2.1% for black mothers with 0-11 years of education. The association of tobacco taxes with reduced smoking in pregnancy continued, but was attenuated, for black mothers of all levels of educational attainment. In the second model, each \$1 increase in cigarette taxes was associated with increases in birth weight (5.4 grams among white mothers and 4.0 grams among black

mothers, both with 0-11 years of education). Similarly, in the group with 0-11 years of education, each \$1 increase in tobacco taxes was associated with a reduction in low birth weight infants (0.08% for white mothers, 0.12% for black mothers) and preterm births (0.07% for white mothers, 0.08% for black mothers). Of note, each \$1 increase in tobacco taxes was associated with an increased number of large for gestational age infants of 0.18% for white mothers and 0.10% for black mothers, both with 0-11 years of education. Overall, the authors conclude that increased tobacco taxes are associated with lower rates of smoking during pregnancy and improvements in birth outcomes, including low birth weight and preterm births. These effects are most apparent among women with the lowest levels of educational attainment.

Adams and colleagues (2012) performed a pooled cross-sectional analysis of live births in 29 states and New York City between 2000 and 2005. Using regression modeling, they estimated the effects of various tobacco control interventions including smoking bans, taxes, and overall tobacco control spending on the rates of smoking during pregnancy. The authors found that each \$1 increase in tobacco taxes or prices results in a 4% to 5% increase in third trimester smoking abstinence after controlling for other tobacco control policies. Furthermore, each \$1 increase in tobacco taxes was also associated with a 4.2% increase in the probability of sustained tobacco cessation at 4 months post-partum.

Full private worksite smoking bans were found to be associated with an estimated increase in third trimester abstinence of approximately 5%.

Of note, cumulative spending on tobacco control did not have an apparent effect on smoking during pregnancy. The results for these outcomes varied by age group and the results appear to be attenuated in older populations.

Models of Care

The available summary literature provides no direct evidence regarding models of care that are associated with effectiveness for these interventions, except where noted for specific interventions above. Overwhelmingly, the individual interventions that were studied were delivered in clinical settings, including interventions like financial incentives. Many of the behavioral interventions rely on the use of interdisciplinary care providers, including trained counselors. The outcomes of maternity care homes for high-risk pregnant women are currently being evaluated by the Center for Medicare and Medicaid Innovation. The included tobacco control policies were mostly implemented at a statewide level, though in some cases local efforts were also included in the analyses. There is limited cost-effectiveness information that is specific to pregnant smokers. The economic analyses that do exist, particularly for financial incentives, suggest that these interventions are either cost-saving or cost-effective and well below commonly accepted willingness-to-pay thresholds.

EVIDENCE SUMMARY

A number of interventions, both at the individual and community levels, have been studied for their effects on smoking cessation during and after pregnancy as well as birth outcomes. At the individual level, behavioral interventions are effective. Among multisector interventions, financial incentives and tobacco control policies (including smoke-free legislation and tobacco taxes) appear to have the best evidence of effectiveness.

Among pharmacologic interventions, only NRT is well studied. NRT may have a modest effect on reducing smoking during pregnancy, but does not appear to encourage sustained smoking abstinence and does not have apparent effects on birth outcomes. No evidence was identified that examined the effectiveness or harms of other pharmacologic treatments such as varenicline, nortriptyline, or electronic/vaporized cigarettes in pregnant women.

Behavioral interventions (among which behavioral counseling is most commonly studied) appear to be effective in reducing smoking during pregnancy and also appear to reduce the incidence of low birth weight and preterm birth.

On the basis of a single RCT, ultrasound with high feedback may increase smoking cessation in late pregnancy.

Contingent financial incentives for smoking cessation appear to be among the most promising interventions and are associated with increased smoking abstinence both during and after pregnancy.

There is limited evidence on programs for partner support for smoking cessation and the existing data shows mixed results.

There is limited evidence on programs to reduce secondhand smoke exposure for pregnant women. Data from a US-based RCT suggests that intensive behavioral counseling may reduce self-reported secondhand smoke exposure in pregnancy, but there were no apparent effects on birth outcomes.

Evidence from interrupted time series examining the effects of smoking bans on perinatal outcomes suggests that these interventions reduce the risk of preterm births.

Much of the evidence for behavioral interventions was conducted in populations of low socioeconomic status. In general, studies of tobacco control policies, particularly tobacco taxes, suggest greater effects in African-Americans, those with lower levels of educational attainment, and younger populations.

In conclusion, selected individual clinical interventions, financial incentives, and tobacco control policy interventions appear to be effective in reducing smoking during pregnancy and thus improving birth outcomes.

OTHER DECISION FACTORS

Resource Allocation

Complications associated with smoking such as preterm birth and low-birth weight can be very high cost and have significant social implications on a future child's development and productivity. Interventions that are effective at reducing these complications would be highly appealing for coverage. Of the clinical interventions, behavioral interventions have the strongest evidence of benefit of health outcomes. Financial incentives have upfront costs, but these costs were modest and the intervention effective. The multisector interventions would have minimal costs for plans but may face concerns from other sectors.

Values and preferences

Pregnant smokers are often motivated to quit because of the potential health risks for their pregnancy and their infant. Some pregnant women would be highly motivated to find safe and effective strategies to assist them. Behavioral interventions, while effective at improving quit rates and health outcomes, take an additional time commitment on behalf of the woman and would be more appealing to some than others. Financial incentives may be quite sought after by some women. For pharmacotherapy, many women are very uncomfortable with use of medications during pregnancy that are not well studied and proven safe. For them, the risks associated with this without a proven benefit is likely to dissuade their use. For the multisector interventions there are strong stakeholder interest groups that would have significant concerns about increasing various tobacco control policies. However, such policies already exist in Oregon and other states, and much of the public favors using tobacco taxes to help fund healthcare services.

POLICY LANDSCAPE

Quality measures

The [National Quality Measures Clearinghouse](#) includes a large variety of quality measures related to screening/assessment for tobacco use, tobacco use status, and access to treatment. None of these measures specifically focus on women who are pregnant.

Starting in 2016, Oregon's Coordinated Care Organization (CCO) Incentive Measures includes: Percentage of adult Medicaid members (ages 18 and older) who currently smoke cigarettes or use other tobacco products.

Payer coverage policies

Section 4107 of the Affordable Care Act requires state Medicaid programs and most commercial insurance plans to cover comprehensive tobacco cessation services for pregnant women, including counseling and pharmacotherapy, without cost sharing (Centers for Medicare and Medicaid Services, 2011).

The Washington Medicaid program covers prescription (including **B**upropion SR (Zyban®) and **V**arenicline tartrate Chantix®) and over-the-counter smoking cessation products (including NRT) for pregnant women through the state's Quitline Program or through a pharmacy. The client must be receiving smoking cessation counseling to be eligible to receive medications. Eight cessation counseling sessions are allowed every 12 months (Washington State Department of Health, 2015).

Multisector Interventions

All the included studies in the systematic review of smoke-free legislation (Been, et al., 2014) assessed jurisdictions that had implemented smoke-free legislation for workplaces including bars and restaurants. Thirty states, including Oregon, have implemented smoke-free legislation for workplaces, bars, and restaurants (Campaign for Tobacco-Free Kids [CTFK], 2016a). Oregon's law was passed in 2007 and implemented on January 1, 2009.

Tobacco taxes have been implemented at the federal levels, state, and local levels. The current federal cigarette tax is \$1.01 per pack. The average state cigarette tax is \$1.61 per pack, ranging from \$.017 per pack in Missouri to \$4.35 per pack in New York. The tax per pack in Oregon is \$1.32 and in Washington it is \$3.025 (CTFK, 2016b). In the U.S., over 600 local jurisdictions (e.g., cities, counties) have levied cigarette taxes, as high as \$3.00 per pack in Cook County, Illinois, and Juneau, Alaska (CTFK, 2015). In Oregon, state law preempts cities and counties from levying tobacco taxes.

Recommendations from others

United States Preventive Services Task Force

The United States Preventive Services Task Force (USPSTF) guideline was published in September 2015 and is informed by the evidence review conducted by AHRQ (Patnode, 2015). The USPSTF reached the following conclusions:

- Clinicians should “ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation...” (A recommendation)
- “[C]urrent evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women.” (I statement)
- “[C]urrent evidence is insufficient to recommend electronic nicotine delivery systems for tobacco cessation in adults, including pregnant women.”

The USPSTF also provided information on the components of effective behavioral interventions (for adults in general, not specific to pregnant women) which are excerpted below:

Intensity

- Both minimal (<20 min in 1 visit) and intensive (≥20 min plus >1 follow-up visit) physician-advice interventions effectively increase the proportion of adults who successfully quit smoking and remain abstinent for ≥6 mo.
- There is a dose–response relationship between the intensity of counseling and cessation rates (i.e., more or longer sessions improve cessation rates).

Duration

- Brief, in-person behavioral counseling sessions (<10 min) effectively increase the proportion of adults who successfully quit smoking and remain abstinent for 1 y.
- Although less effective than longer interventions, even minimal interventions (<3 min) have been found to increase cessation rates in some studies.

Frequency

- Multiple sessions should be provided; according to the Public Health Service guidelines, patients should receive ≥ 4 in-person counseling sessions.
- Cessation rates may plateau after 90 min of total counseling contact time.

Format

- In-person behavioral counseling sessions (individual or group counseling)
- Telephone counseling
- Tailored, print-based self-help materials

Provider

- In-person behavioral counseling sessions: Various types of primary care providers, including physicians, nurses, psychologists, social workers, and cessation counselors
- Telephone counseling: Professional counselors or health care providers who are trained to offer advice over the telephone

Content

- Assessment of smoking status:
 - Ask every patient about tobacco use
 - Advise all tobacco users to quit
 - Assess willingness of all tobacco users to make an attempt to quit
 - Assist all tobacco users with their attempt to quit
 - Arrange follow-up
- Effective counseling interventions provide social support and training in practical problem-solving skills:
 - Training in problem-solving skills includes helping persons who smoke to recognize situations that increase their risk for smoking, develop coping skills to overcome common barriers to quitting, and develop a plan to quit
 - Basic information about smoking and successful quitting should also be provided
 - Complementary practices that improve cessation rates include motivational interviewing, assessing readiness to change, and offering more intensive counseling or referrals

Washington State Department of Health

The Washington State Department of Health issued a revised smoking cessation during pregnancy guideline in 2015. For most clinics, the guideline endorses the use of a brief behavioral intervention based on the “5As” approach created by the American Congress of Obstetricians and Gynecologists. The 5As are ask, advise, assess, assist, and arrange. For clinics that are not able to implement a full 5As

approach, the guideline suggests the “2A & R” approach that includes asking about smoking, advising cessation, and referring to cessation resources outside the clinic. The Washington guideline includes advice for implementation at clinics, provider scripts, and suggestions for sustaining cessation postpartum. The guideline does not recommend the routine use of pharmacotherapy for cessation, but states that in heavy smokers who have failed behavioral interventions that pharmacotherapy may be considered. The guideline also provides additional information about the covered benefits for smoking cessation in the Medicaid program and offers a compendium of outside resources.

North American Quitline Consortium

The North American Quitline Consortium (NAQC) released an issue paper in 2014. Though not strictly a clinical practice guideline it is notable for recommending that pregnant smokers should be offered in-person counseling and that quitlines should be considered an adjunct. It endorses further research into both the effectiveness of quitlines and measures to increase their utilization. It provides established counseling protocols for pregnant and recently postpartum women.

World Health Organization

The World Health Organization released a GRADE-informed guideline in 2013 regarding the prevention and management of tobacco use and secondhand smoke exposure in pregnant women. The recommendations, including the strength of recommendation and evidence quality, is excerpted in the table below on the next page.

WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy (2013)

No.	Recommendation	Strength of recommendation	Quality of Evidence
Identification of tobacco use and second-hand smoke exposure in pregnancy			
1	Health-care providers should ask all pregnant women about their tobacco use (past and present) and exposure to SHS, as early as possible in the pregnancy, and at every antenatal care visit	Strong	Low
Psychosocial interventions for tobacco-use cessation in pregnancy			
2	Health-care providers should routinely offer advice and psychosocial interventions for tobacco cessation to all pregnant women, who are either current tobacco users or recent tobacco quitters.*	Strong	Moderate
Pharmacological interventions for tobacco-use cessation in pregnancy			
3	The panel cannot make a recommendation on use or nonuse of nicotine replacement therapy to support cessation of tobacco use in pregnancy.	Not applicable	Moderate
4	The panel does not recommend use of bupropion or varenicline to support cessation of tobacco use in pregnancy.	Strong	Very Low
5	The panel recommends that further research be carried out in pregnant women on safety, efficacy and factors affecting adherence to pharmacotherapeutic cessation agents.	Strong	Not applicable
Protection from second-hand smoke in pregnancy (smoke-free public places)			
6	All health-care facilities should be smoke-free to protect the health of all staff, patients, and visitors, including pregnant women.	Strong	Low
7	All work and public places should be smoke-free for the protection of everyone, including pregnant women	Strong	Low
Protection from second-hand smoke in pregnancy (smoke-free homes)			
8	Health-care providers should provide pregnant women, their partners and other household members with advice and information about the risks of SHS exposure from all forms of smoked tobacco as well as strategies to reduce SHS in the home.	Strong	Low
9	Health-care providers should, wherever possible, engage directly with partners and other household members to inform them of the risks of SHS exposure to pregnant women from all forms of smoked tobacco, and to promote reduction of exposure and offer smoking cessation support.	Strong	Low

*Recent tobacco quitters may include women who used tobacco before the pregnancy, and who have either spontaneously quit or stopped using tobacco in the pre-conception period or in early pregnancy, before their first antenatal visit.

Association of State and Territorial Health Officials

In 2013, the Association of State and Territorial Health Officials (ASTHO) issued recommendations for smoking cessation strategies for women before, during, and after pregnancy. The eight ASTHO recommendations are excerpted below:

1. Provide training and technical assistance to healthcare and public health providers on helping women quit using tobacco before, during, and after pregnancy.
2. Extend pregnancy-specific and postpartum-specific quitline services to women during and after pregnancy.
3. Promote awareness of cessation benefits and effectiveness of treatment by implementing coordinated media campaigns that specifically target women during childbearing years.
4. Develop customized programs for specific at-risk populations of women who are smokers and of reproductive age
5. Include Women, Infants, and Children (WIC) sites as points for intervening with pregnant and postpartum women.
6. Design and promote barrier-free cessation coverage benefits for pregnant and postpartum women in public and private health plans.
7. Promote cessation service integration aimed at improving birth outcomes.
8. Implement evidence-based tobacco control policies that augment tobacco cessation for women before, during, and after pregnancy.

American Congress of Obstetricians and Gynecologists

In 2010, the American Congress of Obstetricians and Gynecologist (ACOG) released a clinician-directed self-instructional guide and toolkit to help pregnant women quit smoking. ACOG endorses the use of the “5As” approach for screening and brief intervention. The 5As are:

- Ask about smoking
- Advise to quit
- Assess willingness to quit
- Assist patient with the process
- Arrange follow-up

The ACOG instructional guide also provides implementation advice and tools for clinics and providers. ACOG endorses the use of tobacco quitlines. ACOG states that pharmacologic treatments should not be used as first-line smoking cessation strategies, but may be considered with close supervision in women who are unable to quit after a trial of behavioral interventions like the 5As approach.

National Institute for Health and Care Excellence

In 2010, the National Institute for Health and Care Excellence (NICE) released a public health guideline regarding smoking cessation in pregnancy and after childbirth. NICE provides eight recommendations directed at midwives, general practitioners, and staff at the National Health Service (NHS) Stop Smoking

Services. Salient features of the NICE recommendations include comprehensive screening using history and exhaled carbon monoxide testing, early referral to behavioral support through Stop Smoking Services program of the NHS, and education for partners who also smoke. Like others, NICE also recommends that NRT not be considered unless other attempts at cessation are unsuccessful and should only be prescribed for two week intervals contingent on validation of smoking cessation.

REFERENCES

Evidence Sources

- Adams, E., Markowitz, S., Kannan, V., Dietz, P., Tong, V., & Malarcher, A. (2012). Reducing prenatal smoking: The role of state policies. *American Journal of Preventive Medicine*, 43(1), 34-40. DOI: 10.1016/j.amepre.2012.02.030.
- Been, J., Nurmatov, U., Cox, B., Nawrot, T., van Schayck, C., & Sheikh, A. (2014). Effect of smoke-free legislation on perinatal and child health: A systematic review and meta-analysis. *Lancet*, 383(9928), 1549-60. DOI: 10.1016/S0140-6736(14)60082-9.
- Cahill, K., Hartmann-Boyce, J., & Perera, R. (2015). Incentives for smoking cessation. *Cochrane Database of Systematic Reviews 2015, Issue 5*. Art. No.: CD004307. DOI: 10.1002/14651858.CD004307.pub5.
- Coleman, T., Chamberlain, C., Davey, M., Cooper, S., & Leonardi-Bee, J. (2015). Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews*, 12, CD010078. DOI: 10.1002/14651858.CD010078.
- Essex, H., Parrott S., Wu, Q., Li, J., Cooper, S., & Coleman, T. (2014). Cost-effectiveness of nicotine patches for smoking cessation in pregnancy: A placebo randomized controlled trial (SNAP). *Nicotine and Tobacco Research*, 17(6), 636-42. DOI: 10.1093/ntr/ntu258.
- Hawkins, S., Baum, C., Oken, E., & Gilman, M. (2014). Association of tobacco control policies with birth outcomes. *JAMA Pediatrics*, 168(11), e142365. DOI: 10.1001/jamapediatrics.2014.2365.
- Hemsing, N., Greaves, L., O'Leary, R., Chan, K., & Okoli, C. (2012). Partner support for smoking cessation during pregnancy: A systematic review. *Nicotine and Tobacco Research*, 14(7), 767-76. DOI: 10.1093/ntr/ntr278.
- Lopez, A., Skelly, J., White, T., & Higgins, S. (2015). Does impulsiveness moderate response to financial incentives for smoking cessation among pregnant and newly postpartum women? *Experimental Clinical Psychopharmacology*, 23(2):97-108. DOI: 10.1037/a0038810.
- Nabhan, A., & Aflaifel, N. (2015). High feedback versus low feedback of prenatal ultrasound for reducing maternal anxiety and improving maternal health behaviour in pregnancy. *Cochrane Database of Systematic Reviews*, 8, CD007208. DOI: 10.1002/14651858.CD007208.pub2.
- Patnode, C., Henderson, J., Thompson, J., Senger, C., Fortmann, S., & Whitlock, E. (2015). *Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant*

women: A review of reviews for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US). Retrieved from <http://www.uspreventiveservicestaskforce.org/Home/GetFileByID/1954>

Patrick, S., Warner, K., Pordes, E., & Davis, M. (2016). Cigarette tax increase and infant mortality. *Pediatrics*, 137(1), 1-8. DOI: 10.1542/peds.2015-2901.

Tong, V., Dietz, P., Rolle, I., Kennedy, S., Thomas, W., & England, L. (2015). Clinical interventions to reduce secondhand smoke exposure among pregnant women: A systematic review. *Tobacco Control*, 24(3), 217-23. DOI: 10.1136/tobaccocontrol-2013-051200.

Ussher, M., Lewis, S., Aveyard, P., Manyonda, I., West, R., Lewis, B., ... Coleman, T. (2015). Physical activity for smoking cessation in pregnancy: Randomised controlled trial. *BMJ*, 350, h2145. DOI: 10.1136/bmj.h2145.

