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

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	Appropriate in length and content. It accurately describes the problem and lays out the methodology to address.	Thank you for your comment.
Peer Reviewer #2	Introduction	should there be PROs and pain scales	Key Messages: Although this section has text limitations, we note the importance of reporting patient-related outcomes using wound-related pain scales in the Summary and Implications section.
Peer Reviewer #2	Introduction	should these be subdivided into synthetic scaffolds and processed allo and xenografts?	Structured Abstract: Due to space limitations, we did not provide that level of detail here These characteristics are discussed in the body of the report.
Peer Reviewer #2	Introduction	i have thought of a chronic wound as delayed healing after 4 weeks of therapy. Please find references and clarify cell migration is not a phase	Background: We have added text and the appropriate reference as requested. The sentence now reads "Wounds normally transition through four distinct phases: hemostasis, inflammation, proliferation, and remodeling, until the skin's structure and function are restored. Chronic wounds have failed to pass through the normal healing process in an orderly and timely manner and often remain in the inflammation phase.[3,4] A wound may be considered chronic if it has not entered the proliferation phase after 4 weeks of therapy."
Peer Reviewer #2	Introduction	reference	Background/Chronic Wounds, page 2, line 15: We have added the reference as requested.
Peer Reviewer #2	Introduction	please clarify sentence	Background/Chronic Wounds, page 2, line 17: We have added text as requested. The sentence now reads: "Active or healed venous leg ulcers occur in about 1 percent of the general population; however, the prevalence, functional impact and financial burden are greater in the elderly."
Peer Reviewer #2	Introduction	typo	Background/Current Treatments for Chronic Wounds: We have made the revision as requested.
Peer Reviewer #2	Introduction	I think a table to define terms would be very helpful skin substitutes can be from grafts +/- cells, synthetic substrates +/- cells, How do these differ from collagen dressings or alginates? Certainly costs are widely different.	Background/Current Treatments for Chronic Wounds: Please see Guiding Question 2 for further definitions of these terms. Costs are beyond the scope of the report.
Peer Reviewer #2	Introduction	What about PROs pain scales?	Guiding Questions: Under Guiding Question 4, patient--reported outcomes such as return to baseline activities of daily living and function; pain reduction; and exudate and odor reduction are noted as outcomes of interest. Any measure of pain reduction was an acceptable outcome for inclusion.

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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 wounds. We need these interventions to heal big chronic wounds. Most studies use smaller wounds which will probably heal without such expensive interventions to assess clinical efficacy. This broadens the horizon so we can get sponsors to evaluate the real need.	Background/Chronic Wounds: We have added reference to partial wound closure being predictive of complete wound healing under Guiding Question 6, which reads: "Complete wound healing defined as complete reepithelization with no drainage or need for a dressing and confirmation 2-weeks later should be the primary outcome. This is the criteria FDA suggests in 'Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment.'[61] Rate of wound closure should also be reported. KIs suggested that 40 percent to 50 percent wound closure in 4 weeks was a good predictor of successful wound closure. Evidence indicates that 50 percent reduction for diabetic foot ulcers at 4 weeks was a strong predictor of wound healing by 12 weeks when standard of care was used, while percent change in wound area for venous leg ulcers after 4 weeks is predictive of complete wound healing by 24 weeks."
Peer Reviewer #3	Introduction	Often one can get a good base in 4 weeks with quality of care and importantly the use of skin substitutes so auto-grafting is done which heals the wound.	Thank you for your comment.
Peer Reviewer #3	Introduction	Agree with key run in in strategy and would agree that if is there is 50% healing in 31 days should not qualify for evaluation.	We agree with your comment.
Peer Reviewer #3	Introduction	Very well done and excellent introduction	Thank you for your comments.
Peer Reviewer #4	Introduction	Clear, pertinent	Thank you for your comments.
Peer Reviewer #5	Introduction	The authors might consider using the newer and more commonly used term at present, pressure injury, instead of pressure ulcer.	The technical brief is examining skin substitutes for the treatment of pressure ulcers as defined by CMS.
Peer Reviewer #6	Introduction	I use the page numbers printed at the bottom of the manuscript throughout. 1) In lines 43-48 (p. 2), data from the Medicare % Limited Data Set is discussed. Infected wound prevalence is described, followed by estimated costs for various wound types. However, it is unclear whether the estimated costs are just for the infected wounds or for uninfected and infected wounds for the wound types listed. I recommend that this be clarified.	Lines 43-48, page 2: Now reads: "Including noninfected and infected wound costs, the estimated cost of care for …"
Peer Reviewer #6	Introduction	2) Page 3, Standard of Care section. Selection of the proper wound dressing is mentioned here, but it is not clear how the manuscript distinguishes between wound dressings, advanced	Page 3, FDA Regulations for Skin Substitute Products: We have added the following text: For this report, we have not created a definition for a skin substitute product. Instead, we

