Research Review Disposition of Comments Report

February 2, 2020

Research Review Title: *Skin Substitutes for Treating Chronic Wounds*

Draft review available for Public Reviewer from February 13, 2019 to March 8, 2019.

Research Review Citation: Snyder DL, Sullivan N, Margolis DJ, Schoelles K. Skin Substitutes for Treating Chronic Wounds. Technology Assessment Program Project ID No. WNDT0818. (Prepared by the ECRI Institute-Penn Medicine Evidence-based Practice Center under Contract No. HHSA 290-2015-00005-I) Rockville, MD: Agency for Healthcare Research and Quality. February 2020. Available at: *http://www.ahrq.gov/research/findings/ta/index.html*.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for Public Reviewer for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the Public Reviewer period, authors use the commentators' submissions and comments to revise the draft research review.

Commentator &

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	Agree that 100% healing (well defined in report) is simple and measurable. These patients are very complex and for a variety of reasons complete healing is sometimes impossible because of covert multiple underlying factors. 50% healing in 31 days is a reasonable parameter second only to total healing see Margolis references. Healing is not quite as good as complete healing but does demonstrate therapeutic efficacy. It is mentioned in the report but should, in my opinion be an end point especially for larger ui.o	

Commentator & Affiliation	Section	Comment	Response
		therapies, and skin substitutes. It should be noted that the 510(k)-cleared products listed in Table 3 are not considered to be, or evaluated as, skin substitutes by the FDA, but instead are evaluated as wound dressings intended to cover a wound and keep the wound moist. There are a variety of antimicrobial-containing wound dressings, such as silver wound dressings that might be considered advanced therapies. Thus, more discussion on wound dressings/standard of care and how they differ from Advanced Therapies would be helpful	used the products listed under the Centers for Medicare & Medicaid Services (CMS) codes Q4101 to Q4204 as a starting point and looked for similar products listed in FDA product codes to generate a list of products. We included only products indicated for chronic wounds and available commercially in the United States. We note that FDA does not refer to any product or class of products as “skin substitutes,” and we are not proposing an official classification system.” By updating from the 2018 list to the 2019 list we have added 5 new products that were not already included in the report: Restorigin Amniotic Tissue Patches, Coll-a-derm, Genesis Amniotic Membrane, SkinTE, and Geistli3gs13 (t)-11 (ic)-15.7 ( )]TJ3

Commentator & Affiliation	Section	Comment	Response
		been defined, and there is overlap between what is regulated as a wound dressing and what is considered by the manuscript to be a skin substitute. This statement should be revised, placed more in context by providing clear definitions of wound dressings and skin substitutes, or removed.	
KI Reviewer #1	Introduction	There has been a move away from wet to dry dressings for "standard of care" to moist wound healing dressings. I understand that saline gauze dressings are used in many RCTs but the authors could consider making a statement that the field is tending to move in this direction.	Page 11, line 18: Text reads: “However, the methods for achieving each of these wound management principles varies among clinical practice guidelines and clinical studies.[1] Using saline wet-to-dry gauze on any chronic wound is no longer considered part of standard wound care. We excluded any studies that used saline wet-to-dry gauze.”
KI Reviewer #1	Introduction	The major issue that both the authors and others have struggled with has been the definition of skin substitutes. This is particularly true when it comes to certain collagen products that in my opinion, are more advanced dressings than skin substitutes. In my mind, the skin substitute should stay around for a while and provide some structure. Collagen dressings that are changed 3 x weekly would not be. I understand that they are basing their inclusion based on FDA classification, but they may want to mention this as a limitation of the study.	Defining a skin substitute is beyond the scope of the technical brief. “For this report, we have not created a definition for a skin substitute product. Instead, we used the products li.3 (c)-2.6 (t)1.

Commentator & Affiliation	Section	Comment	Response
		lack of documented offloading raise the possibility that the the standard of care (SOC) used in these studies was not consistent with best practices? (1) Which offloading method was employed and how effective was it?, and (2) Given the underutiliz0.52 31. oN36.04 459.48 266.2scn 9 0 0 7 (z731.)8.6 (C.6 (C2 (?,)27 (ar)3.7(en t)27 (ar)3.72 (h)13.(en t)27 1719.3	

Commentator & Affiliation	Section	Comment	Response
		over any wound, including those with exposed muscle, tendon, bone and joint capsule. This includes diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), arterial ulcers, pressure sores, dehisced surgical wounds, wounds requiring an autograft, and others. TheraSkin is not a device, it is human skin, and human skin is the gold standard skin substitute in wound repair (Song, 2013 and Mathes, 2005).	

Commentator & Affiliation	Section	Comment	Response
Osiris Therapeutics, Inc.		significant errors in how our product Grafix was classified. Grafix is a cellular amniotic membrane product. In some sections of the report Grafix is described as cellular, in others Grafix is described as acellular. This is an important distinction and will change other reported findings once corrected.	Guiding Questions 3, Guiding Question 4, and all relevant [illegible] or of the U.S. Department of Healt and Human Services."
			Bacground: Thank you for submiting references on te role of MSCs. We have added the following text to tackground section on Chronic Wounds: "Chronic wounds may also have deficient and defective mesenchymal stem cells (MSCs). MSCs syize growtactrs and cytkines that affect te proliferation and remodeling phases of wound repair. Recruiting MSC int wound may be an essental part of te wound healing process."
Public Reviewer #7: Louis Savant			

Commentator & Affiliation	

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	I believe the authors have clearly stated the limitations of the data which exists. The source paper exclusion of pressure ulcer patients is problematic in practice - many of these compounds are being used in pressure ulcers.	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2: Zack Bridges ACell Inc.	Methods	No comment	Thank you for your review of the report.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Methods	Methods: 1. PAGE 5, Methods Section, AHRQ made the statement regarding discussions with key informants (KIs): "We selected KIs with expertise in chronic wound care, including wound assessment technologies, wound care research, tissue engineering, and dermatology." a. Solsys Medical, citing transparency provisions under the 21st Century Cures Act, contends that the names and affiliations of all key informants utilized by AHRQ should have been included BOTH in the Draft Technical Brief as well as the upcoming Final Technical Brief on AHRQ's 2019 Skin Substitutes for Treating Chronic Wounds given that it is important for reviewers and commenters of both the Draft and Final reports to have transparency of which key informers helped inform all aspects of the draft and upcoming final reports.	We include the list of KIs and Peer Reviewers in the final draft and cannot comment on AHRQ's decision to exclude this information in the draft report.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Methods	Page v: Methods • We question the methods used in terms of the systematic review of literature performed as it did not include the most recent AmnioBand peer-reviewed, PubMed-indexed, 80-patient, multicenter, prospective Randomized Control Trial, DiDomenico et al 2018 (Epub 2018, July 17).	Page v: Methods: Thank you for pointing out the omission of the DiDomenico et al. 2018 study. This study is now included in the final report.