Other Citations

American Congress of Obstetricians and Gynecologists (ACOG). (2010). Smoking cessation during pregnancy: A clinician's guide to helping pregnant women quit smoking. Retrieved from <https://www.acog.org/-/media/Departments/Tobacco-Alcohol-and-Substance-Abuse/SCDP.pdf?la=en>

Association of State and Territorial Health Officials. (2013). Smoking cessation strategies for women before, during, and after pregnancy: Recommendations for state and territorial health agencies. Retrieved from <http://www.astho.org/prevention/tobacco/smoking-cessation-pregnancy/>

National Institute for Health and Clinical Excellence. (2010). Smoking: stopping in pregnancy and after childbirth. Retrieved from <http://www.nice.org.uk/guidance/ph26/resources/smoking-stopping-in-pregnancy-and-after-childbirth-1996240366789>

Campaign for Tobacco-Free Kids. (2016a). Smoke-free states and cities in the United States. Retrieved from <https://www.tobaccofreekids.org/research/factsheets/pdf/0332.pdf>

Campaign for Tobacco-Free Kids. (2016b). State cigarette excise tax rates & rankings. Retrieved from <http://www.tobaccofreekids.org/research/factsheets/pdf/0097.pdf>

Campaign for Tobacco-Free Kids. (2015). Local government cigarette tax rates & fees. Retrieved from <https://www.tobaccofreekids.org/research/factsheets/pdf/0304.pdf>

Centers for Medicare and Medicaid Services. (2011). *Letter to State Medicaid Directors Re: New Medicaid Tobacco Cessation Services*. Baltimore, MD: Centers for Medicare and Medicaid Services. Retrieved from <https://downloads.cms.gov/cmsgov/archiveddownloads/SMDL/downloads/SMD11-007.pdf>

Curtin, S. & Mathews, T. (2016). *Smoking prevalence and cessation before and during pregnancy: Data from the birth certificate, 2014*. National vital statistics reports; vol 65 no 1. Hyattsville, MD:

National Center for Health Statistics. Retrieved from http://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_01.pdf

North American Quitline Consortium. (2014). Quitline Services for Pregnant and Postpartum Women: Learning from Current Literature and Practice. Retrieved from http://c.ymcdn.com/sites/naquitline.site-ym.com/resource/resmgr/Issue_Papers/PregnantPostpartumIssuePaper.pdf

Melvin, C., Dolan-Mullen, P., Windsor, R., Whiteside, H., & Goldenberg, R. (2000). Recommended cessation counseling for pregnant women who smoke: A review of the evidence. *Tobacco Control, 9*, 80-84.

Siu, A. (2015). Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine, 163*(8), 622-34. DOI: 10.7326/M15-2023.

U.S. Department of Health and Human Services. (2006). *The health consequences of involuntary exposure to tobacco smoke: A report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Retrieved from <http://www.surgeongeneral.gov/library/reports/secondhandsmoke/fullreport.pdf>

Washington State Department of Health. (2015). Smoking cessation during pregnancy: guidelines for intervention. Retrieved from http://here.doh.wa.gov/materials/guidelines-smoking-pregnancy/13_PregSmok_E15L.pdf

World Health Organization. (2013). WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy 2013. Retrieved from http://apps.who.int/iris/bitstream/10665/94555/1/9789241506076_eng.pdf?ua=1

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.

DRAFT

APPENDIX A. GRADE INFORMED FRAMEWORK–ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable of benefits and undesirable effects harms	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. <u>An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.</u>
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 <u>in the absence of likely cost offsets</u> —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 issues 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~~concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality balance of evidence, cost benefits and harms, resource allocation, and values and preferences, and other factors.

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

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality balance of evidence, cost benefits and harms, resource allocation, and values and preferences, and other factors, but ~~is not confident~~further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality balance of evidence benefits and harms, cost and resource allocation, and values and preferences, and other factors, but ~~is not confident~~further research or additional information could lead to a different conclusion.

Quality or strength of evidence **Confidence in estimate** rating across studies for the **treatment** **intervention/outcome**¹

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 **of effect**: 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 **of effect** 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 **of effect**: 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.

¹ Includes risk of bias, precision, directness, consistency and publication bias

APPENDIX B. GRADE EVIDENCE PROFILE

Pharmacotherapy Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Pregnancy complications							
Miscarriage 4	RCTs	Low	No	No	No	No	●●●●
Preterm birth 6	RCTs	Low	No <u>Not serious</u>	No <u>Not serious</u>	Yes <u>Serious</u>	No <u>None</u>	<u>Moderate quality</u> ●●●○
			<u>Not serious</u>	<u>Not serious</u>	<u>Serious</u>	<u>None</u>	<u>Moderate quality</u> ●●●○
Low birth weight							
6	RCTs	Low	No <u>Not serious</u>	No <u>Not serious</u>	No <u>Serious</u>	None	●●●● <u>Moderate quality</u> ●●●○
Perinatal/infant death							
4	RCTs	Low	No <u>Not serious</u>	No <u>Not serious</u>	Yes <u>Serious</u>	None	<u>Moderate quality</u> ●●●○
Tobacco abstinence during pregnancy							
<u>All trials</u> 8	<u>RCTs</u>	<u>Low</u>	No <u>Not serious</u>	No <u>Not serious</u>	No <u>Not serious</u>	No <u>None</u>	●●●● <u>High quality</u> ●●●●
<u>Placebo Controlled</u> <u>6</u>	RCTs	Low	<u>Not serious</u>	<u>Not serious</u>	<u>Serious</u>	<u>None</u>	<u>Moderate quality</u> ●●●○
Tobacco abstinence after pregnancy							

Pharmacotherapy Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
3	RCTs	Low	No <u>Not serious</u>	No <u>Not serious</u>	No <u>Serious</u>	<u>None</u>	●●●● <u>Moderate quality</u> ●●●○

Behavioral Interventions Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Pregnancy complications							
Preterm birth 14	RCTs and cluster-randomized trials	Moderate	No <u>Not serious</u>	No <u>Not serious</u>	No <u>Not serious</u>	<u>None</u>	<u>Moderate quality</u> ●●●○
Low birth weight							
42 <u>14</u>	RCTs and cluster-randomized trials	Moderate	No <u>Not serious</u>	No <u>Not serious</u>	— <u>Not serious</u>	<u>None</u>	<u>Moderate quality</u> ●●●○
Perinatal/infant death							
Stillbirth 7	RCTs and cluster-randomized trials	Moderate	No <u>Not serious</u>	No <u>Not serious</u>	<u>Yes</u> <u>Serious</u>	No <u>None</u>	●●●○ <u>Low quality</u> ●●●○
Neonatal Death 4		Moderate	<u>Not serious</u>	<u>Not serious</u>	<u>Serious</u>	<u>None</u>	<u>Low quality</u> ●●●○
Tobacco abstinence during pregnancy							
8 <u>7</u>	RCTs and cluster-randomized trials	Moderate	No <u>Not serious</u>	No <u>Not serious</u>	No <u>Not serious</u>	<u>None</u>	<u>Moderate quality</u> ●●●○

Behavioral Interventions Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Tobacco abstinence after pregnancy							
2	RCTs and cluster-randomized trials	Moderate	No <u>Not serious</u>	No <u>Not serious</u>	No <u>Not serious</u>	<u>None</u>	<u>Moderate quality</u> ●●●○

DRAFT

Ultrasound with High Feedback Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Pregnancy complications							
0							N/A
Low birth weight							
0							N/A
Perinatal/infant death							
0							N/A
Tobacco abstinence during pregnancy							
1	RCT	Moderate	Unknown	Not serious	Serious	None	Low quality ●●○○
Tobacco abstinence after pregnancy							
0							N/A

Financial Incentives Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Pregnancy complications							
0							N/A
Low birth weight							
0							N/A
Perinatal/infant death							
0							N/A
Tobacco abstinence during pregnancy							
8	RCTs	Low to moderate	No Not serious	No Not serious	No Not serious	None	Moderate quality ●●●○
Tobacco abstinence after pregnancy							
8	RCTs	Low to moderate	No Not serious	No Not serious	No Not serious	None	Moderate quality ●●●○

Partner Support Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Pregnancy complications							
0							N/A
Low birth weight							
0							N/A
Perinatal/infant death							
0							N/A
Tobacco abstinence during pregnancy							
4	Mix of RCTs and observational studies	Moderate to High	Yes <u>Serious</u>	Ne <u>Not serious</u>	Ne <u>Not serious</u>	None	<u>Low quality</u> ●○○○
Tobacco abstinence after pregnancy							
0							N/A

Secondhand Smoke Interventions Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Pregnancy complications							
Preterm birth 1	RCT	High	N/A	Ne <u>Not serious</u>	Ne <u>Not serious</u>	None	<u>Very low quality</u> ●○○○
Low birth weight							
1	RCT	High	N/A	Ne <u>Not serious</u>	Ne <u>Not serious</u>	None	<u>Very low quality</u> ●○○○
Perinatal/infant death							
0							N/A
Tobacco abstinence during pregnancy							
0							N/A
Tobacco abstinence after pregnancy							
0							N/A

DRAFT

APPENDIX C. METHODS

Scope Statement

Populations

Women during pregnancy and the postpartum period

Population scoping notes: Includes all forms of tobacco, including e-cigarettes

Interventions

Screening for tobacco use, pharmacotherapy, behavioral interventions (telephonic, in person, individual, group), Internet based interventions, and multisector interventions such as policy, systems, and environmental change

Intervention exclusions: None

Comparators

No care, usual care, other studied interventions

Outcomes

Critical: Pregnancy complications, low birth weight, perinatal/infant death

Important: Abstinence from tobacco during pregnancy, long-term tobacco abstinence

Considered but not selected for the GRADE table: Maternal exposure to secondhand smoke, health benefits to mothers

Key Questions

KQ1: What interventions are most effective and most cost-effective to

- a. Reduce tobacco-related perinatal/infant morbidity and mortality?
- b. Reduce tobacco use prevalence in pregnant women?
- c. Sustain tobacco abstinence after delivery among women who quit tobacco use during pregnancy?

KQ2: Does effectiveness vary by socioeconomic factors such as race, ethnicity, income and educational attainment?

KQ3: What models of care would allow these interventions to be implemented most effectively and cost-effectively?

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 tobacco cessation and pregnancy or pregnant. Searches of core sources were limited to citations published after 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.
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 since 2010. The search was limited to publications in English. For each intervention, a MEDLINE® (Ovid) search was conducted to identify randomized control trials published since the end of the search period for the most recent systematic review.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice and public health 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
ICD-10 Diagnosis Codes	
O99.330	Smoking (tobacco) complicating pregnancy, unspecified trimester
O99.331	Smoking (tobacco) complicating pregnancy, first trimester
O99.332	Smoking (tobacco) complicating pregnancy, second trimester
O99.333	Smoking (tobacco) complicating pregnancy, third trimester
O99.334	Smoking (tobacco) complicating childbirth
O99.335	Smoking (tobacco) complicating the puerperium
P96.81	Exposure to environmental tobacco smoke in the perinatal period
F17.200	Nicotine dependence, unspecified, uncomplicated
F17.201	Nicotine dependence, unspecified, in remission
F17.210	Nicotine dependence, cigarettes, uncomplicated
F17.211	Nicotine dependence, cigarettes, in remission
F17.220	Nicotine dependence, chewing tobacco, uncomplicated
F17.221	Nicotine dependence, chewing tobacco, in remission
F17.290	Nicotine dependence, other tobacco product, uncomplicated
F17.291	Nicotine dependence, other tobacco product, in remission
Z71.6	Tobacco abuse counseling
Z87.891	Personal history of nicotine dependence
ICD-10-CM (Procedure Codes)	
HZ90ZZZ	Pharmacotherapy for substance abuse treatment, nicotine replacement
CPT Codes	
99406	Smoking and tobacco cessation counseling visit; intermediate, greater than 3 minutes up to 10 minutes
99407	Smoking or tobacco cessation counseling visit, intensive, greater than 10 minutes
HCPCS Codes	
G0436	Smoking and tobacco cessation counseling visit for the asymptomatic patient; intermediate, greater than 3 minutes, up to 10 minutes
G0437	Smoking and tobacco cessation counseling visit for the asymptomatic patient; intensive, greater than 10 minutes

Note: Inclusion on this list does not guarantee coverage

HERC Coverage Guidance – Tobacco Cessation During Pregnancy

Disposition of Public Comments

Table of Contents

Commenters.....	1
Public Comments	1

Commenters

Identification	Stakeholder
A	Janice Kay, RN, Umpqua Health Alliance <i>[Submitted May 10, 2016]</i>

Public Comments

ID/#	Comment	Disposition
A1	I think (gut feel) that the “Prenatal ultrasound with high feedback around smoking impact on fetus” would make an important and realistic impact on the mothers who are pregnant and still smoking. I hope this highly recommended.	<i>Thank you for your comments. The current evidence supports a weak recommendation for prenatal ultrasound with high feedback around smoking impacts on the fetus.</i>

Section 4.0

CG - Long-Acting Reversible Contraceptives LARC

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: TIMING OF LONG-ACTING REVERSIBLE CONTRACEPTIVE (LARC) PLACEMENT

DRAFT for 6/2/2016 EbGS meeting materials

HERC Coverage Guidance

Immediate postpartum and postabortion placement of a long-acting reversible contraceptive (LARC) (implant or intrauterine device) is recommended for coverage (*strong recommendation*).

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description*.

RATIONALE FOR DEVELOPMENT OF COVERAGE GUIDANCES AND MULTISECTOR INTERVENTION REPORTS

Coverage guidances and multisector intervention reports are developed to inform coverage recommendations for public and private health plans in Oregon as they seek to improve patient experience of care, population health and the cost-effectiveness of health care. In the era of the Affordable Care Act and health system transformation, reaching these goals requires a focus on population-based health interventions from a variety of sectors as well as individually-focused clinical care.

HERC selects topics for its reports to guide public and private payers 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 implementation or practice
- Represents high costs, significant economic impact
- Topic is of high public interest

Our reports are based on a review of the relevant research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be cost-effective ways to prevent, treat or manage disease at a population level. For some conditions, the HERC has reviewed evidence and identified effective interventions, but has not made recommendations, as many of these policies are implemented in settings beyond traditional healthcare delivery systems.

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.

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Unintended Pregnancy (Critical outcome)	<p>Postabortion IUD: In the intention to treat analysis, the risk of pregnancy at 6 months following an abortion was nearly three-fold higher for women randomized to delayed receipt of an IUD (3/406 randomized to immediate vs. 11/472 randomized to delayed); however, this difference based on the RR did not reach meet statistical significance.</p> <p>Delayed IUD: 233/10,000 (2.3%)</p> <p>Immediate IUD: 74/10,000 (0.74%)</p> <p>ARD 1.59%, NNT 63</p> <p>For 1000 patients treated, 16 fewer unintended pregnancies</p> <p>(RR 0.37; (95% CI 0.12-1.14)</p> <p>●●●○ (Moderate confidence, based on 3 RCTs, N=878 women)</p> <p>In reviewing the original source data there were only total reviewing the 14 unintended pregnancies from an as-treated perspective, of the 671 women ultimately receiving an IUD only 1 experienced a pregnancy following an expulsion of her IUD (0.15%). The remaining 13 pregnancies occurred in the 207 women who never received an IUD (6.3%).</p> <p>each RCT from an as-treated perspective, the 3 observed pregnancies in the immediate IUD arm occurred in women who did not actually receive an IUD as they were allocated, either after declining placement following randomization (2 cases) or bleeding following abortion (1 case). In the delayed arm, 5 pregnancies occurred in women not using an IUD (i.e. did not present for follow up visit, but provided data at 6 months), 1 in a woman who experienced an expulsion of her IUD and then opted for contraceptive pills, and for the remaining 5, the authors do not mention the IUD status.</p>

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
	<p>In the 3 included RCTs, attendance at the follow-up visit for the delayed arm ranged from 33% to 70%, with nearly all women who did attend a return visit having an IUD placed. Real-world attendance at a follow-up abortion visit is reportedly low (25%-60%).</p> <p>●●●○ (Moderate certainty of at least equivalent unintended pregnancy rates; based on 3 RCTs of 878 women)</p> <p><u>Postpartum IUD</u>: The identified systematic review of RCTs did not provide aggregate data on unintended pregnancy. No repeat pregnancies were reported in the 2 RCTs monitoring for repeat pregnancies.</p> <p>●●○○ (Low confidence because no unintended pregnancies were observed, certainty of at least equivalent unintended pregnancy rates; based on 2 RCTs, N=of 192 women)</p> <p><u>Implants</u>: No systematic reviews or RCTs were identified addressing immediate postpartum or postabortion implant use and unintended pregnancy.</p>
<p>Abortion (Critical outcome)</p>	<p><u>IUDs</u>: None of the identified systematic reviews reported on abortion rates in the follow-up period.</p> <p><u>Implants</u>: No systematic reviews or RCTs were identified addressing implants and abortion rates.</p>
<p>Presence of LARC at one year (Important outcome)</p>	<p>None of the identified systematic reviews reported on LARC presence at one year but all reported on presence of an IUD at 6 months based on from an intention to treat analyses perspective.</p> <p>Note that in the numbers reported here, the denominator for LARC presence is the total number of women randomized to either arm (i.e. immediate or delayed), with the numerator consisting of women continuing with an IUD in place at 6 months (those who received an IUD and still had it at 6 months and and women who experienced an expulsion and underwent reinserted reinsertion of an IUD the device).</p> <p><u>Postabortion IUD</u>: Compared to women randomized to delayed IUD insertion following abortion or uterine evacuation for incomplete spontaneous abortion, those in the immediate arm were more likely to have an IUD in place at 6 months</p>

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
	<p>(260/406 randomized to immediate vs. 219/472 for delayed).</p> <p>Delayed IUD 4640/10,000 (46.4%) Immediate IUD 6400/10,000 (64.0%) ARD=17.6%, NNT=6 For 1000 patients treated, 167 more have an IUD in place at 6 months 260/406 randomized to immediate vs. 219/472 for delayed; RR 1.4; (95% CI 1.24-1.58) ●●●○ (Moderate confidence, based on 3 RCTs, N=878)</p> <p>In the largest trial of 575 women, accounting for 80% of the pooled estimate, 100% of women randomized to the immediate arm received their IUD; vs. 71% of the delayed group (representing all women who returned for a post-abortion visit by 6 weeks) received an IUD. At 6 months, 92.3% of women in the immediate group still had an IUD vs. 76.6% of the delayed group; (RR 1.20; (95% CI 1.11-1.31) for this single trial. ●●●○ (Moderate certainty of greater LARC use at 6 months with immediate insertion, based on 3 RCTs of 878 women)</p> <p><u>Postpartum IUD</u>: Compared to women randomized to delayed IUD insertion, those randomized to immediate insertion were more likely to have an IUD in place at 6 months (97/120 for immediate vs. 83/123 for delayed insertion).</p> <p>Delayed 6747/10,000 (67.4%) Immediate 8083/10,000 (80.8%) ARD=13.3%, NNT=8</p> <p>For 1000 patients treated, 125 more continue to have an IUD in place at 6 months (97/120 for immediate vs. 83/123 for delayed insertion; OR 2.04; (95% CI=1.01-4.09) ●●●○ (Moderate confidence, certainty of greater LARC use at 6 months following immediate insertion, based on 4 RCTs, N= of 243 women)</p> <p><i>For both postabortion and postpartum insertion, higher loss to follow-up in the delayed group would bias the result against showing a benefit in these studies.</i></p>