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		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 Geistlich Derma-Gide. These products have been added to the appropriate tables and to the appendix.
Peer Reviewer #6	Introduction	3) Lines 23-36, p3, Advanced Therapies Section: This section does not seem to describe Advanced Therapies. I recommend that advanced therapies be briefly listed or described here. Alternatively, the section title should change to match the topic which is focused on the duration of standard of care procedures and the correlation with complete wound healing at various time points.	Lines 23-26, page 3, Advanced Therapeutics: During the review process we removed the listing of Advanced Therapies but had inadvertently left in the header. We have now removed the header to reflect this change.
Peer Reviewer #6	Introduction	Additionally, this section should address whether the 4 weeks of standard of care (SOC) for chronic wounds is from the time that the wound is identified to the provider, or 4 weeks after new wound fails to heal for 4 weeks and is identified as chronic. That is, are the 4 week periods of standard of care described for new wounds, and when those wounds do not heal, are they then labeled as chronic? Or is this 4 week period described for wounds that have already been determined to be chronic (and thus have been present for 4 weeks before the 4-week SOC period)?	We have also revised paragraph 3 to read: "After being diagnosed as a chronic wound, an initial period of 4 weeks of standard of care without achieving a 50 percent reduction in wound size may signal need for a change or additional therapies."
Peer Reviewer #6	Introduction	4) p. 3 Skin substitutes section: It is unclear whether the manuscript considers skin substitutes to be a part of "standard of care" or advanced therapies. Or perhaps they are neither, but could be used as an adjunct to either SOC or advanced therapy. This should be clarified.	p. 3 Skin substitutes section: We have revised the text as follows: "If chronic wounds fail to respond to standard of care, skin substitutes may be used as an adjunct to established chronic wound care methods to increase the likelihood of complete healing."
Peer Reviewer #6	Introduction	5) Skin Substitutes section, p. 3. This section should be revised to better define what is considered to be a skin substitute. There are statements regarding what an 'ideal" skin substitute should have, but note that many of these statements also overlap with characteristics of wound dressings.	Skin Substitutes section, p. 3. Please see revisions to Guiding Question 1, FDA Regulations for Skin Substitute Products. Categorizing products according to FDA regulatory categories has been removed from the report.
Peer Reviewer #6	Introduction	5) p. 5, lines 3-4. There is a statement "These properties may enhance the wound healing potential of skin substitutes beyond that of wound dressings". However, "wound dressings" has not	p. 5, lines 3-4: This sentence now reads: "These properties may enhance the wound healing potential of skin substitutes beyond that of standard of care."