Commentator & Affiliation	Section	Comment	Response
Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation		difference when you randomize. Moreover, the wound sizes for the studies vary from 1-25cm2. As such, it begs the questions: What happens if the wound sizes were greater than a 15% difference? Is this considered biased? How can one place a tolerance on the percent difference in wound sizes if you had a "randomized" study?	determined that none of the included studies were at high risk of bias.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Methods		

Commentator & Affiliation	Section	Comment	Response
Osiris Therapeutics, Inc.		supported in the literature, and Osiris recommends AHRQ point out the published literature cited for making these statements.	AHRQ. No statement in this article should be construed as an official position of Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services."
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Methods	One thing Osiris has an issue with is the Risk of Bias questions make no mention of manufacturers funding, yet this is cited in the	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7: Louis Savant Osiris			

Commentator & Affiliation	Section	Comment	Response
		or the routine practice conditions where these products are utilized. Real-world effectiveness research evaluates an intervention as it is typically utilized in practice and help determine if efficacy can be translated to routine practice settings. Five recent CERs evaluated the impact of treatment with living cellular construct products (Apligraf or Dermagraft) compared to other types of products in the treatment of venous leg ulcers (VCUs) or diabetic foot ulcers (DFUs). We ask that these studies (citations listed below) and their findings be considered and included in the final report. Marston WA, Sabolinski ML, Parsons NB, Kirsner RS. Comparative effectiveness of a bilayered living cellular construct and a porcine collagen wound dressing in the treatment of venous leg ulcers. Wound Repair Regen. 2014;22(3). doi:10.1111/wrr.12156. Kirsner RS, Sabolinski ML, Parsons NB, Skornicki M, Marston WA. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. Wound Repair Regen. 2015;23(5):737-744. doi:10.1111/wrr.12332. Kraus I, Sabolinski ML, Skornicki M, Parsons NB. The Comparative Effectiveness of a Human Fibroblast Dermal Substitute versus a Dehydrated Human Amnion/Chorion Membrane Allograft for the Treatment of Diabetic Foot Ulcers in a Real-world Setting. Wounds A Compend Clin Res Pract. 2017. Treadwell T, Sabolinski ML, Skornicki M, Parsons NB. Comparative Effectiveness of a Bioengineered Living Cellular Construct and Cryopreserved Cadaveric Skin Allograft for the Treatment of Venous Leg Ulcers in a Real-World Setting. Adv Wound Care. 2018;7(3). doi:10.1089/wound.2017.0738. Sabolinski ML, Gibbons G. Comparative effectiveness of a bilayered living cellular construct and an acellular fetal bovine collagen dressing in the treatment of venous leg ulcers. J Comp Eff Res. 2018;7(8):cer-2018-0031. doi:10.2217/cer-2018-0031.	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	X The authors seem to have singled out wound size/duration and number of comorbidities as the only important baseline parameters, suggesting 15% as the split point. We question how ^Õà as Met	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	Our comments below are specific to questions 3, 4,5, 6, 7 and 10 under “Risk of Bias” (page 7) and address each of these questions separately. *Question 3 - Were the numbers of comorbidities similar (no more than a 15% difference) at the start of treatment between groups?* First, this criteria does not seem to be based on any known standard and in itself will limit the population for clinical trials. Second, this approach implies that all comorbidities have an equal weight in terms of the potential to affect wound healing, and that all are in the same direction (for example, BMI for reasons we don’t full understand can be “protective.”) Third, in the majority of wound care RCTs, it is standard practice to adjust the primary endpoint for *all* imbalances between groups in some type of regression. The authors of the study have ignored this approach altogether. *Question 4 - Were the mean wound sizes at the start of treatment similar (no more than a s altogether [illegible] (of)g0 Td (oup/TT2 1 S2 cs 0.?B0.009 Tw 0.253 061 1 Tf -0.009 T*	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	Question 6 - *Was the method of measure wound condition at enrollment reported?* This question is ambiguous and needs far more definition to make sense. What do the authors mean by "wound condition?"—area, severity of wound, how much slough, necrotic tissue, etc.? In the vast majority of RCTs, there is a screening period during which many of these factors are measured (and inclusion/exclusion criteria are applied) and the wound is debrided if appropriate. We don't understand the purpose nor the origin of this question.	Question 6 states "Was the method of measuring wound condition at enrollment reported? This question is intended to detect selection bias in studies that do not report the method of wound measurement.
Public Reviewer # 10: Marcia Nusgart			

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	This question is difficult to understand. Maybe write it as two sentences or clarify	Guiding Question 4: Guiding Questions were previously approved by AHRQ, CMS, and KIs. Revisions are not possible at this time.
Peer Reviewer #2	Results	summary	Guiding Question 4 Overview: Our medical editor recommended the use of Overview.
Peer Reviewer #2	Results	delete 6%	Guiding Question 4 Overview: We have made the revision as requested.
Peer Reviewer #2	Results	What about a national registry. These work well for determining relevant outcomes and could be used for clinical studies. They are cost effective, enable quality, and enhance standardization to name a few benefits. Societies typically create them and industry supports them. FDA also works closely with them. They include clinical outcomes and PROs. They could include financial analysis as well. This would clearly benefit the wound healing field. There are many examples of these to learn from	Guiding Question 6, Key Points; Summary and Implications: We agree of the 0 9 5855 216.84 2pkee of6 (i)8(c)10.ee o3 (outn)13