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
	<p><u>Implants</u>: No systematic reviews or RCTs were identified addressing implants and presence of LARC at one year or any other follow-up period.</p>
<p>Need for alternate or replacement contraception (e.g., expulsion of IUD, elective, indicated removal of device) (Important outcome)</p>	<p><u>Postabortion IUD Expulsion</u>: IUD expulsions by 6 months were more common in those randomized to immediate postabortion insertion (<u>18/406 for those randomized to immediate insertion vs. 8/472 for delayed</u>). <u>Delayed IUD 169/10,000 (1.7%)</u> <u>Immediate IUD 443/10,000 (4.4%)</u> <u>ARD=2.74%, NNT=37</u> <u>For 1000 patients treated, 27 more experience expulsion per 1000 in immediate group vs. 16 per 1000 in delayed group;</u> (RR 2.64; 99% CI 1.16-6.0)- <u>●●●○ (Moderate confidence, certainty of increased expulsion with immediate insertion postabortion, based on 3 RCTs, N=of 878-women)</u></p> <p><u>Postabortion IUD Removal</u>: Elective or indicated removals of IUDs at 6 months were similar for women undergoing immediate postabortion placement compared to delayed insertion (<u>20/362 for those randomized to immediate vs. 12/428 for delayed</u>). <u>Delayed IUD 280/10,000 (2.8%)</u> <u>Immediate IUD 552/10,000 (5.5%)</u> <u>ARD 2.72%, NNT=37</u> <u>For 1000 patients treated, 27 more remove their IUD device by 6 months with immediate placement</u></p> <p>RR 2.01; (95% CI 0.99-4.06) <u>●●●○ (Moderate confidence, based on 2 RCTs, N=790)</u></p> <p>The RR of 2.01 is misleading because many women in the delayed group never got an IUD and so could not have one removed. For example, in the largest trial for women who actually received an IUD, including 575 women and accounting</p>

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
	<p>for over 90% of the estimate for this intention to treat analysis, 16/258 (6%) in the immediate group requested removal vs. 11/222 (5%) in the delayed group; \downarrowRR 0.98 (95% CI 0.94-1.03).</p> <p>●●●○ (Moderate certainty of equivalent removal rates with immediate placement, based on 2 RCTs of 790 women)</p> <p><u>Postpartum IUD Expulsion</u>: Expulsions by 6 months were more common in those randomized to immediate insertion (19/113 for those randomized to immediate vs. 3/97 for delayed).</p> <p><u>Delayed 309/10,000 (3.1%)</u> <u>Immediate 1681/10,000 (16.8%)</u> <u>ARD=13.7%, NNT=8</u> <u>For 1000 patients treated, 125 more experience expulsion</u> <u>OR 4.89; (95% CI 1.47-16.32)</u> ●●●○ (Moderate <u>confidence</u> certainty of increased expulsions with immediate insertion, based on 4 RCTs, <u>N= of 210 women</u>)</p> <p><u>Postpartum IUD Replacement</u>: When expulsion occurred after post-cesarean placement, replacement was more common for those undergoing immediate IUD placement (3 out of 4 expulsions in immediate group vs. 0 out of 1 in the delayed group, statistical analysis not reported). No data are available about <u>IUDs placed after post</u>vaginal delivery. ●○○○ (Very low <u>confidence</u> certainty of LARC continuation after expulsion, based on one fair quality RCT, <u>N=112</u>)</p> <p><u>Implants</u>: No systematic reviews or RCTs were identified addressing implants and need for alternate/replacement contraception.</p>
<p>Harms (Important outcome)</p>	<p><u>Important harms specific to IUD insertion include uterine perforations and infections.</u></p> <p><u>Postabortion IUD Perforation</u>: No uterine perforations were observed in women randomized to immediate or delayed IUD insertion following first trimester abortion. ●○○○ (Very low <u>confidence</u> certainty of equivalent perforation risk for immediate vs delayed based on no observed perforations in 1 fair quality RCT, <u>N= of 575 women</u>)</p>

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
	<p><u>Postabortion IUD infection</u>: Rates of upper genital tract infections were similar for women undergoing immediate postabortion IUD insertion compared to delayed insertion (5/406 for those randomized to immediate vs. 6/472 for delayed).</p> <p>Delayed IUD 127/10,000 (1.3%) Immediate IUD 123/10,000 (1.2%) (130/10,000 per in 1000 in both groups (1.3%)) ARD=0.04%; NNH=2520 For 1000 patients treated, upper genital tract infection was rare and not statistically different between the groups OR 1.0; (95% CI 0.32-3.14);</p> <ul style="list-style-type: none"> ●●●○ (Moderate confidence certainty of equivalent infection rates, based on 3 trials RCTs, N=of 878 women) <p><u>Postpartum IUD infections</u>: Rates of upper genital tract infections were rare in both groups (no statistical analysis provided).</p> <ul style="list-style-type: none"> ●○○○ (Very low confidence certainty of equivalent infection rates, based on 2 case reports in on case reports 4 RCTs, N=243) <p><u>Implants</u>: No systematic reviews or RCTs were identified addressing implants and harms.</p>

Balance of benefits and harms:

While our data do not show a reduced risk of unintended pregnancy from immediate placement, it is well-established that LARCs are among the most effective forms of contraception, and the unintended pregnancies in the included intention-to-treat studies occurred almost exclusively in women who failed to return for their follow-up appointments; the lack of statistical significance is explained by differential loss to followup. The only “harm” shown by this evidence is an increased risk of IUD expulsion, which is easily remedied and usually without morbidity. Thus, the balance is in favor of immediate placement.

Resource Allocation: The costs of unintended pregnancy are significant. Effective contraception is cost-saving (not just cost-effective). No specific data from RCTs are available to address the impact on total costs based on the timing of insertion alone. However, the evidence supports that immediate postpartum or postabortion placement results in higher LARC use at 6 months. One could logically follow that there would be a decreased rate of unintended pregnancies and abortions; this is consistent with a broad literature on LARC effectiveness. Based on

this, increased LARC use from immediate placement would be cost-saving, and a series of economic analyses support this [conclusion](#).

Economic models on postabortion IUD insertion estimate for every 1000 women undergoing placement, 400 pregnancies, 180 deliveries, and 160 abortions will be averted over 5 years. The cost savings could be significant, with \$810 in direct medical savings in the first year and \$4,296 in savings (including insurance and social program costs) over 5 years [per woman](#).

For post-partum insertion of IUDs, one negative cost impact is the higher associated expulsion rate (17% vs 3%), however, economic models demonstrate cost-savings even up to an expulsion rate of 30%. Over 2 years, postpartum IUD insertion is estimated to provide a [direct medical](#) cost savings of \$282,540 per 1,000 women.

Economic models of immediate implant insertion are estimated to save \$1,263 per patient over 12 months. On a population level, cost savings of an immediate postpartum implant program for Colorado Medicaid was estimated at \$546,950, \$2.46 million, and \$4.53 million at 12, 24, and 36 months, respectively.

Values and Preferences: Reproductive life planning enhances the ability of women who desire contraception to achieve their life, family, and career goals. Most women desire to control their fertility and time their pregnancies. When women who desire contraception are presented with all contraceptive options, over 70% will select a LARC method, including teens. When women select their preferred contraceptive method, continuation rates across all methods are higher. Immediate insertion of LARC following a birth or abortion is generally acceptable to women and may be preferable. Requiring multiple visits to obtain a LARC method decreases use. Most women would prefer to avoid additional procedures (i.e. laparoscopy for intraabdominal device following a uterine perforation or replacement of expelled IUD), however, the rates of perforation are [equivalent-similar](#) and the absolute increase in expulsion when insertion is immediately postpartum may be acceptable to many women because of convenience and the immediate decrease in risk of unplanned pregnancies.

Other Considerations: Information from non-randomized studies estimates that LARC devices are 20 times more effective at preventing unintended pregnancy than contraceptive pills, patches, rings and injections. Continuation rates for LARC devices are also greater than pills, patches, rings, and injection.

Evaluated efforts to expand LARC use (e.g., Colorado, Iowa, St. Louis) are associated with significant reductions in teen pregnancy and abortion.

The CDC's Medical Eligibility Criteria recommends LARC devices as suitable for the vast majority of reproductive aged women. Since 2010, the CDC has endorsed immediate postpartum and postabortion LARC use and supports LARC methods for breastfeeding women.

Missed opportunities for contraception are significant postpartum and postabortion. 30-40% of insured women do not attend a postpartum visit; 40-75% do not attend a postabortion visit, thus increasing the risk of unplanned pregnancy, abortion, or unmet contraceptive needs.

Women who are actively breastfeeding were found to have a 6-fold increased risk of uterine perforation with delayed IUD insertion based on observational prospective data of over 6061,000 women in Europe.

Rationale: While there is strong evidence that LARC use reduces unintended pregnancies and abortions, there is not **strong** direct randomized evidence of LARC placement (immediate postpartum or postabortion vs delayed insertion) resulting in lowering rates of subsequent unintended pregnancy or abortion outcomes [based on intention to treat analysis](#). ~~although there is a trend towards decreased unintended pregnancies with immediate postabortion IUD placement.~~ There is direct evidence that immediate postpartum and postabortion IUD insertion results in higher LARC use rates at 6 months, and logically this translates to lower rates of unintended pregnancy and abortion. While there is an increased rate of IUD expulsion with immediate postpartum insertion, IUD use is still higher at 6 months and economic analyses strongly favor immediate insertion. There is also observational evidence based on a study of 6061,000 women that a 6-fold risk of uterine perforation exists in actively breastfeeding women with delayed insertion compared to immediate insertion. Immediate postpartum LARC is a highly cost-saving strategy even considering IUD expulsion rates, and with the possibility of avoidance of uterine perforation. For implants, while there is no RCT evidence about the differences in pregnancy outcomes based on immediate versus delayed implant placement, use of implants is recommended by the CDC immediately postabortion and postpartum, and the disadvantages associated with an increased risk of an IUD expulsion do not exist for implants.

The strong recommendation for coverage for either type of LARC (IUD or implant) is based on existing evidence and guidelines on the benefits of LARC, lack of significant harms for immediate placement, high cost savings associated with immediate placement, and strong values and preferences.

Recommendation: Immediate postpartum and postabortion placement of LARC (implant or intrauterine device) is recommended for coverage (*strong recommendation*).

*The Quality of Evidence rating was assigned by the primary evidence sources, except where indicated, not the HERC Subcommittee.

Note: GRADE framework elements are described in Appendix A. The GRADE Evidence Profile for these outcomes is provided in Appendix B.

EVIDENCE OVERVIEW

Clinical background

While women have many contraceptive options, intrauterine devices (IUDs) and contraceptive implants – otherwise known as long-acting reversible contraception (LARC) – are 20 times more effective at preventing pregnancy than pills, patches, or rings (Winner, et al., 2012). Because of their high effectiveness, LARC methods are associated with significant reductions in the numbers of unintended pregnancies and abortions (Peipert, et al., 2012; Winner, et al., 2012). The Medical Eligibility Criteria (MEC) published by the Centers for Disease Control and Prevention (CDC) lists LARC devices as safe for the majority of women, including those with common health conditions (e.g., hypertension, migraines, obesity, postabortion, postpartum, breastfeeding). [These LARC options, which include both hormonal and non-hormonal devices](#), have few side effects and are suitable for teens, nulliparous and parous women ~~and include hormonal or non-hormonal options~~ (ACOG, 2015b; CDC 2010, 2012).

Despite LARC's superior effectiveness, LARC use is relatively low among women using contraception in the United States (U.S.). Rates of LARC use from the National Survey of Family Growth (NSFG) show continued growth in the use of LARC, largely driven by increasing IUD use. The most recent NSFG reports a five-fold increase in LARC use from 1.5% in 2002 to 7.2% in 2011-2013; with nearly 11.1% of women in the survey aged 25-34 opting for a LARC device (Branum & Jones, 2015). Increasing LARC use, even by as much as 10% for women 20-29, would be estimated to save nearly \$288 million per year in the U.S. in total costs related to unintended pregnancy (Trussell, et al., 2013).

[The CDC has identified preventing unintended pregnancy as a part of its 6|18 Initiative ~~aims to address six common and costly health conditions by promoting 18 evidence-based interventions. by increasing their coverage, access, utilization and quality. Preventing unintended pregnancy is one of the core six core efforts.~~ The three proposed payer interventions for preventing unintended pregnancy are include 1\) reimbursing for the full range of contraceptive services including actual costs of LARC, 2\) reimbursing for immediate postpartum LARC insertion by unbundling from obstetric global services, and 3\) removing administrative and logistical barriers to LARC \(CDC, 2015\).](#)

The body of literature on the effectiveness and safety of LARC contains many large observational studies on the impact of LARC provision on unintended pregnancy, abortion, and teen pregnancies. The Contraceptive CHOICE project offered no-cost contraception, including LARC devices, to 9,256 women aged 14 to 45 enrolled in a prospective cohort study investigating the population-based impact of eliminating contraception cost-barriers for women on unintended pregnancy, teen pregnancy, abortion, and rates of repeat abortion in St. Louis, compared to Missouri overall. Contraceptive options were presented to women in order of efficacy (i.e. LARC first), with all side effects mentioned, and women then selected their preferred method. When presented with this information the majority of enrollees opted for LARC devices (75%), including teens (70%).

Women opting for pills, patches or the ring were 20 times more likely to experience an unintended pregnancy (Winner, et al., 2012). The teen birth rate for those in the CHOICE cohort was 6.3 per 1000 compared to 34.3 per 1000 in the U.S. The abortion rate in St. Louis during the study period was half the state average for Missouri (Peipert, et al., 2012). A sub-analysis of teens (aged 15-19) found dramatically

lower rates of pregnancy, birth, and abortion in the CHOICE cohort compared to national averages despite the cohort consisting of women at higher risk of unintended pregnancy based on age and demographic factors (Secura, et al., 2014). The CHOICE cohort observed high continuation rates for LARC use over three years, with and users of non-LARC methods were three times more likely to discontinue their initial method over the following three years (Diedrich, et al., 2015).

The Colorado Family Planning Initiative, a five-year project funded by the Susan Thompson Buffett foundation expanded LARC access to Title X-funded agencies across the state by providing funds to put LARC stock on shelves, offer provider trainings, and offer no-cost contraception for Title X-funded clinics. Across participating counties, use of LARC increased from 5% to 19% among 15 to 24 year old women with a 29% decrease from expected fertility rates for 15 to 19 year-olds, and 14% decrease for 20 to 24 year olds. Abortion rates also decreased, 34% and 18% respectively, for these age groups (Ricketts, Klingler, & Schwalberg, 2014). Iowa also observed reductions in abortion rates (from 8.7 per 1000 to 6.7) after LARC use increased from 1% up to 15% through Medicaid expansion and the Susan Thompson Buffett initiative (Biggs, et al., 2015)

Reducing cost-barriers is a key step in expanding LARC access; however, many outpatient settings require multiple appointments and women desiring LARC may be lost to follow-up. Providing LARC in the immediate postpartum or postabortion time period can expand access and prevent loss to follow-up. Rates of attendance at postpartum visits are not optimal, with 2014 national estimates reporting that 76% of privately insured and 62% of publicly insured women attended their postpartum checks (National Committee for Quality Assurance, 2015). Additionally, immediate postpartum IUD insertion may be safer for women than waiting until the postpartum visit. In a large multinational observational study of over 61,000 women in Europe, actively breastfeeding at the time of insertion was associated with a six-fold increased risk of perforation (RR 6.1, 95% CI 3.9-9.6) (Heinemann, Reed, Moehner, & Minh, 2015).

Despite concerns for hormone-mediated myometrial changes in pregnancy, rates of perforation following elective termination are low. In an RCT of 575 women randomized to immediate or delayed IUD placement after first-trimester elective termination, Bednarek and colleagues reported no perforations during 6 months of follow up after insertion (Bednarek, et al., 2011).

National estimates of attendance at a postabortion follow-up visit are low (25-68%) as women travel long distances to receive abortion services, may be concerned about costs related to IUD insertion, or do not have time to return for a separate visit (Bednarek, et al., 2011; Stanek, et al., 2009).

In addition to follow-up barriers, reimbursement for immediate postabortion or postpartum LARC insertion varies by insurer and state. Coverage of LARC provision immediately following an abortion varies by insurance carrier, with Medicaid waivers and Title X programs covering provision, while private insurers require a separate visit. Increasing access to LARC by expanding coverage to include women immediately following an abortion or in the immediate postpartum period eliminates the need for return visits and potential loss to follow-up. Providing increased LARC access in the immediate postpartum or postabortion period may be safer, and reduce unintended pregnancy rates, rapid repeat pregnancies, or repeat abortions in line with findings from outpatient insertion LARC trials (Peipert, et al., 2012; Winner, et al., 2012).

Technology description

Intrauterine Devices

Mirena[®] is a 52mg levonorgestrel-releasing intrauterine system (52 mg LNG-IUS) approved for 5 years of continuous use. The device is a 32x32mm plastic T-shape with monofilament polyethylene strings. The pregnancy rate for Mirena[®] is 0.2 in 100 women with 80% of women continuing at one year (Trussell, 2011).

Liletta[®], approved by the (U.S. Food and Drug Administration (U.S. FDA) in 2015, is also a 52mg levonorgestrel-releasing system (LNG-IUS); however, it is approved for only 3 years of continuous use at the present time (U.S. FDA, 2015). The manufacturer, Actavis, continues to evaluate this device and is anticipating [approval for a](#) similar duration of effectiveness as Mirena[®].

Skyla[®] is a 13.5mg levonorgestrel-releasing system (13.5mg LNG-IUS) approved by the U.S. FDA in 2013 (U.S. FDA, 2013). The duration of action is 3 years. The device is smaller than the Mirena[®] (28x30mm versus 32x32mm), [and comes with a smaller diameter device inserter \(3.8mm versus 4.75mm for the Mirena[®]\), and has been targeted to women who have a smaller uterus.](#)

Paragard[®], a copper (Cu) T380A IUD, has been on the U.S. market since approval in 1984. This hormone-free device is approved for 10 years of use in the U.S. Paragard[®] is as effective as permanent sterilization with a failure rate of 0.8 in 100 women for the first year and 1.9 per 100 women over 10 years. After the first year of use, an average of 78% of women continues with this method. Reasons for discontinuation include heavy menstrual bleeding and pain (ACOG, 2015b; U.S. FDA, 2014).

All IUDs and implants can be removed [when fertility is desired, and](#) at the end of their approved duration [followed by](#) and immediately [replaced](#) with a new device.

Hormonal Implant

Nexplanon[®] replaced Implanon[®] in 2011. Both are etonogestrel-releasing implants that are injected under the skin, typically in the inner arm about 10 cm above the elbow crease. Nexplanon[®] is radiopaque, a change from the Implanon[®] device, to assist in confirming location on imaging studies. The Nexplanon[®] insertion system was also improved over the older Implanon[®] [system device](#). Etonogestrel is highly effective at preventing pregnancy through changes in the hypothalamic-pituitary-ovarian axis that suppress ovulation; 0.05% of women with this device will become pregnant in the first year after insertion. Risks from insertion under the skin of the inner upper arm include bleeding, infection, and bruising or hematoma. After the first year, 84% of women continue with this method. Side effects prompting discontinuation include irregular bleeding, headache, and weight gain (U.S. FDA, 2014; ACOG, 2015b).