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		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 listed under the Centers for Medicare & Medicaid Services (CMS) codes Q4101 to Q4182 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. 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."
KI Reviewer #1	Introduction	A minor point, "autologous keratinocytes" should not be considered a "dermal substitute".	Thank you for the comment. You are correct but this phrase comes from a quote and therefore cannot be corrected.
KI Reviewer #2	Introduction	Well done and well organized introduction. The topic is complex and can be confusing, good job on presenting an organizing framework and classification scheme for providing the information.	Thank you for your comments.
KI Reviewer #3	Introduction	Abstract, Purpose, Methods and Findings along with the Table of Contents is organized and well written.	Thank you for your comments.
KI Reviewer #4	Introduction	This introduction gives a good overview of the application of skin substitutes and how they fit into the treatment of chronic wounds.	Thank you for your comments.
Public Reviewer #1: American Podiatric Medical Association	Introduction	Guiding Questions: We support the notion that inclusion criteria be expanded to include patients that are more representative of clinical practice. Some variables would include higher HbA1c values, tobacco users, patients with varying stages of renal disease, peripheral arterial disease, and differing levels of socio-economic status.	We agree with your comments and stress the importance of including patients that are more representative of clinical practice under Guiding Question 6 and in the Summary and Implications sections.
Public Reviewer #2: Zack Bridges ACell Inc.	Introduction	Background: No comment Guiding Questions: No comment	Thank you.

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Public Reviewer #3: Marc Goldberg BONAPEDA Enterprises LLC	Introduction	Background: The draft report appears to be missing information in 2 key areas. #1. A large-scale review conducted by the Veteran's health administration of various advanced wound care therapies concluded "Our systematic review of randomized controlled trials found discouragingly low strength evidence regarding the effectiveness and comparative effectiveness of advanced wound care therapies for treatment of lower extremity ulcers." Greer N, Foman N, Dorrian J, Fitzgerald P, MacDonald R, Rutks I, Wilt T. Advanced Wound Care Therapies for Non-Healing Diabetic, Venous, and Arterial Ulcers: A Systematic Review. VA-ESP Project #09-009; 2012.	#1: The Greer systematic review was identified in our literature searches but ultimately excluded because all of the included RCTs were published prior to 2012 and included in our 2012 report on skin substitutes.
Public Reviewer #3: Marc Goldberg BONAPEDA Enterprises LLC	Introduction	#2. The draft report neglects to consider the critical role of "offloading" in the treatment of plantar diabetic foot ulcers. There is significant scientific evidence that for many patients the quality of offloading is a determining factor of whether a wound heals or not. Offloading has been long accepted as a fundamental component of effective DFU care, and in fact, when patients with plantar DFUs are properly offloaded as part of a team wound care approach, healing rates of approximately 90% have been commonly reported (without the use of cellular tissue products). In particular, the report fails to differentiate which offloading approach is used in the various different studies, does not indicated whether patients were compliant with offloading, the quality of offloading method used, etc. Considering the key role that offloading plays in healing plantar DFUs, this seems to be a major oversight. The draft report states that one component of standard of care (SOC) for diabetic foot ulcers, is to "apply some form of offloading". The SOC section further states that "the methods for achieving each of these wound management principles varies among clinical practice guidelines and clinical studies." The generally accepted SOC for offloading as cited in the literature is the total contact cast (TCC). However, due to many factors, TCC is used so infrequently that surveys of wound care practitioners indicate a majority of these practitioners do not view TCC as a "gold standard". Guiding Questions: 1. How do the results of this analysis compare with those reported in the VAMC review study? 2. Considering the importance of offloading noted above, does the	#2. Standard of care (including offloading) of included studies is reported in Table C-20 “Description of treatments in 21 RCTs”. Additional information has been added to Next Steps: “Studies should adhere to a rigorous standard of care, ensuring adequate debridement, infection and diabetes management, offloading for diabetic foot ulcers, compression for venous leg ulcers, and pressure redistribution support surfaces for pressure ulcers.” A comparison of the offloading approaches of these studies is outside the scope of this report.