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	Is compliance measured in the studies? I suspect this is a a big part of chronic wounds and a problem we should address	Guiding Question 6, Outcomes: While we agree that adherence to treatment is important for wound healing, we did not identify measures of adherence in the included studies.
Peer Reviewer #3	Results	Although alluded to quality of life is a major need. Does the wound dressing decrease pain, increase mobility, etc? We prescribe biologic agents for Rheumatoid Arthritis at great cost why not wounds? There is little agreement about a standard metric for quality of life and it would be a great help for AHRQ to recommend a standardized tool be developed.	Guiding Question 1: While we have expanded on the importance of reporting patient-related outcomes using wound-related pain scales throughout the document, the recommendation to develop a standardized tool is beyond the scope of the report. srhesr 86.67.64 2[(s)-w [(77.3 (t)2 (he)13.l (r)3.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	1) p. 9 - FDA Regulations for Skin Substitute Products. In this section it is important to note that Class III PMA devices under the product code MGR are considered interactive wound and burn dressings, which may include an intended use of being a skin substitute. Another relevant product code is the MDD product code for dermal replacement device. The Class III devices include combination products (Dermagraft and Apligraft), but they also contain single entity devices (Integra). It is important to distinguish the Class III devices from the unclassified wound dressings reviewed under 510(k). The devices listed in Table 3 are not considered skin substitutes by the FDA and are not cleared or approved to make a claim of being a skin substitute; instead, they are evaluated for their ability to cover a wound and keep it moist and to not delay the normal wound healing process. It is incorrect to state that (lines 16-19, p. 9) "Skin substitutes regulated through premarket submission are primarily combination products..." The majority of the devices listed in Table 3 are single-entity devices, not combination products, which are cleared under the unclassified product code KGN (collagen wound dressing). In some cases, the products may be single-entity devices or combination products (when combined with an antimicrobial or other drug) under product code FRO (wound dressing with a drug). I recommend that the text on page 9 be revised to reflect the information above.	1) p. 9 - FDA Regulations for Skin Substitute Products: Please see revised text regarding the FDA coding information. Most of the references to FDA regulations has been removed. Products are no longer categorized or grouped by FDA regulatory categories.
Peer Reviewer #6	Results	2) The search should have included the 510(k) premarket notification database, searching for clearances under KGN and FRO (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm). While some 510(k) clearances are identified in Table D-3 and D-4 in Appendix D, it does not appear that all cleared products since 2012 are identified. Conducting the search in this manner will likely ide [illegible]	

Commentator & Affiliation	Section	Comment	Response
		manuscript, is not clearly identified in the manuscript. For details about the 510(k) submission pathway for unclassified devices, please see information on the FRO classifsec, 81Fn0/.at,	

Commentator & Affiliation	

Commentator & Affiliation	Section	Comment	Response
KI Reviewer #4	Results	The amount of detail is appropriate in the results section, and the studies are described using clear language and appropriate characteristics. The key messages are well written, explicit and	

Commentator & Affiliation	Section	Comment	Response
		primary studies, we believe it's reasonable to request that a study that captured and reported on this outcome is highlighted.	
Public Reviewer #2: Zack Bridges ACell Inc.	Results	Within guiding question 6 under the discussion related to study design outcomes (page 44) the authors mention that QOL scales including the Diabetic Foot Ulcer (DFU) Scale, are included in ongoing studies. The published study mentioned previously in the technical brief, Frykberg et al. 2016, also measured patient quality of life using the DFU Scale and reported this outcome. While we agree that future studies should capture and report on this outcome, we would ask that the authors add "Quality of Life Scales" as a consideration to the evaluation of primary studies comparing skin substitutes and include a mention of this outcome and cite Frykberg et al. 2016, as an example of a study with reported QOL scores. We believe it is important to make this point clear as to not confuse readers into thinking this outcome has not been captured.	In Guiding Question 6, we make a general statement regarding quality-of-life scales used by included studies and ongoing clinical trials. The sentence reads: “Quality-of-life scales used in included studies or ongoing clinical trials included wound-related quality-of-life scales (Cardiff Wound Impact Schedule, W-QoL) quality-of-life scales specific to diabetic wounds (Diabetic Foot Ulcer Scale), quality-of-life scales specific to venous leg ulcers (Sheffield Preference-based Venous Leg Ulcer 5D), and general quality-of-life scales (Short Form [SF]-36, SF-12v2).”

/Artifact BMC (2378,2 0 3013-71.01Q1b e f 50726f 507230.16Tp-)T

Commentator & Affiliation	Section	Comment	Response
		Substitutes versus Standard of Care and on page 45 under Findings as well as listed in Table 18 on page 35. LifeNet Health designed our intent to treat RCT based upon the December 22, 2011 AHRQ Technology Assessment on Skin Substitutes recommendation to include a comparative arm. Guidance from our reimbursement consultants strongly suggested the primary purpose of the study should be a comparison against SOC to be consistent with previously completed Randomized Trial data but a smaller cohort comparing a similar acellular dermal matrix was acceptable.	

Commentator & Affiliation	Section	Comment	Response
			We have also added a paragraph describing the ASTM International classification system for CTPs.
Public Reviewer #13: Bud Brame LifeNet Health	Results	AHRQ made the following statement in the findings section (p. 15): "Natural human dermis must be sterilized to prevent potential disease transmission." This statement is completely inaccurate. *Tissues obtained from human donors may have the risk of infectious disease transmission; however, industry standards developed by the FDA and AATB may be utilized to minimize and eliminate this risk without requiring sterilization.*[2] Xenografts or "Animal tissues must be sterilized to prevent potential disease transmission" is a more accurate declaration.	Please note the disclaimer in the Front Matter of the report: "The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services." We have removed the sentence referencing the sterilization of natural human dermis to prevent potential disease transmission, but note that the risk of transmission of infectious agents by human tissue products is still a potential risk
Public Reviewer #13: Bud Brame LifeNet Health	Results	In the Findings section (p. 15) AHRQ states, "Cells within the transplanted dermis would typically lead to rejection within 10 to 15 days; therefore, the donated skin tissue must be processed to remove the cells." The statement that cells must be removed or edited to state epidermis rather than dermis and completely remove the verbiage from therefore on as it not accurate." [3]	We have removed the sentence regarding transplanted dermis.
Public Reviewer #13: Bud Brame LifeNet Health	Results		

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #13: Bud Brame LifeNet Health	Results	The review of the data with each of the RCT's mentioned in the Technical report does not mention the number of units required to close a wound on average. Many of the studies mentioned in the report required multiple applications to heal the wounds identified in their studies, which can be a financial burden to the wound care center, CMS, private payer or mostly importantly, the patient. The AHRQ should be transparent with the data finds when summarizing to clearly demonstrate the application requirement of the CTP to repair on chronic wound. [1] Standard Guide for Classification of Cellular and/or Tissue Based Products (CTPs) for Skin Wounds. ASTM International. February 2016 DOI:10.1520/F3163-16 [2] *Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005 Sep;25(3):587-605.*) [3] *Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005 Sep;25(3):587-605*	