Indications

Long-acting reversible contraception devices are indicated for women desiring to avoid pregnancy. Additionally, the Mirena[®], a levonorgestrel releasing intrauterine system (LNG-IUS), is also [FDA](#) approved for the treatment of heavy menstrual bleeding (i.e. menorrhagia) (U.S. FDA, 2009).

The Centers for Disease Control and Prevention (CDC) publish two relevant documents on contraceptive use and practice. The Selected Practice Recommendations for Contraceptive use (SPR), published in 2013, and the Medical Eligibility Criteria (MEC), last updated in 2012. The SPR includes clinical guidance on initiation, follow-up, and side-effect management for all contraceptive methods (CDC, 2013). The MEC provides eligibility criteria for the initiation or continuance of all contraceptive methods, including LARC using four categories: no restriction (category 1), advantages generally outweigh theoretical or proven risk (category 2), theoretical or proven risk usually outweigh the advantages (category 3), or unacceptable health risk, method not to be used (category 4) (CDC, 2012).

The SPR and MEC state that LARC is appropriate for the vast majority of reproductive-aged women, including teens and nulliparous women. They are suitable contraceptive methods for patients with many common health conditions including obesity, controlled hypertension, and diabetes. The copper IUD is often the only option available for women desiring effective contraception without hormones or for whom hormonal contraception is contraindicated.

Intrauterine Devices

The SPR and the MEC support immediate postpartum and postabortion IUD use. The MEC lists IUDs as safe for immediate use following first and second trimester abortions except in the setting of a septic abortion (category 4). Postpartum IUD insertion in the setting of puerperal sepsis also poses an unacceptable health risk for women (category 4).

Situations where any intrauterine system (copper or levonorgestrel) would pose an unacceptable health risk or where the risk outweighs benefits (category 4 or 3 on the MEC, respectively) are rare. Appendix E provides links to the MEC for those interested in additional information.

Hormonal Implant

The MEC categorizes the implant as safe (category 1 or 2) across nearly all conditions. Theoretical or proven risks outweigh the many benefits (category 3) only in rare circumstances. Appendix E provides links to the MEC for those interested in additional [and more specific](#) information [for particular conditions](#).

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 C.

1. What is the comparative effectiveness of offering immediate postpartum or postabortion placement of a long-acting reversible contraceptive?
2. What are the harms of immediate postpartum or postabortion placement of a long-acting reversible contraceptive?

Critical outcomes selected for inclusion in the GRADE table are unintended pregnancies and abortions. Important outcomes selected for inclusion in the GRADE table are presence of LARC at one year, need for alternate/replacement contraception, and harms.

Contextual Question

1. What payer and provider practices and policies promote effective use of LARC?

Evidence review

Intrauterine Devices

Two Cochrane systematic reviews (SR) (Lopez, et al., 2015; Okusanya, Oduwole, & Effa, 2014) identified in the core source search address the use of IUDs in the immediate postpartum or postabortion period.

A Cochrane SR protocol on immediate versus delayed postpartum insertion of a contraceptive implant was published in October 2015 and is still in process (Sothornwit, et al., 2015). Abstract review of the published reference list for the protocol did not reveal any RCTs. No other systematic reviews addressing the use of hormonal implants in the postpartum or postabortion period were identified through the search of core sources.

Table 1. Summary of Included Systematic Reviews of IUD Insertion Timing

Systematic Review Total N	No. and Type of Included Studies	Population	Outcomes of Interest
Lopez, et al. (2015) N=263	4 RCTs	Postpartum women of any age	<u>Primary</u> : successful placement (insertion), subsequent expulsion, method use at study assessment <u>Secondary</u> : pregnancy, perforation, infection, other adverse events
Okusanya, et al. (2014) N=878	3 RCTs	Women of any age or gravidity who received an IUD immediately after induced abortion or uterine evacuation for spontaneous incomplete abortion.	<u>Principal</u> : accidental pregnancy, spontaneous expulsion, uterine perforation, upper genital tract infection Follow-up time: 6 months

Evidence from additional sources

An additional RCT by Levi and colleagues was identified through an interval MEDLINE (Ovid) search performed to capture publications following the 2015 Cochrane review on postpartum insertion (Lopez, et al., 2015).

Contraceptive Implants

The search of core sources did not identify any SRs or RCTs addressing contraceptive implants and [any of](#) the identified priority outcomes.

EVIDENCE SUMMARY

Intrauterine Devices

Lopez [Cochrane] (2015)

The Lopez systematic review and meta-analysis (Lopez, Bernholc, Hubacher, Stuart, & Van Vliet, 2015) included 15 trials investigating postpartum insertion of IUDs. Randomized controlled trials could include immediate post-placental (<10 minutes), early (within 48 hours of delivery), and standard (postpartum visit) insertion options. This update added seven trials published from 2010 to 2014 to the eight previously identified by an earlier 2001 Cochrane review. The newer studies included four full articles and three conference abstracts. Eight RCTs were deemed at high risk of bias; two were of low risk of bias, the remainder at unclear risk.

Five RCTs directly investigated immediate versus delayed insertion; however, one was a conference abstract whose data was reported separately. Two RCTs addressed immediate versus early insertion (<48 hours). The remaining trials, many from the 2001 review, investigated insertion of different devices or insertion techniques instead of timing of insertion, and included devices no longer in general use.

Trials limited participants to a single IUD option. In the seven recent trials on timing, three offered the 52mg-LNG-IUS and in four, the CuT380A IUD.

Timing included post-vaginal birth (three studies), post-cesarean delivery (two studies), or both (two studies).

Okusanya [Cochrane] (2014)

The Okusanya systematic review and meta-analysis (Okusanya, Oduwole, & Effa, 2014) included 12 trials investigating insertion of IUDs following elective termination or uterine evacuation for spontaneous pregnancy loss (i.e. miscarriage). Six trials were deemed at high risk of bias, the remaining six of unclear risk. Overall, this Cochrane SR stated that most of the 12 RCTs were at “moderate risk of bias” due to incomplete reporting on blinding (performance bias) and incomplete outcome data (attrition bias). Seven evaluated immediate insertion of different IUDs or modified IUDs. Nine of the included trials were published over 10 years earlier. A total of five trials investigated immediate versus delayed insertion of IUDs (at a separate visit); however, one was a conference abstract and not included in the analysis. Trials limited participants on IUD options.

Levi (2015)

This RCT offered intra-cesarean or delayed insertion at 6 weeks or more postpartum to women 18-45 undergoing planned (70%) and unplanned cesarean deliveries. The primary outcome was IUD use at 6 months postpartum with relevant secondary outcomes including expulsion and discontinuation.

Critical Outcome: Unintended Pregnancy

Intrauterine Devices

Postabortion

In their meta-analysis of three recent trials involving 878 patients comparing immediate postabortion to delayed IUD insertion, Okusanya and colleagues report a nearly three-fold increase in pregnancy for those randomized to delayed insertion (9 unintended pregnancies per 1000 compared 23 per 1000 in the delayed group), however the result was not statistically significant (RR 0.37, 95% CI 0.12-1.14, n=878, 3 studies).

Postpartum

In the four trials included in the 2015 Cochrane review comparing immediate postpartum to delayed IUD insertion, pregnancy in the first 6 months postpartum was rare. Two trials did not observe any subsequent pregnancies; two did not provide unintended pregnancy outcome data. No statistical analysis was provided.

In their single RCT, Levi and colleagues identified two pregnancies in the study group. One occurred in a woman randomized to interval placement who never received the insertion. The other occurred over a year after insertion in a woman with an IUD that had migrated into the abdominal cavity after being visualized on ultrasound in the uterus at 6 months as strings were not visualized on postpartum evaluation.

Critical Outcome: Abortion

Intrauterine Devices

Neither SR provided outcome data on the occurrence of abortion in the follow-up period.

Important Outcome: Presence of LARC at one year

Intrauterine Devices

Both systematic reviews provided aggregate outcome data on the presence of LARC at six months, rather than at the desired outcome interval of one year.

Postabortion

Okusanya and colleagues report use of an IUD at 6 months was higher for those randomized to immediate postabortion placement compared to delayed insertion (65.0% vs. 46.4%, RR 1.40, 95% CI 1.24-1.58, n=878, 3 studies).

Postpartum

Lopez and colleagues reported continuation at six months was higher for women randomized to immediate postpartum insertion compared to delayed insertion at the postpartum visit (80.8% vs. 67.4%, OR 2.04, 95% CI 1.10-4.09, n=243, 4 studies).

In [the additional](#) single RCT investigating immediate vs. delayed post-cesarean placement, of the 42 women that provided data at one year continuation rates were not statistically different by timing of

insertion (Levi, et al., 2015). However, this trial was halted early due to low enrollment, only enrolling half the number calculated [as needed](#) from [the](#) power estimates and [with](#) a third of those randomized ~~were~~ lost to follow-up.

Important Outcome: Need for alternate/replacement contraception

Intrauterine Devices

Postabortion

Removal rates of IUDs at six months were similar for women undergoing immediate postabortion placement and delayed insertion (56 per 1000 immediate vs. 28 per 1000 delayed, RR 2.01, 95% CI 0.99-4.06, n=790, 2 studies). Okusanya and colleagues do not report on replacement device rates or selection of an alternate contraceptive method by participants.

Postpartum

For women receiving an IUD in the postpartum period, rates of expulsion in the following six months were higher for those in the immediate placement arm (168 per 1000 women immediate vs. 31 per 1000 delayed, OR 4.89, 95% CI 1.47-16.32, n=210, 4 studies). Lopez and colleagues do not report on replacement device rates or selection of an alternate contraceptive method by participants. However, even with expulsions, women allocated to immediate insertion were more likely to have an effective LARC in place at six months.

Levi and colleagues report four expulsions in women allocated to intraoperative placement, all within the first three weeks postpartum. Three women [had their IUD](#) replaced ~~their IUDs~~ following expulsion. In women allocated to interval IUD placement, only one experienced an expulsion, she did not opt for replacement. No statistical analysis was provided. Five women subsequently had their IUD removed for bleeding, pelvic pain, or both. In the delayed group, two women had IUD removals during the study period, for bleeding and pelvic pain.

Important Outcome: Harms

Intrauterine Devices

Postabortion

Genital tract infections were similar across groups (OR 1, 95% CI 0.32-3.14, n=878, 3 studies).

Uterine perforations were not reported as outcomes in either SR. ~~As mentioned above, in their RCT, Levi and colleagues reported on a single case of pregnancy among 42 enrollees, occurring in a woman subsequently found to have an intraabdominal copper IUD which, while the strings were not visualized at 6-week postpartum evaluation, the device was visualized by ultrasound as intrauterine at that time.~~

Postpartum

Genital tract infections were rare in trials investigating postpartum insertion of IUDs. Two studies reported no infections in either arm; two studies reported a single infection in both treatment arms.

In their RCT of IUD insertion for women undergoing cesarean delivery, Levi and colleagues report a single case of endometritis out of 42 enrollees occurring in the intraoperative placement group five days

postpartum and the device was removed. [As mentioned above, in their RCT, Levi and colleagues also reported on a single case of pregnancy among 42 enrollees, occurring in a woman subsequently found to have an intraabdominal copper IUD which, while the strings were not visualized at 6 week postpartum evaluation, the device was visualized by ultrasound as intrauterine at that time.](#)

CONTEXTUAL QUESTION:

PAYER AND PROVIDER POLICIES TO PROMOTE LARC

A 2014 Center for Evidence-based Policy Medicaid Evidence-based Decisions Project (MED) report on Medicaid policies and programs to encourage use of LARC identified several common barriers and best practices to LARC enhance uptake (Ray, Leof, & King, 2014).

Barriers to LARC Uptake

Administrative Barriers

[Obstetric care is billed and coded using a global diagnosis related group \(DRG\); costs are reimbursed in a block payment accordingly. When a LARC device is provided during an inpatient obstetric stay, the additional costs of the device itself and the insertion procedure are not captured in the DRG and thus goes unpaid in the current system.](#)

Cost of LARC Devices

Many LARC devices have a high initial cost compared to shorter acting contraceptive methods (e.g., pills, patch, ring). However, comparing total annual costs, LARC devices actually have the lowest costs (Trussell, et al., 2009; 2013). In 2015, Liletta[®], a 52mg-LNG IUS, was approved by the FDA. The distributor, Medicines360, is providing the device at very reduced rates (\$50) for those enrolled in 340b pharmacy programs (OHA, 2015), reduced rates for bulk purchases, and they also offer a reduced cost starter pack (see Address Device Costs [section below on next page](#)).

Clinics and providers may express concerns about high upfront costs to stock LARC devices. If payers reimburse below provider costs (or do not reimburse in an inpatient setting), there is a disincentive for providers to use them. Furthermore, the high initial cost of the devices creates a barrier to facilities having stock-in-hand, thus preventing same day insertions when patients choose LARC devices. Same-day-insertion is a best practice (see Address Device Costs [section below](#)).

Provider Barriers

Providers may not understand current patient eligibility criteria for LARC devices, lack sufficient training to insert LARC devices in the postabortion or postpartum period, or be unclear on appropriate billing and coding so that they are reimbursed for the device and procedure costs.

Patient Barriers

Women may inappropriately believe they need to have previously delivered a child, be older, or have failed another contraceptive method to be eligible for LARC. Women may believe their insurer does not

cover LARC options for contraception [or that the device is too expensive](#). Patients often [are required need](#) to return for a second visit to have devices inserted, a [barrier requirement](#) that reduces LARC utilization.

System Barriers

Patients receive family planning services in a variety of settings, including private practices (from family medicine, pediatric and obstetrics/gynecology clinicians, or certified nurse midwives), community health centers, Title X clinics, and federally qualified health clinics (FQHCs). [Systems barriers in these various settings may include coding and billing, initial device cost, reimbursement, provider training, and outdated clinical policies](#). Solutions for each of the challenges described [below](#) may need to be modified depending on the setting.

~~Billing, coding, and reimbursement challenges include coding an outpatient procedure in an inpatient environment, billing for the procedure in addition to the global delivery diagnosis related group (DRG), and receiving adequate reimbursement for the cost of the device (inpatient and outpatient). These challenges may create financial disincentives to providing LARC in both inpatient and outpatient settings.~~

Solutions to Overcome LARC Barriers

[Address Administrative Barriers](#)

[Policies that facilitate payment for immediate postpartum LARC insertion may increase use of the devices. Hospitals are unlikely to bundle a LARC device into the global delivery fee given the cost of the devices. As of February 2016, seventeen state Medicaid programs in seventeen states and the District of Columbia accept claims and provide reimbursement for devices, allowing physicians to bill for a LARC device and insertion immediately postpartum and the facility to be paid for the device outside of the bundled payment for delivery.](#)

For example, in Washington State, reimbursement for providing an immediate postpartum LARC is billed separately from the global DRG for delivery and the facility delivery claim through [the use of a separate an](#) outpatient claim. Reimbursement is offered through three different claims processes: 1) the facility's pharmacy point of sale system, 2) as a separate professional claim filed by the facility (when facility supplies device), or 3) a separate professional claim by the provider (when provider supplies device). Washington does not reimburse for unbundling the delivery (Washington State Health Care Authority, 2015).

~~Hospitals would hesitate to bundle a LARC device into the global delivery fee given their expense and unclear reimbursement rate for the device itself.~~

[Address Device Costs](#)

Policies that increase reimbursement for LARC devices may increase LARC uptake.

Same-day insertions are a best practice for both providers and patients. Creating systems for providers to have LARC device stock on hand is necessary for same-day insertions and may require payers to develop funding options for providers who are unable to afford the up-front costs of stocking LARC devices (e.g., buying an initial starter kit, partnering with other funding sources).

Contracting with specialty pharmacies to deliver devices for patients within 24 hours can help those providers who are unable to keep stock on hand. These contracts can also include options to return unused devices. Specialty pharmacies can also bill insurers directly, relieving the office of the device billing burden.

~~Policies that facilitate immediate postpartum LARC insertion may increase use of the devices. As of February 2016, seventeen state Medicaid programs and the District of Columbia accept claims and provide reimbursement for devices, allowing physicians to bill for a LARC device and insertion immediately postpartum and be paid outside of the bundled payment for delivery.~~

Liletta® manufacturers, Actavis and Medicines360 offer the Liletta AccessConnect program with two purchasing options (Actavis Pharma, 2015). Each purchasing option is described in detail on their website, <https://www.lilettahcp.com/access/purchasing>.

1. **Volume Discount Program:** Liletta® can be purchased directly from Actavis with volume-based discounts starting at \$599.38 per device for 1 to 5 units and decreasing to \$537.50 when ordering over 100 units.
2. **Specialty Pharmacy:** Currently, Actavis is partnering with Accredo to act as their specialty pharmacy provider.

Additionally, Actavis offers a significantly discounted rate to participants of the 340B Drug Pricing Program. In their guide to Intrauterine Devices, the Bixby Center at the University of California, San Francisco reports that the device will cost \$50.00 for sites participating in the 340B program. The Oregon Health Authority reproductive health newsletter also reported this price in April, 2015.

Develop LARC Champions

Increased provider knowledge on eligibility, more advanced procedure skills, and building skills for appropriate billing and coding may increase uptake of LARC by providers and practices. Partnering with stakeholders such as the local affiliates of professional societies (e.g., American College of Obstetricians and Gynecologists [ACOG], American Academy of Family Physicians [AAFP], American Academy of Pediatrics [AAP], American College of Nurse-Midwives [ACNM]), FQHCs, Title X clinics, and hospital organizations to develop LARC champions that can assist in dissemination of knowledge and skills. Champions can advocate for LARC use in their communities, and provide procedure training, and billing and coding assistance to providers and staff.

Dispel Patient and Provider Myths

Dispelling myths that inappropriately exclude teens and nulliparous women from LARC devices is an important strategy that can be targeted to both patients and providers. Payers and providers can use the medical eligibility criteria, published by the Centers for Disease Control and Prevention (CDC) to guide physician practices (CDC, 2012). Using patient information materials that emphasize the efficacy and safety of LARC options and correct misinformation on eligibility can increase uptake. Appendix E provides links to the MEC and efficacy-based contraceptive options tools.

Coordinate with Stakeholders

Health systems and payers can work to reduce unintended pregnancy rates through improving inter-conception care and encouraging pregnancy intention screening for all patients to help connect women to the resources that fit their reproductive life plans. Pregnancy intention screening can be delivered outside of traditional medical settings including substance use treatment centers and social service agencies, connecting women to family planning services. These conversations can include information on the efficacy, safety, and cost-effectiveness of LARC methods and include referrals to providers or integrate family planning services into their services.

Since 2015, effective contraception use is a Coordinated Care Organization incentive metric in Oregon. Effective contraception includes sterilization, IUDs/IUSs, implants, injections, pills, patches, rings or diaphragms. Efforts to promote inter-conception care may address the state incentive metric on contraceptive use.

Payers can review claim systems to ensure coding and billing systems capture the 90% enhanced federal Medicaid match for family planning services and also to distinguish between devices acquired through 340b clinics and those devices eligible for Medicaid pharmacy rebates. Stakeholders may be unaware of the federal match for family planning services.