Commentator & Affiliation	Section	Comment

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response
		than other allogenic cell types, they still contain maternal DNA and are therefore immunogenic.	
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	9. PAGE 19, Findings Section. AHRQ made the statement: "Theraskin (Table 13) is a cryopreserved human, living, split-thickness allograft that contains fibroblasts and keratinocytes. The	

Commentator & Affiliation	Section	Comment	Response
		makers will replace the AHRQ 2012 report on Skin Substitutes for Treating Chronic Wounds with the new 2019 report, when it is made Final. As such, relevant product studies from the 2012 report should be carried over into the 2019 Technical Brief and the Appendices. For example, with TheraSkin, Solsys Medical expects that both of the following references from the 2012 report be included in the 2019 AHRQ Technical Brief: a. DiDomenico L, Landsman AR, Emch KJ, Landsman A. A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. Wounds. 2011 Jul;23(7):184-189. b. Landsman AS, Cook J, Cook E, Landsman AR, Garrett P, Yoon J, Kirkwood A, Desman E. A retrospective clinical study of 188	A Dt-2.7 (tdc)10.7 (l)-0.7 abe (n®)7.6 (v)10.7 cenlat ulogrJtou E, L 7 (f)2

Commentator & Affiliation	Section	Comment	Response
		Wounds. 2011 Jul;23(7):184-189. TheraSkin DFU healing rates at both 12 and 20 weeks were 67.7% compared to Apligraf 41.3% (12 Weeks) and 47.1% (20 weeks). Statistically significant conclusion: TheraSkin is non-inferior to Apligraf. ii. Budny AM, Ley A. Cryopreserved allograft as an alternative option for closure of diabetic foot ulcers. Podiatry Management. 2013 Aug:131-136. A total of 9 patients' charts were reviewed and included in a case series with 11 wounds, all treated with TheraSkin. 7 of the 11 wounds (63.6%) healed after an average of 12.0 weeks (range 7-19). Results of this retrospective real-world case series reproduced clinical outcomes found in larger published studies for TheraSkin. iii. Wilson TC, Wilson JA, Crim B, Lowery NJ. The use of cryopreserved human skin allograft for the treatment of wounds with exposed muscle, tendon, and bone. Wounds. 2016 Apr;28(4):119-125. TheraSkin achieved closure in 93.3% of large (average 16cm2), difficult to heal wounds (containing exposed muscle, tendon and bone) using an average of 2 grafts. Full granulation was achieved with TheraSkin at 36.14 days, and closure at 133 days. Statistically significant conclusion: TheraSkin is effective in healing difficult DFUs with exposed structure. iv. Landsman A, Rosines E, Houch A, Murchison A, Jones A, Qin X, Chen S, Landsman AR. Characterization of a cryopreserved split-thickness human skin allograft: TheraSkin. Adv Skin Wound Care. 2016 Sep;29(9). This study concluded that TheraSkin contains 26,000 viable cells/mm3. Physiologically, the maximum number of viable cells is limited to 40,000/mm3. It is estimated that Apligraf contains 12,600 viable cells/mm3 and that Dermagraft contains 4,400 viable cells/mm3. It was found that the amount of the type I and type III collagen, as well as the ratio of type I to type III collagen in TheraSkin is equivalent to fresh unprocessed human split-thickness skin.	
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results		

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	16. PAGE 32, Findings Section, AHRQ made the statement	

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response
		c. Reduced recidivism: TheraSkin® had significantly fewer reoccurrences over the course of the year following treatment (p = 0.0417). d. Intent-to-treat healing rates were higher for wounds treated with TheraSkin® across all grades of DFUs, demonstrating TheraSkin® is effective across wounds of varying severity. Statistical significance is observed for Wagner Grade 4 wounds (p=0.0401). DFU with Wagner Grade above 2 are associated with higher risk of amputation. (Source: Oyibo SO, Jude EB, Tarawneh I, Nguyen	

Commentator & Affiliation	Section	Comment	Response
Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC		population seen in clinical practice." a. Solsys Medical agrees with ARHQ and the KIs on this concept. However, RWE, as described in previous comments above, would be much more reliable than RCTs in this case given that broader patient selection with comorbidities and in poor health which are representative of clinical practice is extremely difficult to do in an RCT, would come at a huge cost, and would take years to accomplish. Again, this is another reason why Solsys Medical urges AHRQ to consider RWE and why Solsys Medical is planning a number of future well-designed, matched cohorts clinical studies (provided in comments above) which focus on RWE.	evidence (<5 RCTs) had been identified (see Methods). The approach and the inclusion criteria used in this technical brief were reviewed and approved by the KIs. The protocol was also posted on AHRQ's website for public review.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A.			

Commentator & Affiliation	Section	Comment	Response
		patient populations and the largest number of clinical sites participating. FDA has provided industry guidance on “Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment” based on standards identified during review of the first PMA product, Apligraf.	


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Commentator & Affiliation	Section	Comment	Response
		• different site personnel assessed the wound status and the study included no evidence of any effort to ensure assessor blinding to tbe producte h6 473.4b64 553.8 62.519 0.481 re f 230.16 3.4 (perr re W n BT (us)-2H4h15.3 TD [(t)h15.3 a)13.4 (per)17 (peo)15.3 (h6 47	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	Given the limitations in the risk assessment tool used and our concern about the accuracy of risk level attached to many of the studies reviewed, we urge AHRQ to consider using an alternative tool to measure risk of bias. As an alternative to the methodology described in the draft report, we ask recommend that AHRQ use the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology to assess clinical wound care publications. GRADE domains include: 1) Inconsistency, 2) Indirectness, 3) Imprecision, 4) Publication bias, 5) Qualitative outcome, and 6) Overall certainty of evidence. We believe that this tool would better capture the risk-of-bias in wound care studies than the ten question assessment used in the draft.	GRADE is used to measure strength of evidence of an evidence base, and not individual studies. As implemented by the EPC Program, it includes the domain of "study limitations," which is determined from the risk of bias of the individual studies.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*COMMENTS ON GUIDING QUESTIONS* *Guiding Question 1: What skin substitutes currently used to treat chronic wounds are being regulated by the U.S. Food and Drug Administration (FDA) under the following pathways: PMA, 510(k), PHS 361[21 CFR 1270 and 1271]?* There is particular confusion about device classification, patient risk, and device effectiveness concerning wound care products. The FDA device classificat (i)10.7 (i)12.6 (c)2r009 Tc 0.009 Tw 0.24 3 0 Td e4 Tc .9 0 0 9v1* /Tw 3.147 0 Td 2.611 (he)]TJ 0 Tc 0 T	

Commentator & Affiliation	Section	Comment	Response
[redacted]		study, and both showed statistically significant benefit for [redacted]g chronic venous ulcers. Those two RCTs were for	

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Commentator & Affiliation	Section	Comment	Response
		The following are examples but are not all inclusive: CollaSorb® collagen dressing, Endoform™ dermal s	nclus

Commentator & Affiliation	Section	Comment	Response
		that contains living cells, growth factors, and an architecturally-preserved human ECM scaffold that vascularizes. Around 7-14 days after application, the epidermal cells and any antigenic components are removed but the dermal scaffold and the matrix is retained. The tissue is safely procured according to industry standards developed by the FDA and AATB within 24-hours postmortem from an organ donor. According to the manufacturer, living cells survive through procuring, cryopreservation, and thawing. FDA 0.2290 Tc 0 Tx-0.02 re f* BT /CS0 cs 0 scn -0.009 Tc 0.009 TI-0.009 Tc 0.069 Tw 0.253 0 Td [(o)-13 (r)4 (gan)]TJ 0 Tc 0 T3.5	

Commentator & Affiliation	Section	Comment	Response
		study populations. This allows for valid comparison of the results between the groups. Therefore, studies have exclusion criteria (i.e. uncontrolled diabetes, poor vascularization, immunosuppressive drugs, end stage renal disease, infection, or required restrictions by FDA labeling). These factors are 4	

Commentator & Affiliation	Section	Comment	Response
		8. Afib 19.9% 9. Alzheimer's 22% 10. Asthma 30.6% 11. COPD 27% 12. Depression 34% 13. Cancer 13.8% The US Wound Registry (USWR) which hosts the Cellular and/or Tissue based Therapy Registry (CTPR: ClinicalTrials.gov Identifier: NCT02322554) was able to conduct an evaluation of the difference between patients with chronic wounds and the subjects enrolled in clinical trials.wcal	

Commentator & Affiliation	Section	Comment	Response
		· Renal impairment/ESRD/Renal dialysis/Renal transplant · Any organ transplant · In diabetics, HbA1c > 8-10 · Nutritional impairment/Albumin < 3.0 mg/dl · Osteomyelitis · Peripheral arterial disease Using the above exclusion criteria, among 8,611 wound center outpatients, approximately 88% would have been excluded from all pivotal wound care RCTs. Even more troubling, based on propensity scoring, 3 of 4 major trials that brought new products to market enrolled patients healthier than the "man on the street." The value of real-world data was again clearly demonstrated in 2007 when the FDA required the company KCI (now Acelity) to evaluate the safety of Negative Pressure Wound Therapy (NPWT) in comparison to moist wound care in the outpatient setting. The USWR was able to assess the risk of infection and bleeding in nearly 1,000 NPWT patients, 200 of whom were on Coumadin, compared to nearly 9,000 moist wound care patients. NPWT RCTs had excluded all patients on anticoagulants so the only way to evaluate the safety of NPWT among patients on blood thinners was via real-world data.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	The most common wounds are NOT diabetic foot	

Commentator & Affiliation	Section	Comment	Response
Alliance of Wound Care Stakeholders		factors that affect this complex process. The USWR in collaboration with the Institute for Clinical Outcomes Research (ICOR) created a risk stratification for wounds now called the Wound Healing Index (WHI). 789 The WHI can be used to create matched cohorts for retrospective comparative effectiveness (CER). Using USWR data, it is possible to control nearly every aspect of patient care mathematically.10 The WHI also makes it possible to quantify the difference between real world patients and the subjects enrolled in RCTs. In	

Commentator & Affiliation	Section	Comment	Response
		cases shown outcomes similar to that seen in RCTs, and in some case shown significant differences. In addition to the RWE studies, there are several studies that we believe that AHRQ should have reviewed as part of this TA. They incl(tQ q47.601 0 0.007 Tc 0.007 Tw 0.253 0 Td [(ca)2-2J Td [7t)-113st	

	Commentator & Affiliation	Section	Comment			Response
					systematic reviews provide the highest level of evidence for products if the review shows that a study is a quality study, these should not be omitted from this analysis.	
					x *Raspovic KM, Wukich DK, Naiman DQ, et al. Effectiveness of viable cryopreserved placental membranes for management of diabetic foot ulcers in a real world setting. Wound Repair Regen. doi: 101111/wrr12635. Accessed 27 July 2018.*	
3.1(Td)]ThTw		*0*	*(tt787*	*(e)-15*	x *Jd(s)-4.3*	

SOC based on data reported by Sheehan et al. *Diabetes Care* 26:1879–1882, 2003 that shows percent area reduction (PAR) of a wound at 4 weeks is a good predictor of the 12-week healing rate. Margolis et al. *Diabetes Care* 22:692–695, 1999 showed SOC continued for 12 weeks has a healing rate of 24%, and at

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		addressed by currently registered organi72 Tw 9 0 0 9 370.2 513.12 T	

Commentator & Affiliation	Section	Comment	Response
Manuel Pubillones, MD Noridian Helathcare Services		addition to other wound care modalities compared to other wound care modalities in patients with different types of chronic wounds, for patient.	
Public Reviewer #12: Joseph Rolley Integra LifeSceinces		Li scn 42D(o)13.3 (l)-0.7 (l)-0.6 (ey)]TJ 0 Tc 0 Tw 6388f* B 51[(U)6.61124 (i)e'6(e)-4 7 efIs	

Commentator & Affiliation	

Commentator & Affiliation	Section	Comment	Response
Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation		contains sweat glands and hair follicles, we believe this also needs to be added to this description.	glands, hair follicles, and cells involved in immune function, growth, and repair. The subcutaneous layer is composed of adipocytes that form a thick layer of adipose tissue.”
Public Reviewer #6: Daniel G. D eletal			

Commentator & Affiliation	Section	Comment	Response
		Biologics), Edison, NJ, USA AlloPatch® is an aseptically processed donated human reticular dermal tissue for use as a chronic or acute wound covering AmnioBand® Musculoskeletal Transplant Foundation (dba MTF Biologics), Edison, NJ, USA AmnioBand® is an aseptically processed human allograft placental matrix comprised of amnion and chorion for use as an acute or chronic wound covering	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 13, Guiding Question 1 Overview: In deference to our donor and donor families, we ask that any reference to "human cadaver" dermis or any variation thereof (e.g. use of the term "cadaver") be replaced with the term donated human dermis (or a variation thereof e.g. dermal allograft). We at MTF honor the gift of donation and to use the term "cadaver" dehumanize the deceased donor and is disrespectful towards his or her family who has donated this gift of life. Once again, we commend the use of the term "human placental membranes" stated in that same line as opposed to "amniotic membrane."	Page 13, Guiding Question 1 Overview: (a4 (i)-oQ q 5010.7 9#6