Resource Allocation

Cost-effectiveness Reports

Postabortion IUD Insertion

A 2013 analysis by Salcedo, Sorensen, and Rodriguez estimated cost-effectiveness of immediate IUD provision compared to routine placement at a follow-up visit from the public payer perspective (Salcedo, Sorensen, & Rodriguez, 2013). Compared to planned insertion at follow up, the immediate insertion of an IUD (including copper or LNG-IUS options) following an elective termination is estimated to save \$111 per woman over the first year in direct medical costs alone, and \$810 over 5 years. With the addition of public health insurance and social program costs, the savings increases to \$1956 over 1 year, and \$4296 over 5 years. Providing immediate postabortion IUDs to 1000 women will avoid over 400 pregnancies, 180 deliveries and 160 abortions over 5 years. In sensitivity models, planned follow-up placement was estimated to have greater savings only when expulsion rates reached over 30% in the immediate insertion group or nearly 90% of women attended their postabortion follow-up visit.

Postpartum IUD Insertion

Washington and colleagues designed a model comparing costs and health outcomes for immediate post-placental or delayed (6-8 weeks postpartum) IUD insertion. Per 1,000 women over 2 years, immediate postpartum IUD insertion is estimated to prevent an additional 88 unintended pregnancies and provide medical cost savings of \$282,540. Models included an 18% expulsion rate following immediate postpartum insertion. While there is a higher expulsion rate following immediate postpartum insertion, the additional device costs are offset by reductions in unintended pregnancy (Washington, et al., 2015). In this analysis the cost of an IUD needed to be over \$10,000 for the intervention to no longer be cost-saving. Similar to estimates from Salcedo and colleagues, expulsion rates needed to reach over 38% to favor delayed insertion (Washington, et al., 2015).

Both IUD [economic](#) analyses were performed before the Liletta® device entered the market in 2015. Liletta® was developed to decrease the cost of IUDs for lower-resource settings and Medicines360, the distributor, offers Liletta® to 340b pharmacy benefit participants at approximately \$50 per device, and [about under-\\$500](#) for other purchasers (Oregon Health Authority, 2015). In the prior analyses, the costs for an IUD [in the two economic models described above](#) were estimated at \$650 in the postabortion model, and at \$810.77 (\$410.77-\$1210.77) in the postpartum model. Actual savings may be greater with increasing use of Liletta®, particularly in settings with access to 340b pricing.

Postpartum Implant Insertion

Gariepy and colleagues estimated the cost-effectiveness of immediate implant insertion compared to insertion at 6 weeks postpartum over the subsequent year. While cost-effectiveness estimates of the contraceptive implant insertion report higher costs than delayed insertion, the increased likelihood of receipt of the device immediately postpartum and reduction in unintended pregnancy (2.4% for delayed vs. 21.6% for immediate) is estimated to save \$1,263 per patient (Gariepy, Duffy, & Xu. 2015). Limiting estimates to only 1 year limits the validity of cost-effectiveness estimates as the contraceptive implant maintains a low failure rate across the three years of approved use and therefore cost savings may increase over a longer time frame.

A Colorado-based prospective study of pregnant adolescents (13-22 years of age) offered immediate postpartum implant insertion found that continuation rates were high (97% at 6 months, 86% at 12 months) and pregnancy rates lower in the immediate insertion group compared to those not receiving a device in hospital and going on to either receive an implant, other contraceptive method, or no method (pregnancies in the implant group 2.6% vs 20.1% in comparison at 12 months, 17.7% vs. 83.7% at 36 months) (Han, Teal, Sheeder, & Tocce, 2014).

Using their observations, the authors then created an economic model to estimate costs over 6, 12, 24, and 36 months of a theoretical publicly funded immediate postpartum implant program provided to 1000 women (compared to hypothetical cohort of 1000 women not receiving an implant). While costs were greater at 6 months in the immediate implant group (\$72,606 more, relating to device costs), by 12, 24, and 36 months the cost savings through averted pregnancies, even after including costs of device removal, was estimated to save Colorado Medicaid, \$546,950, \$2.46 million, and \$4.53 million respectively.

Births, abortions, and miscarriages resulting from unintended pregnancies are estimated to [have](#) cost [U.S.](#) public payers \$21.0 billion in 2010 (Sonfield & Kost, 2015). Effective contraception is cost-saving (not just cost-effective). Increasing LARC use, through immediate postpartum or postabortion placement of IUDs, results in higher LARC use at six months (Lopez et al., 2015; Okusanya, et al., 2014). While there is a higher expulsion rate associated with postpartum compared to delayed insertion of IUDs (17% vs 3%), economic models demonstrate cost-savings even up to an expulsion rate of 30% (Salcedo, et al., 2013; Washington, et al., 2015).

The expulsion rate for immediate postabortion IUD insertion is greater following immediate insertion, (4% vs. 1.7%) (Okusanya, et al., 2014). In the largest trial, by Bednarek and colleagues ([which was conducted in Oregon](#)), expulsion rates needed to differ by 8% or more for immediate placement to be inferior (Bendarek, et al., 2011). Economic models estimate cost savings for immediate postabortion insertion up to a 30% expulsion rate (Salcedo, Sorensen, & Rodriguez, 2013). Economic models on postabortion IUD insertion estimate for every 1000 women undergoing placement, 400 pregnancies, 180 deliveries, and 160 abortions will be averted (Salcedo, et al., 2013).

Contraceptive implants are effective, have high continuation rates in nonrandomized studies, and are not at risk of expulsion. Therefore significant cost savings would also be projected with these devices (Han, et al., 2014; Diedrich, et al., 2015).

Values and preferences

For women who choose it, reproductive life planning enhances women's ability to achieve their life, family, and career goals. Clinicians are encouraged to discuss contraceptive options and pregnancy planning with women at every visit (ACOG, 2016a; Gavin, et al., 2014). Most women desire to control their fertility and time their pregnancies. When women desiring contraception are presented with all contraceptive options, over 70% will select a LARC method, including teens, and the majority continues to use a LARC method at 12 and 36 months (Rosenstock, et al., 2012; Peipert, et al., 2012). When women select their preferred contraceptive method, continuation rates across all methods are higher. Immediate insertion of LARC following a birth or abortion is generally acceptable to women and may be preferable. Consolidating gynecological interventions (delivery or abortion, and IUD placement) may improve convenience and lessen associated discomforts with these procedures (including if there is anesthesia or analgesia involved). Requiring multiple visits to obtain a LARC method decreases uptake of [these, and indeed any](#) ~~this~~ form of contraception. The one [potential](#) deterrent to immediate versus delayed IUD insertion is the increase in [the risk of](#) expulsion, which is inconvenient for the woman and adds [some short-term](#) cost [for the system](#). There are [no](#) additional harms associated with immediate [IUD](#) insertion, and no deterrents to immediate versus delayed insertion of implants. Many women would likely choose immediate insertion of a LARC [in the](#) postpartum or postabortion [time frame](#).

Other considerations

Information from non-randomized studies estimates that LARC devices are 20 times more effective at preventing unintended pregnancy than contraceptive pills, patches, rings, and injections. Continuation rates for LARC devices are also greater than pills, patches, rings, and injections (Winner, et al., 2012).

Evaluated efforts to expand LARC use (e.g., Colorado, Iowa, St. Louis) are associated with significant reductions in teen pregnancy and abortion (Ricketts, et al., 2014; Biggs, et al., 2015; Peipert, et al., 2012).

The CDC's MEC recommends LARC devices as suitable for the vast majority of reproductive-aged women (CDC, 2012). Since 2010, the CDC has endorsed immediate postpartum and postabortion LARC use and supports LARC methods for breastfeeding women (CDC, 2010).

The National Committee on Quality Assurance (NCQA) reports 30-40% of insured women do not attend a postpartum visit and 40-75% do not attend a postabortion visit, thus increasing the risk of unplanned pregnancy, abortion, or unmet contraceptive needs.

POLICY LANDSCAPE

Quality measures

In Oregon, effective contraception use became a Coordinated Care Organization incentive metric in January 2015. Effective contraception includes sterilization, IUDs/IUSs, implants, injections, pills, patches, rings, or diaphragms.

No quality measures related to LARC were identified when searching the [National Quality Measures Clearinghouse](#).

Payer **coverage policies** initiatives

[In April 2016, the Center for Medicaid and CHIP Services released an informational bulletin highlighting state efforts to improve access to LARC for Medicaid enrollees \(Centers for Medicare and Medicaid Services, 2016\). The five strategies featured in the bulletin mirror those addressed above and include:](#)

- [1. Provide timely, comprehensive contraception coverage](#)
- [2. Raise payment rates for LARC and other devices](#)
- [3. Reimburse for immediate postpartum LARC by unbundling payment from obstetric services](#)
- [4. Remove logistical barriers to managing supply of LARC devices](#)
- [5. Remove administrative barriers for LARC provision](#)

[The bulletin also mentions efforts in Illinois, Louisiana, and South Carolina to expand LARC access, including efforts through managed care contracting and quality improvement work.](#)

-In addition, federal law requires coverage of all methods of birth control for most commercial health insurance plans and Medicaid Alternative Benefit Plans (see <http://www.dol.gov/ebsa/faqs/faq-aca26.html>).

At this time, Oregon has no specific guidance about the use of LARC in the immediate postpartum period, and coverage does not consistently occur [across payers and settings](#).

Washington's Family Planning Provider Guide outlines the reimbursement for immediate postpartum LARC insertion:

The agency reimburses professional services for immediate postpartum IUD or contraceptive implant insertion procedures if billed separately from the professional

global obstetric procedure codes and the facility (including hospital inpatient) delivery claim. The agency does not pay separately for unbundled services billed by a hospital.

The agency reimburses for the IUD or contraceptive implant device in one of the following ways:

- Through the facility's pharmacy point of sale system;
- As a separate professional claim submitted by the facility when the facility supplies the device; or
- As part of the professional claim when the device is supplied by the provider performing the insertion (Washington State Health Care Authority, 2015).

In their interview with 40 Medicaid agencies, Moniz and colleagues developed common themes differing in states with a policy covering immediate postpartum insertion of LARC and those not considering coverage. These themes include differences on beliefs of the health benefits of LARC, budget impacts, and competing demands for Medicaid agencies. Those with a coverage policy often reported "clear cost savings" and "common sense" approach to covering immediate postpartum insertion while those without coverage expressed concern about upfront costs, need to maintain cost-neutrality, and concern that providing payment for inpatient procedures outside of global payments may set a precedent for other medical specialties desiring separate payment outside of the diagnosis-related group code or DRG (Moniz, et al., 2015).

No coverage policies for postpartum or postabortion insertion of LARC were found in a search of provider manuals for Aetna, Cigna, Moda, and Regence commercial plans.

The Oregon Health Plan and CCARE, Oregon's Medicaid family planning waiver, will cover the provision of an immediate postabortion LARC device.

Professional society guidelines

The American College of Obstetricians and Gynecologists (ACOG) has several position statements and a clinical practice guideline on LARC (reaffirmed in 2015). The ACOG congress recommendations include offering LARC methods at the time of delivery, abortion, or dilation and curettage for miscarriage as a best practice (ACOG, 2015a), and ACOG also recommends LARC for adolescents (ACOG, 2014).

In their 2014 policy statement, the American Academy of Pediatrics (AAP) encouraged pediatricians to counsel adolescents on contraception in order of efficacy, starting with the most effective methods (i.e. LARC) first (American Academy of Pediatrics, 2014). The AAP also recommends encourage offering LARC to postpartum teens in the immediate postpartum period, including while still in the hospital, based on evidence from systematic reviews combined with ACOG and CDC recommendations (Ott & Sucato, 2014).

REFERENCES

Evidence Sources

- Levi, E. E., Stuart, G. S., Zerden, M. L., Garrett, J. M., & Bryant, A. G. (2015). Intrauterine device placement during Cesarean delivery and continued use 6 months postpartum: A randomized controlled trial. *Obstetrics & Gynecology*, *126*(1), 5-11. DOI: 10.1097/aog.0000000000000882.
- Lopez, L. M., Bernholc, A., Hubacher, D., Stuart, G., & Van Vliet, H. A. (2015). Immediate postpartum insertion of intrauterine device for contraception. *Cochrane Database of Systematic Reviews*, *6*, CD003036. DOI: 10.1002/14651858.CD003036.pub3.
- Okusanya, B. O., Oduwole, O., & Effa, & E. E. (2014). Immediate postabortal insertion of intrauterine devices. *Cochrane Database of Systematic Reviews*, *7*, Cd001777. DOI: 10.1002/14651858.CD001777.pub4.

Other Citations

- [American Academy of Pediatrics. \(2014\). Contraception for adolescents: Policy statement. *Pediatrics*, *134*\(4\), e1244-1256. DOI:10.1542/peds.2014-2299.](#)
- American College of Obstetricians and Gynecologists. (2016a). *Reproductive life planning to reduce unintended pregnancy*. Retrieved from <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Reproductive-Life-Planning-to-Reduce-Unintended-Pregnancy#15a>
- American College of Obstetricians and Gynecologists. (2009, reaffirmed 2015a). *Increasing access to contraceptive implants and intrauterine devices to reduce unintended pregnancy*. Retrieved from <https://www.acog.org/-/media/Committee-Opinions/Committee-on-Gynecologic-Practice/co642.pdf?dmc=1&ts=20160316T2021181564>
- American College of Obstetricians and Gynecologists. (2005, reaffirmed 2015b). Long-acting reversible contraception: Implants and intrauterine devices. Retrieved from: <http://www.acog.org/Resources-And-Publications/Practice-Bulletins/Committee-on-Practice-Bulletins-Gynecology/Long-Acting-Reversible-Contraception-Implants-and-Intrauterine-Devices>
- American College of Obstetricians and Gynecologists. (2007, reaffirmed 2014). *Adolescents and long-acting reversible contraception: Implants and intrauterine devices*. Retrieved from <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Adolescents-and-Long-Acting-Reversible-Contraception>
- American Congress of Obstetricians and Gynecologists. (2016b). *Medicaid reimbursement for postpartum LARC by state*. Retrieved from <http://www.acog.org/About-ACOG/ACOG-Departments/Long-Acting-Reversible-Contraception/Coding-and-Reimbursement-for-LARC/Reimbursement-Resources-for-Postpartum-LARC-Initiation/Medicaid-Reimbursement-for-Postpartum-LARC-By-State>

- Bednarek, P. H., Creinin, M. D., Reeves, M. F., Cwiak, C., Espey, E., & Jensen, J. T. (2011). Immediate versus delayed IUD insertion after uterine aspiration. *New England Journal of Medicine*, *364*(23), 2208-2217. DOI: 10.1056/NEJMoa1011600.
- Biggs, M. A., Rocca, C. H., Brindis, C. D., Hirsch, H., & Grossman, D. (2015). Did increasing use of highly effective contraception contribute to declining abortions in Iowa? *Contraception*, *91*(2), 167-173. DOI: 10.1016/j.contraception.2014.10.009.
- Branum, A. M., & Jones, J. (2015). *Trends in long-acting reversible contraception use among U.S. women aged 15–44. NCHS data brief, no 188*. Hyattsville, MD: National Center for Health Statistics. Retrieved from <http://www.cdc.gov/nchs/data/databriefs/db188.pdf>
- Caddy, S., Yudin, M. H., Murphy, K. E., Hakim, J., Money, D. M., Ogilvie, G., ... & Castillo, E. (2014). Best practices to minimize risk of infection with intrauterine device insertion. *Journal of Obstetrics and Gynaecology Canada*, *36*(3), 266-274. Retrieved from <http://sogc.org/wp-content/uploads/2014/03/gui305CPG1303E.pdf>
- [Centers for Disease Control and Prevention. \(2015\). The 6|18 Initiative evidence summary: Prevent unintended pregnancy. Retrieved from http://www.cdc.gov/sixteen/pregnancy/index.htm](http://www.cdc.gov/sixteen/pregnancy/index.htm)
- Centers for Disease Control and Prevention. (2013). U.S. selected practice recommendations for contraceptive use, 2013: Adapted from the World Health Organization selected practice recommendations for contraceptive use, 2nd edition. *MMWR Recommendations and Reports*, *62*(Rr-05), 1-60. Retrieved from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6205a1.htm>
- Centers for Disease Control and Prevention. (2012). Update to CDC's U.S. medical eligibility criteria for contraceptive use, 2010: Revised recommendations for the use of contraceptive methods during the postpartum period. *MMWR Morbidity and Mortality Weekly Report*, *60*(26), 878-883. Retrieved from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6026a3.htm>
- Centers for Disease Control and Prevention. (2010). U.S. medical eligibility criteria for contraceptive use, 2010. *MMWR Morbidity and Mortality Weekly Report*, *59*(04), 1-6. Retrieved from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm>
- [Centers for Medicare and Medicaid Services. \(2016\). State Medicaid payment approaches to improve access to long-acting reversible contraception: CMCS informational bulletin. Retrieved from https://www.medicaid.gov/federal-policy-guidance/downloads/CIB040816.pdf](https://www.medicaid.gov/federal-policy-guidance/downloads/CIB040816.pdf)
- Diedrich, J. T., Zhao, Q., Madden, T., Secura, G. M., & Peipert, J. F. (2015). Three-year continuation of reversible contraception. *American journal of obstetrics and gynecology*, *213*(5), 662-e1. DOI: 10.1016/j.ajog.2015.08.001.
- Garipey, A. M., Duffy, J. Y., & Xu, X. (2015). Cost-effectiveness of immediate compared with delayed postpartum etonogestrel implant insertion. *Obstetrics & Gynecology*, *126*(1), 47-55. DOI: 10.1097/AOG.0000000000000907.
- Gavin, L., Moskosky, S., Carter, M., Curtis, K., Glass, E., Godfrey, E., ... Zapata, L. (2014). Providing quality family planning services: Recommendations of CDC and the U.S. Office of Population Affairs.

MMWR Morbidity and Mortality Weekly Report, 63(RR-4), 1–54. Retrieved from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6304a1.htm>

- Han, L., Teal, S. B., Sheeder, J., & Tocce, K. (2014). Preventing repeat pregnancy in adolescents: Is immediate postpartum insertion of the contraceptive implant cost effective? *American journal of obstetrics and gynecology*, 211(1), 24-e1. DOI: 10.1016/j.ajog.2014.03.015.
- Heinemann, K., Reed, S., Moehner, S., & Do Minh, T. (2015). Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices. *Contraception*, 91(4), 274-279. DOI: 10.1016/j.contraception.2015.01.007.
- Moniz, M. H., Dalton, V. K., Davis, M. M., Forman, J., Iott, B., Landgraf, J., & Chang, T. (2015). Characterization of Medicaid policy for immediate postpartum contraception. *Contraception*, 92(6), 523-531. DOI: 10.1016/j.contraception.2015.09.014.
- National Committee on Quality Assurance (2015). *State of health care quality*. Retrieved from: <http://www.ncqa.org/report-cards/health-plans/state-of-health-care-quality>
- Oregon Health Authority (2015). *April Oregon Reproductive Health Program Newsletter*. Retrieved from: https://public.health.oregon.gov/HealthyPeopleFamilies/ReproductiveSexualHealth/Resources/Documents/Update_Newsletters/2015/RH_Update_Newsletter_4-24-15.pdf
- Ott, M. A., & Sucato, G. S. (2014). Contraception for adolescents: [Technical report](#). *Pediatrics*, 134(4), e1257-1281. DOI: 10.1542/peds.2014-2300.
- Peipert, J. F., Madden, T., Allsworth, J. E., & Secura, G. M. (2012). Preventing unintended pregnancies by providing no-cost contraception. *Obstetrics & Gynecology*, 120(6), 1291-1297. DOI: <http://10.1097/AOG.0b013e318273eb56>.
- Ray, M., Leof, A., & King, V. (2014). *Medicaid policies and programs to increase the use of long-acting reversible contraception*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.
- Ricketts, S., Klingler, G., & Schwalberg, R. (2014). Game change in Colorado: widespread use of long-acting reversible contraceptives and rapid decline in births among young, low-income women. *Perspectives on Sexual & Reproductive Health*, 46(3), 125-132. DOI: 10.1363/46e1714.
- Rosenstock, J. R., Peipert, J. F., Madden, T., Zhao, Q., & Secura, G. M. (2012). Continuation of reversible contraception in teenagers and young women. *Obstetrics and Gynecology*, 120(6), 1298-305. DOI: <http://10.1097/AOG.0b013e31827499bd>.
- Salcedo, J., Sorensen, A., & Rodriguez, M. I. (2013). Cost analysis of immediate postabortal IUD insertion compared to planned IUD insertion at the time of abortion follow up. *Contraception*, 87(4), 404-408. DOI: 10.1016/j.contraception.2012.11.011.
- Secura, G. M., Madden, T., McNicholas, C., Mullersman, J., Buckel, C. M., Zhao, Q., & Peipert, J. F. (2014). Provision of no-cost, long-acting contraception and teenage pregnancy. *New England Journal of Medicine*, 371(14), 1316-1323. DOI: 10.1056/NEJMoa1400506.