Commentator & Affiliation	Section	Comment	Response
Musculoskeletal Transplant Foundation		placental membranes but request that the term “human cadaver dermis” be stricken and replaced with “donated human dermis” again in deference to donor and donor families. We would also add the following citation as a further reference to harsh processing damaging placental tissue.	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 16, Table 6. Acellular/Dermal replace from human amniotic membrane o Again, we request the term “amniotic” be replaced with “placental.”	Page 16, Table 6: We replaced “human amniotic membrane” with “human placental membrane” throughout the document.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o As on Page 11, Table 4, we ask that the registered trademark “AmnioBand®” be the referenced device name and all references to “AmnioBand Allograft Placental Matrix” be deleted. Furthermore, we ask that the “Manufacturer” information be changed to read so that the row within Table 6 now reads: Device Manufacturer Regulatory Information AmnioBand® Musculoskeletal Transplant Foundation (dba MTF Biologics), Edison, NJ, USA HCT/P	Page 11, Table 4: AmnioBand has been changed as requested.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page 20: Guiding Question 2: Overview • Page 20, 1st paragraph, 11th line, please replace the term “human cadaver dermis” with “donated human dermis” for the reasons previously disclosed. • Page 20, 12th line, please replace the term “human amniotic membranes” with “human placental membranes” for the reasons previously disclosed.	Page 20: Guiding Question 2: We have replaced the text “human cadaver” with “donated human dermis. and “human amniotic membrane” as “placental membranes.”
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 21, Figure 1, Acellular portion of algorithm adapted from Davison-Kolter et al. Skin Substitute Classification System: 3.47 (pl)-0. a n d m u l u l n 7 s 6	

Commentator & Affiliation	Section	Comment	Response
Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation		conduct information including at least method of patient enrollment, care setting, and use of run-in-period." We believe a run-in period is important as they can separate out "good healers" from others. Both the Zelen et al. (2018) AlloPatch RCT and the DiDomenico et al. (2018) AmnioBand RCT have always included a 2-week run in period prior to randomization of the subjects. • Page 22, regarding statement (i) "Measurement and assessment methods including method of assessment(s); frequency and time points for assessments(s); and blind of assessors." Within our studies healing validation was adjudicated by an independent panel of physicians blinded to patient study group assignments, as well as being blinded to the principal investigator's assessment.	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 24, Key Points, 4th bullet point regarding "the 13 distinct skin substitutes examined in 17 RCTs, we believe AmnioBand should be included in this section as the brief is missing the DiDomenico et al. (2018) RCT published online July 2018. Currently, the technical brief only includes the DiDomenico et al (2017) RCT.	Page 24, Key Points, 4th bullet point: We have replaced DiDomenico 2016 study with the DiDomenico 2018 study.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 24, Key Points, 6th bullet point "Eighty-two percent of studies enrolled fewer than 60 patients per arm. All studies were manufacturer-funded, and most studies were conducted in U.S. wound care centers" We question why the minimum range was set at 60 patients per arm. Sample sizes should be prospectively calculated based on achieving at least a 95% confidence level and the statistical standard 80% power to detect a pre-determined difference of interest in proportion healed with treatment from standard of care (SOC). The power and confidence levels should be conventional for clinical trials and the sample sizes should be deemed sufficient for the endpoint which is to show superiority of treatment to SOC control (FDA 1998). Moreover, it should be recognized that the majority of pharmaceutical studies are funded by manufacturers for reasons limited, in part, the independent appropriations of the studies. The statement in this section as is leaves one with the impression that this is a limited to skin	


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Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 25, 3rd paragraph regarding Guo et al. 2017 meta-analysis. This study is outdated and should not be included in AHRQ Technology Assessment Technical Brief to be reported out sometime in 2019 or thereafter. It does not include the most recent AlloPatch peer-reviewed, PubMed-indexed, 80-patient, multicenter, prospective RCT (Zelen et al. 2018) and therefore is not update-to-date. In this paragraph it states “50 percent of studies enrolled fewer than 25 patients per arm.” The Zelen 2018 study enrolled 80 patients, 40 per arm and we believe this is	

Commentator & Affiliation	Section	Comment	Response
Osiris Therapeutics, Inc.		document, and incorrectly listed as an “acellular” product in other parts of the document. Since the AHRQ may be used by CMS and other payers to define products, possibly for coverage or reimbursement purposes, it is critical that the AHRC be corrected to accurately describe all products, including Grafix. There are many examples of this. Examples include: Page 19: Four amniotic membrane-derived products claim to have viable cells: Affinity human amniotic allograft, FloGraft amniotic fluid-derived allograft, Grafix, and GrafixPL Prime (correct) • Page 20, Table 11 – Grafix is listed as a cellular product (correct) • Pages 25, 26, 27, 31, 32, 33, 34, 36, 37, 38 Grafix is listed as acellular (incorrect) • Page 28 should include Grafix under the cellular vs standard of care. Page 29 should include Grafix RCT as Cellular vs. Cellular • In the Appendix, Grafix is listed as acellular in the evidence tables on pages C-9 and C-18, C-23 (this incorrectly describes the product in the context of the evidence as it is presented. For example, the Grafix vs. Dermagraft RCT compares to cellular products to each other. This is important.) All of the incorrect classifications need to be corrected. Also, correctly classifying Grafix as cellular is going to change some of the findings in the Systematic Reviews section starting on Page 24 when comparing cellular and acellular products	

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Osiris Therapeutics, Inc.		be classified as acellular dermal, cellular dermal, and cellular epidermal and dermal substitutes.	

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Commentator & Affiliation	Section	Comment	Response
		study. Four AEs involved the study wound in the hFDS group, and only one AE involved the study wound in the vCPM group. All 5 of these AEs were wound-related infections. Six of seven serious adverse events (SAEs) in the hFDS group involved the index ulcer: five events of active osteomyelitis or cellulitis infection and one abscess. Four SAEs were reported in the vCPM treatment group. Pe4f6 (n 13.3 (l)-0.76ev)10.7 C /P <<1.307 -1.1d-4 13.3 (l)-0.7e-0.7 (op7 (er)3.7 7 (s)-2..6 (ol)-0.6 (s)-2.7 (ed)13.3)-11 ( )]2.6 ( )13.	