- Sonfield, A. & Kost, K. (2015). *Public costs from unintended pregnancies and the role of public insurance programs in paying for pregnancy-related care: National and state estimates for 2010*. New York: Guttmacher Institute. Retrieved from: <http://www.guttmacher.org/pubs/public-costs-of-UP-2010.pdf>
- Sothornwit, J., Werawatakul, Y., Kaewrudee, S., Lumbiganon, P., & Laopaiboon, M. (2015). Immediate versus delayed postpartum insertion of contraceptive implant for contraception (protocol). *The Cochrane Library*, 10, CD011913. DOI: 10.1002/14651858.CD011913.
- Stanek, A. M., Bednarek, P. H., Nichols, M. D., Jensen, J. T., & Edelman, A. B. (2009). Barriers associated with the failure to return for intrauterine device insertion following first-trimester abortion. *Contraception*, 79(3), 216-220. DOI: 10.1016/j.contraception.2008.09.003.
- Trussell, J., Henry, N., Hassan, F., Prezioso, A., Law, A., & Filonenko, A. (2013). Burden of unintended pregnancy in the United States: Potential savings with increased use of long-acting reversible contraception. *Contraception*, 87(2), 154-161. DOI: 10.1016/j.contraception.2012.07.016.
- Trussell, J. (2011). Contraceptive failure in the United States. *Contraception*, 83(5), 397-404. DOI: 10.1016/j.contraception.2011.01.021.
- Trussell, J., Lalla, A. M., Doan, Q. V., Reyes, E., Pinto, L., & Gricar, J. (2009). Cost effectiveness of contraceptives in the United States. *Contraception*, 79(1), 5-14. DOI: 10.1016/j.contraception.2008.08.003.
- U. S. Food and Drug Administration (2015). Liletta: Drug approval package. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206229s000lbl.pdf
- U. S. Food and Drug Administration (2014). Nexplanon: Drug approval package. Retrieved from <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm400441.htm>
- U. S. Food and Drug Administration (2013). Skyla: Drug approval package. Retrieved from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159_skyla_toc.cfm
- U. S. Food and Drug Administration. (2009). *FDA approves additional use for IUD Mirena to treat heavy menstrual bleeding in IUD users*. Retrieved from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm184747.htm>
- Washington, C. I., Jamshidi, R., Thung, S. F., Nayeri, U. A., Caughey, A. B., & Werner, E. F. (2015). Timing of postpartum intrauterine device placement: A cost-effectiveness analysis. *Fertility and sterility*, 103(1), 131-137. DOI: 10.1016/j.fertnstert.2014.09.032.
- Washington State Health Care Authority. (2015). *Washington Apple Health family planning provider guide*. Retrieved from http://www.hca.wa.gov/medicaid/billing/documents/guides/familyplanningprovider_bi.pdf
- Winner, B., Peipert, J. F., Zhao, Q., Buckel, C., Madden, T., Allsworth, J. E., & Secura, G. M. (2012). Effectiveness of long-acting reversible contraception. *New England Journal of Medicine*, 366(21), 1998-2007. DOI: 10.1056/NEJMoa1110855.

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.

DRAFT

APPENDIX A. GRADE INFORMED FRAMEWORK – ELEMENT DESCRIPTIONS

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
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 in the absence of likely cost offsets—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 issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences, and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences, and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences, and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, values and preferences, and other factors, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome¹

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 estimate of effect: 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

¹ Includes risk of bias, precision, directness, consistency and publication bias

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 estimate of effect 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 estimate of effect: 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.

DRAFT

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
Unintended Pregnancy							
Postabortal IUD							
3	RCTs	Moderate	Not <u>s</u> erious	Not serious	Not serious	Intention to treat analysis and differential loss to follow up underestimates the benefit of immediate insertion None	Moderate quality confidence in-estimate-of effect ●●●○
Presence of LARC at six months							
Postabortion IUD							
3	RCTs	Moderate	Not serious	Not serious	Not serious	None	Moderate quality confidence in-estimate-of effect ●●●○
Postpartum IUD							
4	RCTs	Moderate	Not serious	Not serious	Not serious	None	Moderate quality confidence in-estimate-of effect ●●●○
Need for alternate/Replacement contraception							
Postabortal IUD (based on removal or expulsion by 6 months)							
3	RCTs	Moderate	Not <u>s</u> erious	Not serious	Not <u>s</u> erious	Intention to treat analysis and differential loss to follow up underestimates the benefit of	Moderate quality 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
						immediate insertion	
Postpartum IUD (based on expulsion by 6 months)							
4	RCTs	Moderate	Not serious	Not serious	Not serious	None	Moderate quality confidence in estimate of effect ●●●○
Harms							
Postabortion IUD (based on upper genital tract infection only)							
3	RCTs	Moderate	Not serious	Serious	Not serious	None	Low quality confidence in estimate of effect ●●○○

APPENDIX C. METHODS

Scope Statement

Populations

Women in the postpartum or postabortion period who desire contraception

Population scoping notes: *None*

Interventions

Offering immediate postpartum or postabortion placement of a long-acting reversible contraceptive (LARC)

Intervention exclusions: *None*

Comparators

Usual care: Offering immediate non-LARC forms of contraception, scheduling delayed LARC placement, delaying discussion of options until 6 weeks postpartum or postabortion

Outcomes

Critical: Unintended pregnancies, abortions

Important: Presence of LARC at one year, need for alternate/replacement contraception, harms

Considered but not selected for the GRADE table: Device expulsion, discontinuation of contraception for any reason other than desire to conceive

Key Questions

KQ1: What is the comparative effectiveness of offering immediate postpartum or postabortion placement of a long-acting reversible contraceptive?

KQ2: What are the harms of immediate postpartum or postabortion placement of a long-acting reversible contraceptive?

Contextual Questions

1: What payer and provider practices and policies promote effective use of LARC?

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 long-acting reversible contraception or LARC. In addition, a search was conducted using the MeSH term contraception and the words postpartum, postabortion, or postabortion. Searches of core sources were limited to citations published in the past five years.

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, technology assessments and RCTs published in the past five years.

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, RCTs, or clinical practice guidelines.

APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
ICD-10 Diagnosis Codes	
Z30.019	Encounter for initial prescription of contraceptives, unspecified
Z30.49	Encounter for surveillance of other contraceptives (<i>includes implantable subdermal contraception insertion, removal, and surveillance</i>)
Z30.430	Encounter for insertion of intrauterine contraceptive device
Z30.432	Encounter for removal of intrauterine contraceptive device
Z30.433	Encounter for removal and reinsertion of intrauterine contraceptive device
Z30.431	Encounter for routine checking of intrauterine device
CPT Codes	
58300	IUD insertion
58301	IUD removal
11981	Insertion, non-biodegradable drug delivery implant
11982	Removal, non-biodegradable drug delivery implant
11983	Removal with reinsertion, non-biodegradable drug delivery implant
HCPCS Level II Codes	
J7297	Levonorgestrel-releasing intrauterine contraceptive system, 52mg, 3 year duration (Liletta®)
J7298	Levonorgestrel-releasing IU contraceptive system, 52mg, 5 year duration (Mirena®)
J7300	Intrauterine copper contraceptive (Paragard®)
J7301	Levonorgestrel-releasing intrauterine contraceptive system, 13.5mg (Skyla®)
J7302	<i>Levonorgestrel-releasing intrauterine contraceptive system, 52mg (discontinued 12/31/2015 replaced with J7297 or J7298 as appropriate)</i>
J7307	Etonogestrel (contraceptive) implant system, including implant and supplies (Nexplanon®)

Note: Inclusion on this list does not guarantee coverage

APPENDIX E. RESOURCES

American College of Obstetricians and Gynecologists: Immediate Postpartum LARC Resources

<http://www.acog.org/About-ACOG/ACOG-Departments/Long-Acting-Reversible-Contraception/Coding-and-Reimbursement-for-LARC/Reimbursement-Resources-for-Postpartum-LARC-Initiation>

Center for Disease Control & Prevention Medical Eligibility Criteria

<http://www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm>

Center for Disease Control & Prevention Contraception Options

<http://www.cdc.gov/reproductivehealth/unintendedpregnancy/contraception.htm>

Dr. Sarah Prager of the University of Washington created a training course, offered through CARDEA, on immediate postpartum IUD insertion. The course is available for a nominal \$15 and providers continuing nursing and medical education credits.

<http://www.cardeaservices.org/resourcecenter/inserting-long-acting-reversible-contraception-larc-immediately-after-childbirth>



May 26, 2016

500 Summer Street NE, E-65
Salem, OR 97301
Voice (503) 373-1985
FAX (503) 378-5511

Dear Medical Directors:

In developing our Coverage Guidance on Timing of Long-Acting Reversible Contraceptive (LARC) Placement, we have become aware that administrative issues, rather than coverage policy per se are discouraging the use of highly effective LARC devices (intrauterine devices and subdermal implants). While placement of LARC devices is already covered for most plans, administrative issues are preventing patients from receiving these devices at the point when they are most likely to achieve the objective of preventing unintended pregnancy. The LARC devices are safe and effective, and are more cost-effective than any other contraceptive method. For example, one cost-effectiveness analysis found that over 2 years, placement of a postpartum IUD was associated with a savings of \$282,540 per 1,000 women. They cannot be effective or cost-saving, however, unless they are placed.

In order for placement to occur, an appropriate device must be offered and placed at a time convenient to the woman desiring contraception, preferably when she is already receiving care for another condition. Best practices for timing of insertion include placement immediately following birth or abortion, as well as same-day placement in the outpatient setting. Currently, due to administrative barriers, women are often required to return for one or more visits in order to receive a LARC device. Many women do not return for follow up visits, including postpartum visits. Others may become pregnant before such a visit can occur. In order to offer immediate placement, providers must be confident that they and the facilities in which they work will be appropriately compensated for the devices and related care. We have heard reports of major hospital systems halting placement of these devices in the postpartum setting due to reimbursement issues and are aware of others that simply do not offer postpartum LARC placement unless funded through a grant for a very limited population.

As you implement the changes related to this coverage guidance, we urge you to address the following administrative barriers, if they are present in your plans and provider networks.

- Lack of reimbursement for the cost of these devices when provided after an in-hospital birth due to global DRG-based payment for delivery services
- Lack of reimbursement to professionals and facilities for the service of placing these devices in the inpatient setting
- Inadequate inventory of these devices to allow for their placement on a timely basis in all settings of care
- Reimbursement rates to providers which are lower than the provider's cost of the devices
- Lack of providers able to perform postpartum placement of IUDs
- For devices provided through a pharmacy benefit, lack of a mechanism for providers to recoup the cost of the device if a device assigned to a particular woman is not placed
- Lack of provider reimbursement when LARC removal, replacement or re-insertion is required

- Any prior authorization requirements, which can delay or block placement of these devices
- Payer refusal to pay for two distinct services on the same day (e.g., a birth or the termination of pregnancy followed by LARC placement)

We have attached an Informational Bulletin from the Center for Medicaid and CHIP Services which outlines these issues as well as options other states have implemented to resolve them. Appendix E of our coverage guidance contains some helpful resources for plans and providers wishing to remove barriers to LARC for their population.

We hope that this information will help you as you work with your plan and contracted providers to ensure effective access to these important devices.

Sincerely,

<Signature>

Somnath Saha, MD, Chair, Health Evidence Review Commission

<Signature>

Wiley Chan, MD, Chair, Evidence-based Guidelines Subcommittee

CMCS Informational Bulletin

DATE: April 08, 2016

FROM: Vikki Wachino, Director
Center for Medicaid and CHIP Services

SUBJECT: State Medicaid Payment Approaches to Improve Access to Long-Acting Reversible Contraception

In July 2014, the Center for Medicaid and CHIP Services (CMCS) launched the Maternal and Infant Health Initiative to improve maternal and infant health outcomes. The initiative has two primary goals: 1) increasing the rate and improving the content of postpartum visits; and 2) increasing access and use of effective methods of contraception. Medicaid provides coverage for more than 70 percent of family planning services for low-income Americans. Given this important role, CMCS sought to identify approaches to Medicaid reimbursement that promote the availability of effective contraception.¹ This Informational Bulletin describes emerging payment approaches several state Medicaid agencies have used to optimize access and use of long-acting reversible contraception (LARC).

Background

Beyond preventing unplanned pregnancies, research indicates that effective contraception helps prevent poor birth spacing, thereby reducing the risk of low-weight and/or premature birth.² It can also be essential to a woman's long-term physical and emotional well-being. LARCs—intrauterine devices (IUDs) and contraceptive implants—are highly effective methods of birth control that last between 3 and 10 years (depending on the method) without requiring daily, weekly, or monthly user effort.³ The Centers for Disease Control and Prevention has identified LARCs as among the most effective family planning methods with a pregnancy rate of less than 1 pregnancy per 100 women in the first year. For comparison, the contraceptive pill has a rate of 9 pregnancies per 100 women in the first year, while the male condom has rate of 18 pregnancies per 100 women in the first year.⁴ While Medicaid agencies typically reimburse for multiple types of contraception, LARCs possess a number of advantages: they are cost-effective, have

¹ Sonfield A and Gold RB. (2012). Public Funding for Family Planning, Sterilization and Abortion Services, FY 1980–2010, New York: Guttmacher Institute, <<http://www.guttmacher.org/pubs/Public-Funding-FP-2010.pdf>>.

² Agustin Conde-Agudelo, MD, MPH; Anyeli Rosas-Bermúdez, MPH; Ana Cecilia Kafury-Goeta, MD (2006). Birth Spacing and Risk of Adverse Perinatal Outcomes: A Meta-analysis. *JAMA* 295 (15): 1809-1823.

³ Trussell J. Contraceptive efficacy. In: Hatcher R, Trussell J, Nelson A, Cates W, Kowal D, Policar M, eds. *Contraceptive Technology*. 20th ed. New York, NY: Ardent Media; 2011:779–863.

⁴ U.S. Centers for Disease Control. Effectiveness of Family Planning Methods. http://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/contraceptive_methods_508.pdf. Accessed March 28, 2016.

high efficacy and continuation rates, require minimal maintenance, and are rated highest in patient satisfaction.⁵

Despite these known advantages, LARC utilization in the U.S. remains relatively low when compared to rates in other countries. As of 2009, LARC utilization rates among contraception users in the U.S. are higher for women covered by Medicaid (11.5 percent) than the national rate (8.5 percent).⁶ But more can be done to increase the use of this form of contraception. Two reasons cited for the low utilization of LARCs in the U.S. are (1) administrative and reimbursement barriers that result in high upfront costs for devices and (2) payment policies that reduce (or do not provide) reimbursement for devices or placement.^{7,8} States have flexibility in how they reimburse for LARC, and by promoting access to contraceptive methods of choice—and the support necessary to use chosen methods effectively—states can support not only the health of women and their children, but also reduce the number of unintended pregnancies.

LARC Utilization and Medicaid Reimbursement

Payment challenges related to LARC utilization exist in both fee-for-service (FFS) and managed care environments, as well as in inpatient and outpatient settings (primary, specialty, or other ambulatory care).

In the inpatient setting, for example, the use of a single prospective payment for labor and delivery services may not sufficiently address the additional costs associated with the provision of LARC. There are significant advantages to providing LARC immediately after delivery while the woman is still under hospital care.⁹ But many states do not provide additional payment for the cost of LARC, and do not provide additional payment to either the hospital or the practitioner for placement or insertion services.

In outpatient settings, payment rates may be insufficient for LARC devices and/or for placement services. LARC placement may require significant up-front costs to providers, primarily costs to obtain devices prior to placement. For devices covered through a patient's pharmacy benefit, and in the absence of prior arrangements (or state policy), providers may not be able to return a dispensed device if it is not used for the specific patient for whom it was dispensed; these devices must then be discarded at a financial loss to the provider.

If states limit provider payment to an initial LARC placement, but do not provide payment for replacement or reinsertion when necessary, providers may face further disincentives.

⁵ Peipert JF, Zhao Q, Allsworth JE, Petrosky E, Madden T, Eisenberg D, Secura G. (2011) Continuation and satisfaction of reversible contraception. *Obstet Gynecol.* 117(5):1105-13.

⁶ Finer LB, Jerman J, Kavanaugh ML. (2012). Changes in use of long-acting contraceptive methods in the United States, 2007-2009. *Fertility and Sterility* 98(4), 893-89

⁷ Committee Opinion No. 615. American College of Obstetricians and Gynecologists. 2015. Access to contraception. *Obstet Gynecol*: 125: 250-5.

⁸ Rodriguez, MI, Evans, M, Espey, E. (2014). Advocating for immediate postpartum LARC: increasing access, improving outcomes, and decreasing cost. *Contraception.* 90, 468-471.

⁹ Long-acting reversible contraception: implants and intrauterine devices. Practice Bulletin No. 121. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2011; 118:184-96.

Additionally, providers may be hesitant to insert LARC devices for women when continued coverage for individuals is uncertain in the event there is later need for removal of the LARC.

Finally, some states or Managed Care Organizations (MCOs) require prior authorization and, as part of the prior authorization, may question medical necessity absent failure using another birth control method (sometimes called step therapy).

State Medicaid Payment Strategies to Optimize LARC Utilization

To assist states in optimizing the existing statutory flexibilities in this area, this Informational Bulletin identifies LARC reimbursement strategies implemented by states. Information on challenges and opportunities were obtained through several sources, including a September 2014 Technical Review Panel on Contraceptive Services in Medicaid and the Children's Health Insurance Program (CHIP) and a scan of state policies and interviews with several state Medicaid officials. Emerging approaches to mitigate challenges in fourteen states, identified as of March 2015, involve a combination of contractual, payment strategies, and policy guidance. Additional states may also use similar strategies which fall into five broad categories:

1. Provide timely, patient centered comprehensive coverage for the provision of contraceptive services (e.g., contraception counseling; insertion, removal, replacement, or reinsertion of LARC or other contraceptive devices) for women of child-bearing age.
2. Raising payment rates to providers for LARC or other contraceptive devices in order to ensure that providers offer the full range of contraceptive methods.
3. Reimbursing for immediate postpartum insertion of LARC by unbundling payment for LARC from other labor and delivery services.
4. Removing logistical barriers for supply management of LARC devices (e.g., addressing supply chain, acquisition, stocking cost and disposal cost issues).
5. Removing administrative barriers for provision of LARC (e.g., allowing for billing office visits and LARC procedures on the same day; removing preauthorization requirements).