Commentator & Affiliation	Section

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Commentator & Affiliation	Section	Comment	Response
MiMedx Group, Inc.		the opportunity of keeping clinical trial costs down, surrogate endpoints that are carried forward as an assumed conclusion can in certain circumstances increase the risk of detection bias and reporting bias especially when evaluating the statistical significance between treatment and control cohorts in larger multicenter RCTs. Furthermore, in the future utilizing the GRADE approach to the systematic review process would properly weight a study's quality and true impact on guiding clinical practice standards. (2) The GRADE review method has now been adopted as part of The Centers for Medicare & Medicaid Services (CMS) Local Coverage Determinations (LCDs) development process and must now be utilized by all overseeing Medicare Administrative Contractors (MACs).	
Public Reviewer #18:			

Commentator & Affiliation	Section	Comment	Response
		Methods: Our three comments in this section reference a perceived error of omission we noted in Methods 1. Data Collection, subsections b. Grey Literature Search and c. Published Literature Search. As well, we have a recommendation for improvement under these same subsections. 1) Error of Omission As stated in the key messages, one of the main goals of this review titled “Skin Substitutes for Treating Chronic Wounds” was to identify and assess randomized controlled trials (RCTs) as well as suggest best practices for future studies. The Methods section notes a systematic search of published	

Commentator & Affiliation	Section	Comment	Response
		2) Additional Recommendation for Improvement	

Commentator & Affiliation	Section	Comment	Response
		1) EpiFix (dHACM) study outcomes (EpiFix® with Standard of Care vs. Standard of Care (SOC) alone): Per-Protocol (PP) • EpiFix at 12 weeks = 81% of patients who received weekly EpiFix plus SOC had complete healing by 12 weeks. • Blinded adjudicators identified 17% of EpiFix patients had poorly debrided wounds • 95% of wounds treated with EpiFix remained closed at 16 weeks • Standard of Care at 12 weeks = 55% of patients who received weekly SOC had complete healing in 12 weeks. • Blinded adjudicators identified 11% of SOC patients had poorly debrided wounds • 86% of wounds treated with SOC-alone remained closed at 16 weeks • Subjects identified in the PP cohort as having inadequate debridement were 71% less likely to heal within 12 weeks when controlling for covariates. (p=0.005) Intent-To-Treat (ITT) • EpiFix at 12 weeks = 70% of patients who received weekly EpiFix plus SOC had complete healing by 12 weeks. • Standard of Care at 12 weeks = 50% of patients who received weekly SOC had complete healing in 12 weeks. • Subjects identified in the INT cohort as having inadequate debridement were 64% less likely to heal within 12 weeks, when controlling for covariates. (p=0.022) 2) EpiCord (dHUC) Study Outcomes (EpiCord with Standard of Care vs. Standard of Care (SOC) alone): Per-Protocol (PP) • 81% of patients who received dHUC plus SOC had complete healing by 12 weeks. • Blinded adjudicators identified 66% of study patients received adequate debridement • 96% of wounds remained closed at 16 weeks • Standard of Care at 12 weeks = 54% of patients who received Alginate plus SOC had complete healing in 12 weeks. • Blinded adjudicators identified 74% of Control patients received adequate debridement • 85% of wounds remained closed at 16 weeks	

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion	I do agree with the future direction suggestions -	

Commentator & Affiliation	Section	Comment	
Peer Reviewer #6	Discussion	6) p. 39 Guiding Question 4 Overview. This section should note that there was variation in Standard of Care across studies and the SOC may not be equivalent across the different studies.	p. 39 Guiding Question 4 Overview: We have added the following text: “Studies examining acellular dermal substitutes versus standard of care indicated more effective complete wound healing and a shorter time to heal with acellular skin substitutes for diabetic foot ulcers and venous leg ulcers. Standard of care varied across these studies, which may have contributed to differences in outcomes.”
Peer Reviewer			

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion	10) p. 43 line 36-39: "Failure to heal after 6 weeks of treatment ...may be an appropriate criteria for..." This statement is not a recommendation on study design; instead, it appears to be a recommendation on clinical care guidelines. It should be removed, or revised to reflect a recommendation on study design (i.e., what is the study question? There does not seem to be any therapy studied in the recommendation).	p. 43 line 36-39: We have revised the text to read: "In addition, KIs suggested that studies should treat patients for a minimum of 12 weeks to determine healing and then follow them until 6 months to determine wound recurrence. Skin substitutes would be applied as recommended by the product labeling and by a trained healthcare provider. Failure to heal after 6 weeks of treatment with a skin substitute may be an appropriate criterion for discontinuing use of a skin substitute and switching to another advanced therapy option was also suggested."
Peer Reviewer #6	Discussion	11)p. 43 Outcomes line 52-55: Note that Complete Wound Closure is not the only clinical outcome that is described as a potential endpoint in the FDA guidance, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071324.pdf Potential endpoints related to Improved Wound Healing include, Incidence of complete wound closure, accelerated wound closure, facilitation of surgical wound closure, quality of healing (cosmesis and function). There are additional potential endpoints for Improved Wound Care. I recommend that these additional endpoints be dis.7 (i)-0es9(nt)15.3 (s)-2.7 (be-0.b8734nt)15.3 (s1-2 (l)29.3 (ounhy5.3 (s).147 TD4D)9m (m)-3a7 TD4D)9m (or)3.7 D4Dm	

Commentator & Affiliation	Section	Comment	Response
KI Reviewer #1	Discussion	The authors could consider mentioning publication bias. Most of these studies are industry sponsored. Despite the fact that people are supposed to register clinical trials, most negative clinical trials are never published. This gives a biased view of results, The authors may want to mention this as a limitation of their studies.	Page 47, Summary and Implications, Evidence Gaps section: We have added text to this section after our review of ongoing

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response
Osiris Therapeutics, Inc.		decisions about treatment choices. We also want to point out that tax-payer dollars are currently being used to pay for products with no evidence the product is more effective than SOC or placebo; and that patients are sharing in the cost for these products.	
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Discussion	On Page 46 the following statement must be revised to accurately reflect corrections to how Grafix is classified throughout the TA: "Only one study compared cellular dermal substitutes with standard of care." The above statement should state, "There are	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2: Zack Bridges ACell Inc.	Conclusion	Next Steps: In the section "What Should Future Studies Have in Common", consider also adding commentary on standardizing minimum wound size or evaluating the "rate of wound closure". Given the wide variability in wound sizes represented by the	