The following [table](#) summarizes state efforts to optimize LARC utilization, followed by a detailed summary of the approaches three states use. CMS is available to provide technical assistance to states who are interested in reviewing options for modifying LARC policies. For additional information on this Informational Bulletin, please contact Karen Matsuoka at karen.matsuoka@cms.hhs.gov or 410-786-9726.

Table 1. State Medicaid Payment Strategies to Optimize Long-Acting Reversible Contraception (LARC) Utilization in 14 States

A scan of state reimbursement policies on LARC was conducted in 2014, resulting in the identification of payment practices in 14 states. This table describes the payment strategies that these 14 states used to optimize LARC utilization. The payment strategy noted for each state is intended to be a short title, while the policy description provides an overview of the key components of the state Medicaid policy that supports the strategy. The implementation considerations are specific details about how the state implements the payment strategy while maintaining compliance with the state policy.

State Effective Date	Payment Strategy	Policy Description	Implementation
<p>Alabama April 2014</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting or outpatient practice setting.</p>	<p>1. Covers the cost of the LARC device/drug implant as part of the hospital’s cost, and the insertion of the device/drug implant is billable to Medicaid when the insertion occurs immediately after a delivery before discharge from an inpatient setting.</p> <p>2. Covers the cost of the LARC device/drug implant as part of the hospital’s cost, and insertion is billable to Medicaid when the insertion is provided in an outpatient setting after delivery and immediately after discharge from an inpatient setting.</p>	<p>1. Inpatient: the hospital must use an International Classification of Diseases (ICD-9) delivery diagnosis code within the range 630 – 67914 and must use the ICD-9 surgical code 69.7 (insertion contraceptive device) to document LARC services provided after the Delivery.</p> <p>2. Postpartum LARC in the outpatient hospital setting immediately after discharge from inpatient settings, should be billed on a UB-04 claim form using one code from each of the following with family planning modifier (FP):</p> <ul style="list-style-type: none"> • 58300 Insertion of IUD • 11981-FP Insertion, non-biodegradable drug delivery implant • 11983-FP Removal with reinsertion <p>ICD-9 diagnosis codes:</p> <ul style="list-style-type: none"> • V255 Encounter for contraceptive management, insertion of implantable

State Effective Date	Payment Strategy	Policy Description	Implementation
			subdermal contraceptive <ul style="list-style-type: none"> • V2511 Insertion of intrauterine contraceptive device • V2502 Initiate contraceptive NEC • V251 Insertion of IUD Physician bill on CMS 1500 form using the same coding as above and also indicate Place of Service: <ul style="list-style-type: none"> • 21 Inpatient hospital setting • 22 Outpatient hospital setting
California July 1, 2015	Reimbursement of LARC	General acute care hospitals may submit claims for the long-acting reversible contraceptive methods on an outpatient claim, even when treatment is provided on an inpatient basis	Hospital LARC claims should be billed using the following Healthcare Common Procedure Coding System (HCPCS) codes: <ul style="list-style-type: none"> • J7300 • J7301 • J7302 • J7307
Colorado October 2013	Temporary system work-around for reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting.	Medicaid Management Information System (MMIS) was scheduled for an update to the APR DRG ¹ , in January 2014 to automatically report if a claim includes LARC insertion. For a temporary system work around: <ul style="list-style-type: none"> • The insertion will be reimbursed and paid separately from the global 	1. To receive a LARC payment in addition to the APR DRG, the hospital must include the ICD-9 and Current Procedural Terminology (CPT) codes that are included in the Colorado Medical Assistance Program Revenue Codes UB04/institutional billing form on the same claim as the hospital stay. 2. The “trigger” for LARC payment will be the inclusion of these codes:

¹ 3M™ All Patient Refined Diagnosis-Related Group (APR DRG) Classification System for adjusting data for severity of illness (SOI) and risk of mortality (ROM).

State Effective Date	Payment Strategy	Policy Description	Implementation
	<p>Reimbursements for LARCs outside of the normal encounter (per visit) rate for Rural Health Centers (RHCs)</p>	<p>obstetric fee code.</p> <ul style="list-style-type: none"> • State will cover two LARC devices every five years. <p>RHCs may receive reimbursement for IUDs and implants used for contraceptive purposes in addition to their normal encounter rate reimbursements.</p> <p>Federally Qualified Health Centers (FQHC) do not receive an additional payment for LARCs since the FQHC encounter payment rates are based on “full-cost” reimbursement calculations.</p>	<ul style="list-style-type: none"> • V25.11 – encounter for insertion of intrauterine contraceptive device; and/or • V25.13 – encounter for removal and reinsertion of intrauterine contraceptive device. <ol style="list-style-type: none"> 1. For devices purchased under the 340B Program, individual providers and RHCs must bill the actual acquisition cost for the device. 2. Reimbursement will be based on the actual 340B acquisition cost. For devices not purchased through the 340B program, reimbursements are the lower of the provider’s charges or the rate on the Department’s practitioner fee schedule, whichever is applicable. 3. Reimbursement is separate from any encounter payment the RHC may receive for implanting the device. 4. When a LARC is inserted, removed, or reinserted during a visit, the practitioner must use the appropriate diagnostic code, such as, V25.11 or V25.5, and use the family planning modifier (FP) on the claim form.

State Effective Date	Payment Strategy	Policy Description	Implementation
<p>Georgia April 2014 for practitioner reimbursement;</p> <p>Hospital reimbursement to begin in 2016</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting.</p>	<ol style="list-style-type: none"> 1. Reimburses hospitals and practitioners the cost of the LARC device outside of the global obstetric fee for delivery. 2. Georgia policy, regardless of delivery system (FFS or Managed Care Organization (MCO)) defines “immediate postpartum” as within ten minutes of birth. 3. Devices should be available in the birthing suite to ensure timely insertion. 	<ol style="list-style-type: none"> 1. LARC insertion is considered an add-on benefit and is not included in the DRG reimbursement process. 2. Practitioners receive additional reimbursement when one of the following four devices, indicated by their respective J code, is inserted within ten minutes of birth: <ul style="list-style-type: none"> • J7300 • J7301 • J7302 • J7307
<p><u>Illinois</u> October 2012</p> <p>July 2014</p>	<p>Contraceptive Devices in FQHCs and RHCs</p> <p>Dispensing Fee Incentive</p>	<p>FQHCs and RHCs may receive reimbursement for LARC devices (IUDs and single rod implantable devices) for contraceptive purposes.</p> <p>340B providers may receive a dispensing fee add-on when dispensing highly-effective contraceptives</p>	<ol style="list-style-type: none"> 1. For devices purchased under the 340B Program, the FQHC or RHC must bill the actual acquisition cost for the device. 2. Reimbursement will be based on the actual 340B acquisition costs and must include modifier “UD” in conjunction with the appropriate procedure code. For devices not purchased through the 340B program, reimbursements are the lower of the provider’s charges or the rate on the Department’s practitioner fee schedule, whichever is applicable.

State Effective Date	Payment Strategy	Policy Description	Implementation
<p>October 2014</p>	<p>Increased reimbursement for insertion and removal of LARC in the outpatient setting.</p> <p>Allowed reimbursement for office visit along with LARC insertion/removal procedure on the same day.</p> <p>Outpatient provider office stocking.</p>	<p>1. Increased reimbursement rate for insertion/removal procedures of LARC.</p> <p>2. Provide reimbursement for evaluation/management (E/M) visits, where a practitioner and beneficiary discuss contraceptive options, in addition to same day LARC insertion or removal procedures.</p> <p>3. Pilot program to ensure practitioners have sufficient devices stocked, with automatic re-supply as needed.</p>	<p>3. Reimbursement is separate from any encounter payment the FQHC or RHC may receive for implanting the device.</p> <p>1. When a LARC is inserted, removed, or reinserted during a visit, the practitioner uses a modifier V25 on the claim along with the type of visit:</p> <ul style="list-style-type: none"> • Postpartum visit (CPT 59430) • Initial or annual preventive visit (CPT 99381-99397) <p>2. A practitioner must order the device and document the insertion procedure in both the hospital's and the practitioner's medical record:</p> <p>3. The hospital must use its fee-for-service National Provider Identifier (NPI) to bill the appropriate device or implant (by specific National Drug Code (NDC) on the claim.</p> <p>The hospital must use the appropriate family planning ICD-9-CM diagnosis code (or upon implementation, ICD-10-CM) on the claim.</p>
<p>July 1, 2015</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient setting.</p>	<p>Medicaid allows hospitals separate reimbursement for the LARC device provided immediately postpartum in the inpatient hospital setting.</p>	
<p>Iowa March 2014</p>	<p>Reimbursement of LARC insertion immediately</p>	<p>1. Medicaid allows the insertion of IUDs and other LARC devices</p>	<p>1. Practitioners may bill for the professional service associated with insertion of the</p>

State Effective Date	Payment Strategy	Policy Description	Implementation
	postpartum in the hospital setting.	<p>before the beneficiary leaves the hospital following delivery.</p> <p>2. Payment for these services is allowed for both practitioners and hospitals.</p>	<p>LARC with the appropriate CPT code.</p> <p>2. If a practitioner supplies the LARC, the practitioner may also bill for the device(s).</p> <p>3. When hospitals provide the LARC services, the claim must be submitted as an outpatient claim, separate from the inpatient DRG claim for the delivery. The outpatient claim will be based on the fee schedule for the HCPCS Level II procedure code billed.</p>
<p><u>Louisiana</u> June 2014</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting.</p>	<p>1. Hospitals and practitioners are reimbursed for LARCs as an add-on service in addition to their daily per diem rate for the inpatient hospital stay (DRG rate) or professional services rate, respectively.</p> <p>2. Reimbursement amount is determined by:</p> <ul style="list-style-type: none"> • LARC service provided (insertion or reinsertion) • IUD or non-biodegradable drug delivery implant • The beneficiary’s age (0 – 15 years or 16+ years) <p>3. Medical management, including prior authorization and step</p>	<p>1. In FFS: Hospitals use the appropriate LARC J-code on their hospital stay claim.</p> <ul style="list-style-type: none"> • On a paper claim (CMS 1500) “DME” must be written in bold, black print on the top of the form. • If the hospital bills electronically, the 837P must be used with the Durable Medical Equipment (DME) file extension. <p>2. Payment for the LARC is equal to the DME fee schedule, and added to the amount of the hospital’s per diem payment.</p> <p>3. If a LARC device is expelled after insertion, the state applies a pre-determined cost of reinsertion and replacement device to the standard DRG or professional services rates.</p> <p>4. MCO contracts with the state prohibit</p>

State Effective Date	Payment Strategy	Policy Description	Implementation
	<p>departments or family planning agencies.</p>	<p>into the hospital’s provider base rate calculation.</p> <p>2. Hospital-based practitioners bill the professional claim for surgical procedure through the hospital. The professional claim for hospital-based providers does not include the device.</p> <p>3. Community-based practitioners are reimbursed separately for the professional service of inserting the device as well as the device itself (if supplied by the physician) on the claim.</p>	<p>2. Family planning agencies that participate in MassHealth are reimbursed for the LARC device and insertion when billed with the appropriate code:</p> <p>11981 - Insertion, non-biodegradable drug delivery implant 11983 - Removal with reinsertion, nonbiodegradable drug delivery implant 58300 - Insertion of intrauterine device (IUD) J7301 Levonorgestrel-releasing intrauterine contraceptive system, 13.5 mg J7302 Levonorgestrel-releasing intrauterine contraceptive system, 52 mg S4989 Contraceptive intrauterine device, including implants and supplies</p> <p>3. The community based practitioner is reimbursed separately for the professional service of inserting the device as well as for the device itself if supplied by the physician. Billing is done on a professional claim and paid according to a fee schedule.</p> <p>4. Regular HCPCS updates to capture new device availability</p>
<p>Montana January 2015</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting.</p>	<p>LARCs inserted at the time of delivery are excluded from the PPS inpatient APR-DRG group. Montana Medicaid is allowing PPS hospitals to unbundle the LARC device and the insertion from the inpatient delivery claim.</p>	<p>These services can now be billed as an outpatient service on a 13X type of bill, and will be paid at the OPSS rates. The following HCPCS/CPT codes are allowed:</p> <ul style="list-style-type: none"> • J7300 • J7301 • J7302

State Effective Date	Payment Strategy	Policy Description	Implementation
			<ul style="list-style-type: none"> • J7307 • 11981 • 58300
<p>New Mexico 2014</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting.</p>	<p>1. Practitioners receive reimbursement for insertion in the hospital and for the device if the practitioner supplied it.</p> <p>2. Hospitals are reimbursed for the device as a medical supply company.</p> <p>3. Insertion within the same surgery as a Cesarean section is considered incidental to the surgery, and therefore not reimbursed. However, the practitioner will still be reimbursed for the device.</p>	<p>1. Hospitals are reimbursed for the device if:</p> <ul style="list-style-type: none"> • The facility is enrolled in the New Mexico Medicaid program as a medical supplier (provider type 414); a separate NPI is not required. • Date of service is the same as the DRG date of service. • Hospital’s professional claim (837P electronic claim or CMS-1500 form) is submitted as a medical supply company. • Claim includes the appropriate HCPCS procedure code and NDC number for the device. • Place of service (POS) code is 21 (inpatient hospital). • The billing taxonomy number for a medical supplier appears on the claim (typically 332B00000X). <p>2. Practitioners are reimbursed for the device and insertion if:</p> <ul style="list-style-type: none"> • Billed on the same professional claim (837P electronic or CMS-1500 paper) as the delivery procedure. • Claim indicates the device HCPCS code and NDC number.

State Effective Date	Payment Strategy	Policy Description	Implementation
			<ul style="list-style-type: none"> • Claim indicates procedure CPT codes (most likely 58300 or 11981). • Claim indicates the POS as 21 (inpatient hospital).
<p>New York April 2014</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting.</p>	<ol style="list-style-type: none"> 1. Reimbursement provided for the LARC device and insertion during postpartum inpatient hospital stay. 2. Medicaid will reimburse for the replacement of IUDs once every five years (Skyla every three years) per manufacturer recommendations. Reimbursement will be provided for an IUD sooner than five years if medically necessary. 	<ol style="list-style-type: none"> 1. Hospitals include the LARC invoice separately from the inpatient labor and delivery claim. 2. Physicians, midwives, and nurse practitioners may submit a separate claim to FFS Medicaid for their professional services.

State Effective Date	Payment Strategy	Policy Description	Implementation
<p><u>South Carolina</u> March 2012</p>	<p>Reimbursement of LARC insertion immediately postpartum in the inpatient hospital setting.</p> <p>Outpatient procedure using specialty pharmacy.</p>	<p>1. Allows reimbursement to the practitioner and hospital for delivery and all costs associated with LARC.</p> <p>2. In the outpatient setting, practitioners may order a LARC device for delivery to the practitioner’s office by a specialty pharmacy.</p> <p>3. Increased LARC reimbursement rate to cover slightly more than the practitioner’s cost to purchase LARC devices to stock in their office.</p>	<p>1. Inpatient reimbursement guidelines for the cost of the LARC in addition to the DRG for labor and delivery:</p> <ul style="list-style-type: none"> • Using the HCPCS code. • Using device J-codes. • Using a family planning modifier on the physician claim when billing for insertion <p>2. Hospitals are reimbursed for the device by submitting:</p> <ul style="list-style-type: none"> • The ICD-9 Surgical Code • The ICD-9 Diagnosis Codes • A UB-04 or Institutional Claim so that a gross-level credit adjustment can be generated. <p>3. Payments to hospitals through FFS:</p> <ul style="list-style-type: none"> • DRG portion of the claim will be paid in the regular weekly claims payment cycle. • The LARC reimbursement will process as a gross level credit adjustment and will appear on a future remittance advice on a monthly quarterly basis. <p>4. Outpatient reimbursement guidelines for the cost of the device:</p> <ul style="list-style-type: none"> • Device can be shipped for a specific patient overnight from specialty

State Effective Date	Payment Strategy	Policy Description	Implementation
			<p>pharmacy.</p> <ul style="list-style-type: none"> • Device billed directly to Medicaid FFS or the MCO. • The practitioner’s office has 30 days to return the unopened device to the specialty pharmacy if the device is not used for the specific patient for which it was ordered. The cost of the device is then credited back to Medicaid FFS or the MCO. <p>5. Reimbursement for LARC through MCO’s: The LARC policy is a FFS benefit; however, provision of LARC is estimated and included in the MCO’s per member per month (PMPM) rate. Reimbursement methodology may differ between FFS and MCO’s. The state currently includes coverage for the provision of LARCs in both its contractual language and its rate setting methodology with the MCO’s. MCOs in the state individually contract with providers and negotiate their rates; claim filing procedures differ based on the MCO.</p>
Texas	Pharmacy reimbursement	1. Texas Health and Human	1. State currently contracts with two

State Effective Date	Payment Strategy	Policy Description	Implementation
<p>August 2014</p>	<p>for LARC devices.</p>	<p>Services (HHS) allows providers the option to prescribe and obtain a limited number of LARC products from specialty pharmacies and to return unused and unopened LARC products through a “abandoned unit return” program.</p> <p>2. Practitioners may continue to obtain LARC products, then bill for them when they are used under the medical benefit.</p>	<p>specialty pharmacies to deliver Mirena and Skyla to practitioners (Walgreens Specialty Pharmacy, LLC and CVS Caremark Specialty Pharmacy).</p> <p>2. Practitioners continue to bill for the insertion of the LARC product.</p> <p>3. If the patient was eligible for Medicaid on the date of service when the LARC product was prescribed and ordered, but the patient is no longer eligible for Medicaid, when the LARC product is inserted, Medicaid will cover the device but will not reimburse for the insertion procedure claim.</p>

Detailed Payment and Policy Approaches of Three Selected States

Below is a more detailed description of the strategies used by three states (Illinois, Louisiana and South Carolina) to optimize LARC utilization and illustrate the range of approaches they have employed within existing state authorities.

The states were selected based on the range of changes they have implemented and the length of experience they have had implementing these innovative approaches. For example, the state of South Carolina was the first state to implement an immediate postpartum payment for LARC separate from the labor and delivery Diagnosis-Related Group (DRG) payment. Since establishing the policy, the state has addressed implementation challenges and seen improvement in its rates. These more detailed state examples provide greater insight for states considering which options may be most viable to address payment barriers for their Medicaid enrollees.

Illinois

Long-Acting Reversible Contraception (LARC) Optimization Strategies

SUMMARY

This document describes payment strategies the Illinois Department of Healthcare and Family Services (HFS) incorporated into its Family Planning Action Plan to increase access to safe and effective LARC.

BACKGROUND

In 2014, HFS implemented the Family Planning Action Plan to increase access to family planning services for Medicaid beneficiaries by: 1) providing comprehensive and continuous coverage for family planning services; and 2) aligning policies and reimbursement to providers to promote provision of highly effective contraception.¹

- In 2010, 52 percent of all pregnancies (128,000) in Illinois were unintended.²
- Its unintended birth rate was 57 per 1,000 women aged 15-44.
- This same year, the reported public expenditures for family planning client services in Illinois totaled \$57 million, of which \$40.7 million was paid by Medicaid.³
- Illinois has the 21st highest pregnancy rate in the nation among adolescents between ages 15 and 19.