Commentator & Affiliation	Section	Comment	Response
		understanding regarding any of that which we believe the assessment should have provided.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Conclusion	Moreover, we are in agreement with the statements recognizing that the data reviewed (RCTs) is not the best evidence to review when assessing the evidence for chronic wound care patients, as the exclusion criteria eliminates most of the patients that would benefit from the treatment of CTPs. There was recognition by the AHRQ that real world	

Commentator & Affiliation	Section	Comment	Response
		websites. If there are discrepancies between what is in the literature/manufacturer website other sources vs. what is on the public FDA website, this should be identified in the manuscript and Appendix D where appropriate. Similarly if there is any public information on the FDA website for these human tissues, the	

	Section	Comment	Response
Chief Medical Officer, Solsys Medical, LLC			

Commentator & Affiliation	Section	Comment	Response
Noridian Helathcare Services			
Public Reviewer #18: William H. Tettelbach, MD, FACP, FIDSA, FUHM, CWS MiMedx Group, Inc.	Appendix	Appendixes: Links to EpiFix (dHACM) and EpiCord (dHUC) RCTs https://onlinelibrary.wiley.com/doi/full/10.1111/iwj.12976 https://onlinelibrary.wiley.com/doi/full/10.1111/iwj.13001 References: (1) Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care. 2003 Jun;26(6):1879-82. PMID: 12766127 (2) The GRADE working group. 2000. http://www.gradeworkinggroup.org. Accessed February 10, 2019. (3) Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. 2019 Feb;16(1):19-29. doi: 10.1111/iwj.12976. Epub 2018 Aug 22. PMID: 30136445 (4) Tettelbach W, Cazzell S, Sigal F, Caporusso JM, Agnew PS, Hanft J, Dove C. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. Int Wound J. 2019 Feb;16(1):122-130. doi: 10.1111/iwj.13001. Epub 2018 Sep 24. PMID: 30246926 (5) Bianchi C, Cazzell S, Vayser D, Reyzelman AM, Dosluoglu H5, Tovmassian G; EpiFix VLU Study Group. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix®) allograft for the treatment of venous leg ulcers. Int Wound J. 2018 Feb;15(1):114-122. doi: 10.1111/iwj.12843. Epub 2017 Oct 11. PMID: 29024419t	Thank you for providing the links to the two Tettelbach 2019 studies which are now included in the final report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	I think this report is a clear summary of the field as it stands today. I would only suggest a stronger statement about the funding source bias in the data available.	Summary and Implications: under Evidence Gaps we note the following: “Industry funds the large majority of published studies, which raises concern about possible publication bias or selective outcome reporting in that poor results may not be published. A reexamination of 15 ongoing clinical trials in the 2012 report “Skin Substitutes for Treating Chronic Wounds” with the status of completed/currently recruiting on Clinicaltrials.gov indicated a status of completed (10)... Of the nine (64.3%) trials without publications,…five trials 3.4 (l)-0.3 (c)-2.6 (

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3: Marc Goldberg BONAPEDA Enterprises LLC	General	General Comments: A key problem in the treatment of plantar	

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response
Musculoskeletal Transplant Foundation		tissue for use as a chronic or acute wound covering." Additionally, we ask the same for our placental tissue, AmnioBand®. Please use the registered trademarked name "AmnioBand®" throughout the document only; and that any reference to the product description be changed to "AmnioBand® is an aseptically processed human allograft placental matrix comprised of amnion and chorion for use as an acute or chronic wound covound coHh[3dc	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	General	Please contact Antonio Montecalvo at (781) 401-1055 or AMontecalvo@Organo.com with any questions or to further discuss these comments.	Thank you for your review of the report.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	General	The Alliance	

Commentator & Affiliation	Section	Comment	Response
		stakeholders. While the TA Program provides 3 weeks for public review of its draft reports, we request in the future to allow stakeholders more time to evaluate	

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response
		LCD for these	

Commentator & Affiliation	Section	Comment	Response
		CTPs are defined primarily by their composition and [redacted]	

Commentator & Affiliation	Section	Comment	Response
[redacted]		families, we ask that any reference to “human cadaver” dermis [redacted] he term “cadaver” be replaced with the term	

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response
		the methodology, the most favorable estimates of product efficacy (i.e., those that were statistically significant compared with compression therapy) were used. These included statistically adjusted results for Apligraf as reported in the product insert and the biweekly application for Talymed. Based on the reported efficacy of targeted AWCMs, the researchers calculated the number needed to treat ("NN T") to achieve one additional treatment success (i.e., complete wound closure) over that which was achieved with standard therapy alone; 95% CIs were estimated using the Wilson score method proposed by Newcombe. Cost efficacy, defined as the incremental cost per additional successfully treated patient, was then calculated by multiplying the NNT associated with each treatment by the product acquisition cost per treated VLU episode. According to the results from the analysis, "[i]n all 3 studies, investigators reported the percentage of patients achieving complete wound closure within a specific duration of 12 to 24 weeks and defined 'complete wound closure' as the full epithelialization of the wound and the complete absence of drainage from the wound site." Ultimately, this study constitutes the first comparison of clinical and cost efficacy of AWCMs among patients with VLUs. Analyses were based on the proportion of patients achieving complete wound closure, identified by FDA as the most objective and clinically meaningful wound-healing endpoint, reported in RCTs based on intent-to-treat populations. Given that this study assesses three of the available skin substitutes identified by AHRQ in its Draft Technology Assessment and appears to meet the study criteria set forth by the agency to be included as part of the report, we respectfully request that AHRQ incorporate this study and corresponding analysis into the Final Technology Assessment. We appreciate the opportunity to submit a Public Reviewer on the Draft Technology Assessment and provide information on	

Commentator & Affiliation	Section	Comment	Response
		Technology Assessment for "Skin Substitutes for Treating	

Commentator & Affiliation	Section	Comment	Response
		compared to standard care alone for treating venous leg ulcers. Standard care included a nonadherent absorptive primary dressing and a multilayer compression bandage including a zinc oxide impregnated bandage, padding and a self-adherent elastic wrap. After 20 weeks, a statistically significant difference at the p=0.005 level was observed for wounds receiving Talymed plus standard care once every other week versus standard care alone (86.4 percent versus 45 percent, intention to treat analysis with last observation carried forward) . More wounds were healed in the Talymed group when applied once every three weeks compared to the control group (65 percent vs. 45 percent), but the difference was not statistically significant. Similar wound healing rates (45 percent) were reported for patients receiving one application of Talymed compared to control."4	