To address the rate of unintended pregnancies, the state Medicaid agency implemented several payment strategies to increase access to safe and effective LARC, such as IUDs, in an effort to reduce the number of unintended pregnancies. These strategies are: 1) increased provider reimbursement for insertion and removal of LARC in the outpatient practice setting; 2) provide reimbursement for an evaluation/management (E/M) visit on the same day as LARC insertion or removal procedures; 3) provision for reimbursement of actual LARC acquisition costs under the 340B program to Federally Qualified Health Centers and Rural Health Centers; provision for hospital reimbursement of LARC in addition to the DRG reimbursement for labor and delivery; 5) increased providers' 340B federal drug pricing program dispensing fee to encourage providers to supply LARC and other highly effective methods; and 6) established statewide Medicaid policy for family planning and reproductive health services to improve access to LARC methods.

ILLINOIS MEDICAID REIMBURSEMENT FOR LARC

Effective July 1, 2015, HFS implemented a policy to allow hospitals to receive separate reimbursement for LARC devices provided immediately postpartum in the inpatient setting, in

¹ Illinois Department of Healthcare and Family Services (2014). Important family planning policy change and payment increases. Retrieved from <http://hfs.illinois.gov/assets/101014n1.pdf>.

² Guttmacher Institute (2014). State facts about unintended pregnancy: Illinois. Retrieved from <http://www.guttmacher.org/statecenter/unintended-pregnancy/pdf/IL.pdf>.

³ Sonfield A and Gold RB, Public Funding for Family Planning Sterilization and Abortion Services, FY 1980–2010, New York: Guttmacher Institute, 2012, < <https://www.guttmacher.org/pubs/Public-Funding-FP-2010.pdf> >.

addition to the DRG reimbursement for labor and delivery. Providers not employed by the hospital may bill the respective Current Procedural Terminology (CPT) code for LARC insertion in addition to the labor and delivery fee.⁴

Illinois also implemented several other payment strategies that are intended to increase access to LARC placement in the outpatient practice setting.

Reimbursement of LARC Procedures in the Outpatient Practice Setting

In October 2014, HFS increased the reimbursement rate for the insertion, removal, and reinsertion of IUDs and implants in the outpatient practice setting.⁵ HFS increased the reimbursement rate for implant insertions by 20 percent and doubled the reimbursement rate for IUD insertions. LARC insertion and removal procedures may be reimbursed on the same day as evaluation and management visits. Physicians can receive the increased reimbursement for LARC insertion by including the LARC insertion CPT code on their billing form. Physicians can also use the relevant CPT codes to bill for the removal and reinsertion of implants, and removal of IUDs.

Federally Qualified Health Centers (FQHC) and Rural Health Center (RHC)

Effective October 13, 2012, FQHCs and RHCs may elect to receive reimbursement for implantable contraceptive devices. To the extent that the implantable contraceptive device was purchased under the 340B Drug Pricing Program, the FQHC or RHC must bill the actual acquisition cost for the device. Reimbursement is made at the FQHC or RHC's actual 340B acquisition cost for implantable contraceptive devices purchased through the 340B program. For implantable contraceptive devices not purchased through the 340B program, reimbursement is based on the lower of the provider's charges or the rate on the Department's practitioner fee schedule, whichever is applicable. Reimbursement for the device is separate from encounter payment for related procedures.

Additional Dispensing Fees to Providers

Effective July 2014, HFS increased the dispensing fee add-on payment to \$35 for providers who dispense highly-effective contraceptives through the 340B federal drug pricing program. In order to receive the additional fee, providers must identify 340B purchased drugs by reporting modifier "UD" in conjunction with the appropriate procedure code and actual acquisition cost for the birth control method on the claim form.

⁴ Illinois Department of Healthcare and Family Services (2015). Informational Notice: Hospital Billing and Reimbursement for Immediate Postpartum Long-Acting Reversible Contraceptives. Retrieved from <http://www.hfs.illinois.gov/html/063015n.html>.

⁵ Illinois Department of Healthcare and Family Services (2014). Important family planning policy change and payment increases. Retrieved from <http://hfs.illinois.gov/assets/101014n1.pdf>.

Approaches for Managed Care Entities

The state's actuarially sound rates include reimbursement for LARC devices and clinical insertion. The state's external quality review organization (EQRO) has developed a family planning readiness review tool and reviews the plans' family planning policies and procedures. Additionally, the MCO contract was revised to include language that provider policies/protocols shall not present barriers that delay or prevent access, such as prior authorizations or step-therapy failure requirements; and that clients should receive education and counseling on all FDA-approved birth control methods from most effective to least effective, and have the option to choose the preferred birth control method that is most appropriate for them.⁶

Pharmaceutical Pilot Programs in Outpatient Settings

HFS is piloting a new program with Bayer HealthCare (Mirena and Skyla) and Teva Pharmaceuticals (Paragard) to make these products available in physician offices without upfront physician costs. This will allow for an inventory of these LARC devices so that they are available when a patient returns for a postpartum visit, or at their annual reproductive health visit. If the patient decides she wants to use this type of contraception, it can be inserted immediately and the patient will not have to return for a second visit. This will improve the efficiency of this program and should lead to increased use of these devices. If deemed successful, the pharmaceutical companies plan to scale the program to a national level.⁷

OUTCOMES

While the impact of these payment strategies have not yet been assessed, Illinois expects that improved access to contraceptive care for low-income women will result in savings due to a decrease in unintended pregnancies and the associated costs.

⁶ Wheal, L. (2015). Interview with Illinois Medicaid.

⁷ Illinois Department of Healthcare and Family Services (2014). Family Planning and Reproductive Health Services. Retrieved from <http://www.hfs.illinois.gov/assets/062614n1.pdf>.

Louisiana

Long-Acting Reversible Contraception (LARC) Optimization Strategies

SUMMARY

This document describes a payment strategy the Louisiana Medicaid agency implemented to increase access to safe and effective LARC.

BACKGROUND

Prior to June 2014, Louisiana covered LARC devices under the pharmacy benefit. In the clinical setting, the pharmacy reimbursement rate for LARC devices was approximately \$300 less than what the LARC devices cost; hence, physicians who provided LARC devices in the hospital setting suffered financial loss.⁸ Furthermore, physicians were not reimbursed for 30 percent of the LARC devices ordered at the time of consent in the hospital, due to the failure of the patients for whom the device was ordered to return for subsequent insertion in the office practice setting.⁹

- In 2010, 60 percent of all pregnancies (53,000) in Louisiana were unintended.
- That same year, the reported public expenditures for family planning client services in Louisiana totaled \$39.3 million; this includes \$34.5 million through Medicaid.¹⁰

To address the high rate of unintended pregnancies, Louisiana Medicaid initiated a process to increase LARC utilization that included: 1) LARC reimbursement for insertion immediately after delivery in the inpatient hospital setting; 2) provider education; 3) adjustments in its State Plan Amendment (SPA) to allow more flexibility in inpatient and outpatient LARC reimbursement; and 4) the inclusion of LARC reimbursement requirements in its MCO contracts.

LOUISIANA MEDICAID REIMBURSEMENT FOR LARC

Effective June 2014, the Louisiana Department of Health and Hospitals implemented a LARC reimbursement policy as a central component to reducing the number of unintended pregnancies among low-income women. This policy increases access to LARC placement in the inpatient hospital setting immediately after delivery and before the patient is discharged from the facility by:

- Allowing hospitals to receive reimbursement for the full cost of five LARC devices (Skyla, ParaGard, Nexplanon, Merina, and Norplant) in addition to the DRG that is normally paid to hospital.¹¹ Manufacturer wholesale prices are re-evaluated and re-adjusted annually.

⁸ Gee, R. (2014). Interview with Louisiana Medicaid Medical Director.

⁹ Gee, R. (2015). Interview with Louisiana Medicaid Medical Director.

¹⁰ Guttmacher Institute (2014). State facts about unintended pregnancy: Louisiana. Retrieved from <http://www.guttmacher.org/statecenter/unintended-pregnancy/pdf/LA.pdf>.

¹¹ Louisiana Medicaid Management Information System (2015). Louisiana Medicaid professional services fee schedule. Retrieved from http://www.lamedicaid.com/provweb1/fee_schedules/FEESCHED.pdf.

- Allowing hospitals or physicians receive additional fees for LARC insertion.
- Eliminating the use of medical management activities, such as prior authorization or step therapy, for LARC devices or procedures.¹²

Hospital Reimbursement of LARC Insertion Immediately Postpartum

The recent changes in Louisiana Medicaid payment policies provide reimbursement to acute care hospitals for LARC devices inserted immediately postpartum and prior to discharge.^{13,14} The state is separately reimbursing the hospital both for the cost of the LARC device as well as its insertion procedure in order to clearly demonstrate to hospitals that they are fully reimbursed for LARC costs according to the Louisiana Medicaid fee schedule for durable medical equipment (DME).¹⁵

Louisiana MCOs have also supported and willingly adopted coverage and the reimbursement policy for postpartum LARC insertion. The hospital and the provider must submit their claims to the MCO for payment. The reimbursement rates are established by the MCO.¹⁶

Practitioner Reimbursement of LARC Insertion

Practitioners who insert a LARC device immediately post-delivery receive separate reimbursement for this service as defined in the Professional Services Program.¹⁷ In the event that a LARC device is expelled after insertion, Louisiana factors the cost of the expulsion into the reimbursement and also pays for reinsertion of a new LARC. Adding the LARC devices to the physician schedule rather than just the pharmacy schedule allows the physician to store the device in office and not have to provide it to a specific individual.¹⁸

Capitated Managed Care Implementation

Louisiana Medicaid is completing a three year transition from a FFS reimbursement model to mandatory managed care, which will account for 95 percent of all Medicaid enrollees by December 2015. Based on retrospective data, Louisiana Medicaid negotiates blended capitated

¹² Gee, R. (2015). Interview with Louisiana Medicaid Medical Director.

¹³ Hospitals record the appropriate LARC J-code on the paper CMS1500 claim form with “DME” written in bold, black print on the top of the form when submitting their claim to the Fiscal Intermediary (FI). When the hospital bills electronically, the 837P must be used with the DME file extension. The Louisiana Medicaid DME fee Schedule J codes are only intended for use on Inpatient Claims.

¹⁴ Foubister, V. (2013). Case study: Louisiana’s poor rankings make improving birth outcomes a state imperative. Quality Matters. Retrieved from <http://www.commonwealthfund.org/publications/newsletters/quality-matters/2013/february-march/case-study>.

¹⁵ Louisiana Department of Health and Hospitals (2014). Long acting reversible contraceptives (LARCs) for inpatient hospitals. Retrieved from <http://dhh.louisiana.gov/assets/docs/BayouHealth/HealthPlanAdvisories/2014/HPA14-9.pdf>.

¹⁶ Gee, R. (2014). Interview with Louisiana Medicaid Medical Director.

¹⁷ Practitioners include the LARC insertion code with the family planning modifier on their billing form (CMS 1500 or electronic equivalent). The reimbursement is dependent on the LARC service provided and the patient’s age. The global CPT codes include: 11981 - Insertion, non-biodegradable drug delivery implant; and 58300 - Insertion of intrauterine device (IUD).

¹⁸ Gee, R. (2015). Interview with Louisiana Medicaid Medical Director.

per member per month (PMPM) fees to account for projected LARC insertions. MCO contracts require hospital and practitioner reimbursement for LARC devices and procedures at a minimum of the FFS fee schedules for the same DME or CPT codes, respectively. In addition, the MCOs are not permitted to require prior authorization for LARC devices or procedures.

All five Louisiana Medicaid MCOs voluntarily adopted the LARC reimbursement strategy. The MCO contracts contain a requirement for developing birth outcomes quality improvement programs that align with the state's goals, and a one percent withhold of MCO administrative fees to fund shared savings-based pay for performance (P4P) incentives. These provide clear boundaries and predictable revenues that allow MCOs maximum flexibility in their interactions with their network providers and the incentives they offer providers and/or patients.

The Louisiana Medicaid agency achieved the legal authority to require MCOs to fully participate in LARC quality improvement efforts in four phases:

1. Applied non-payment strategies such as provider and MCO education and outreach to establish expectations for MCO performance;
2. Presented a compelling case for the political support needed to establish birth outcomes as the state's highest health priority;
3. Submitted a SPA to include LARC utilization payment policies as a strategy to improve birth outcomes; and
4. Aligned MCO contractual requirements with state Medicaid FFS payment strategies to increase LARC utilization.¹⁹

ANTICIPATED OUTCOMES

Changes to reimbursement of LARC devices and procedures in the hospital were initiated in 2014. The Louisiana Medicaid Medical Director reports that due to these payment policy changes, voluntary election of LARC insertions increased from nine percent (7,000) of all child-bearing aged enrollees in 2013 to 11 percent (10,000) in 2014.

¹⁹ Gee, R. (2015). Interview with Louisiana Medicaid Medical Director.

South Carolina

Long-Acting Reversible Contraception (LARC) Optimization Strategies

SUMMARY

The South Carolina Birth Outcomes Initiative (SCBOI) launched in July 2011 to improve maternal and infant health outcomes and to reduce Medicaid costs. The SCBOI has supported the development and implementation of a LARC payment policy, which is a central component of South Carolina's effort to reduce the number of unintended pregnancies among low-income women and at-risk adolescents.

BACKGROUND

Low-income women of childbearing age who are sexually active with limited access to effective contraception and family planning services are likely to have unintended pregnancies and increase Medicaid spending.³⁰

- In 2010, public expenditures for family planning services in South Carolina totaled \$33.7 million, including \$25 million paid by Medicaid.³¹
- In 2011, South Carolina ranked as the 12th highest state in teen pregnancy.³²
- Only 50% of Medicaid-covered postpartum women in South Carolina attend the postpartum visit.

To address this problem, South Carolina Department of Health and Human Services (SCDHHS) leveraged their Birth Outcome Initiative (BOI), an active collaborative of hospitals, providers, and policymakers, to increase LARC placements through changes to existing payment policies. Payment policy changes included 1) increased reimbursement for LARC devices; 2) reimbursement of LARC insertion immediately postpartum; and 3) supply management through the pharmacy benefit.

SOUTH CAROLINA MEDICAID REIMBURSEMENT FOR LARC

The selected payment strategies are intended to increase access to LARC placement in both the inpatient hospital setting as well as the outpatient practice setting. Key elements of the reimbursement strategy include:

- Funding the full costs of four LARC devices (Skyla, ParaGard, Nexplanon, and Mirena).

³⁰ Guttmacher Institute (2014). State facts about unintended pregnancy: South Carolina. Retrieved from <http://www.guttmacher.org/statecenter/unintended-pregnancy/SC.html>.

³¹ Sonfield A and Kost K, Public Costs from Unintended Pregnancies and the Role of Public Insurance Programs in Paying for Pregnancy-Related Care: National and State Estimates for 2010, New York: Guttmacher Institute, 2015, <<http://www.guttmacher.org/pubs/public-costs-of-UP-2010.pdf>>.

³² U.S. Department of Health and Human Services Office of Adolescent Health (2014). South Carolina adolescent reproductive health facts. Retrieved from <http://www.hhs.gov/ash/oah/adolescent-health-topics/reproductive-health/states/sc.html#>.

- Providing additional fees for insertion, device, and removal (if medically necessary) in addition to the DRG fee that is paid to hospital.
- Eliminating prior-authorization or step therapy requirements for LARC procedures.

Reimbursement of LARC Insertion Immediately Postpartum in the Hospital

In March 2012, the South Carolina became the first state in the country to change its reimbursement policy in order to increase LARC placement immediately after delivery and prior to hospital discharge.³³ Prior to that time, hospitals were not incentivized to perform this procedure due to the lack of payment for this activity (beyond the existing DRG payment). South Carolina's Medicaid program now reimburses hospitals the cost of the LARC device as well as payment to the physician for its insertion immediately post-delivery. This LARC reimbursement is provided in addition to any other payments for maternity related services.

Hospitals receive this increased payment through a quarterly adjustment for prior month's claims (credit adjustment). To receive reimbursement for the LARC device itself, hospitals must include on each Uniform Billing (UB-04) claim for delivery services the Healthcare Common Procedure Coding System (HCPCS) code that represents the device. As well as the International Classification of Diseases (ICD-9) Surgical and Diagnosis Codes that best describe the service delivered.

Physicians may also receive reimbursement for immediate post-delivery LARC insertion by including on their billing form (CMS 1500 or electronic equivalent) the LARC insertion code with the family planning modifier.

After the first year of implementation, South Carolina Medicaid learned that hospitals were not receiving the additional LARC payments; further implementation guidance and system changes were needed. In the second year of implementation, all Medicaid providers received specific billing instructions identifying how to capture appropriate reimbursement for all fees covered by the payment policy. By the third year of implementation, providers were receiving appropriate reimbursement, including retrospective payments that previously had not been billed or processed accurately.³⁴

These new payments reimburse all costs and clinical efforts associated with LARC placement and promote a highly cost-effective, preventive health practice. However, payment alone is not sufficient to ensure LARC placements. This strategy also requires continued collaboration with MCOs, hospitals, and physicians to ensure that all stakeholders understand the purpose of these increased payments and the impact LARC will have on reducing unintended pregnancies and Medicaid costs.

Reimbursement of LARC Insertion in the Outpatient Practice Setting

³³ Health Management Associates (2013). Medicaid reimbursement for immediate post-partum LARC. Retrieved from <https://www.acog.org/~media/Departments/LARC/HMAPostpartumReimbursementResource.pdf>.

³⁴ Giese, M. (2015). Interview with SCDHHS Director of Birth Outcomes Initiative.

SCDHHS also addressed the initial costs to providers for stocking LARC devices in its SCBOI “specialty benefit” in the spring of 2014. The new payment policy allows a physician to order a LARC device for a specific Medicaid recipient which is shipped to the physician’s office by a specialty pharmacy which is designated by either the state Medicaid agency’s Pharmacy Benefit Manager or by the individual MCO’s. The device can be shipped overnight and is billed directly to Medicaid FFS or the MCO so that the physician does not incur the initial cost of the device. The physician’s office has 30 days to insert the LARC for the specific patient for which it was ordered and bill Medicaid the insertion fee only, or to return the unopened device to the specialty pharmacy if the device is not used. The cost of the device is then credited back to Medicaid or the MCO.

Capitated Managed Care Implementation

Managed care enrollment is mandatory in South Carolina. As a result, approximately 90 percent of all Medicaid births are covered by the six fully capitated MCOs. Although the Medicaid agency did not require its capitated MCOs to adopt this payment policy, all six of them did so voluntarily.

In the first year of implementation of the policy, South Carolina did not develop a payment mechanism specifically for the MCOs to provide this service. Instead, the additional fees associated with LARC payments were prospectively estimated and included in the actuarially sound MCO per member per month (PMPM) rate. The MCO then provides the additional payments to the clinicians in the MCO’s network through their negotiated contractual rates. It is not possible to compare the differences in LARC utilization between the MCO and FFS populations (90 percent and 10 percent, respectively).

The MCOs use their regular claims processing cycles to pay for these LARC services and don’t have a special process like FFS Medicaid, which was described earlier.

OUTCOMES

As noted above, South Carolina initiated changes to the reimbursement of LARC devices and procedures in the hospital setting in March 2012 and issued a clarification bulletin for billing in 2013 which allowed for appropriate claims payment dating back to the inception of the policy. Although the impact of both of these policy changes has not yet been fully evaluated, South Carolina has documented that their rate of voluntary election of inpatient insertions has gone from approximately 0% to 16%. South Carolina also has seen a 110% increase in inpatient LARC utilization between FY2013 through FY 2015.