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		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 underutilization of TCC, are there other effective offloading methods available that could achieve higher utilization rates; thereby reducing the need for advanced wound care therapies altogether?	
Public Reviewer #4: Belinda Marcus Center for Vascular Intervention	Introduction	PAGE 3, Background Section, AHRQ made the statement: "Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient's skin." Skin substitutes should have functional and structural characteristics that closely match autologous skin. The ideal skin substitute would be durable, completely autologous, and endothelialized and contain adnexal structures and adult stem cells, but such a construct does not yet exist.20". This statement is incorrect. Not only does it exits but human skin allografts (HSAs) are considered the gold standard in wound repair. Please see the following references: (a) Song DH, Nelgian PC. Plastic Surgery: Volume 4: Lower Extremity, Trunk and Burns. Elsevier Inc. 2013. and (b) Mathes SJ. Plastic Surgery: Volume 2: General Principles. Elsevier – Health Sciences Division 2005.	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." This statement was referenced from the Ferreira et al. 2011 article "Skin substitutes: current concepts and a new classification system" and is used as general background material as to what characteristics skin substitutes should contain.
Public Reviewer #4: Belinda Marcus Center for Vascular Intervention	Introduction	Theraskin is a donated, cryopreserved, human, split-thickness allograft. It provides the chronic, stagnating wound bed with fully functional, replicating cells; growth factors; cytokines; and Type I, III, and IV collagens, all of which have the "greatest possible similarity with the patient's skin" because IT IS HUMAN SKIN. Each component of human skin has been shown to be present in Theraskin through the paper: 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).	We believe Theraskin is adequately described under Cellular Skin Substitutes. We have updated the product description in Table D-9 in Appendix D, since we did not intend to provide extensive product descriptions in Table 13.
Public Reviewer #5:	Introduction	Background: 1. PAGE 3, Background Section, AHRQ made the statement: "Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to	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

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Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC		achieve the greatest possible similarity with the patient's skin." Skin substitutes should have functional and structural characteristics that closely match autologous skin. The ideal skin substitute would be durable, completely autologous, and endothelialized and contain adnexal structures and adult stem cells, but such a construct does not yet exist.20".	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." Background, page 3: This statement was referenced from the Ferreira et al. 2011 article "Skin substitutes: current concepts and a new classification system" and is used as general background material as to what characteristics skin substitutes should contain.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Introduction	a. Solsys Medical would like AHRQ to consider that human skin allografts (HSAs), including TheraSkin, were not reviewed nor included in Reference 20 utilized by AHRQ (Nathoo, 2014), so the statement made in the draft indicating that a skin substitute construct matching autologous skin does not yet exist is not accurate. We request that AHRQ consider inclusion of several surgical textbooks (See references: (a) Song DH, Nelgian PC. Plastic Surgery: Volume 4: Lower Extremity, Trunk and Burns. Elsevier Inc. 2013. and (b) Mathes SJ. Plastic Surgery: Volume 2: General Principles. Elsevier – Health Sciences Division. 2005.) which provide a more robust framework on HSAs not considered by Nathoo et. al, indicating HSAs as a key player/gold standard in wound management and healing.	We have revised the text to read: "The ideal skin substitute would be durable, completely autologous, and endothelialized and contain adnexal structures and adult stem cells."
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Introduction	b. In fact, according to the surgical textbooks by Song and Mathes, human skin allografts (HSAs) are considered the gold standard in wound repair.	We appreciate your submission of additional references for the Background section, however the materials do not seem specific to chronic wound management.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Introduction	i. Furthermore, TheraSkin is a living human split-thickness skin allograft (HSA) that is cryopreserved using state of the art and proprietary quality processes to maintain all three major components in healing -- living cells, signaling molecules, and a native extracellular matrix (ECM) that vascularizes. (See reference: 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).) It is recovered, processed, distributed and utilized in compliance with the FDA Human Cells, Tissues and Cellular and Tissue Based Products (HCT/P) Section 361 regulations. As such, TheraSkin can be used to or repair skin	We believe Theraskin is adequately described under Cellular Skin Substitutes. We have updated the product description in Table D-9 in Appendix D per requests. We did not intend to provide extensive product descriptions in Table 13.

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		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).	
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Introduction	2. PAGES 3-4, Background Section, AHRQ made the statement: "Growth factors and other components of the skin substitute may promote cell proliferation, reduce wound degradation caused by matrix metalloproteinases within the wound, and promote wound vascularization. These properties may enhance the wound healing potential of skin substitutes beyond that of wound dressings." a. However, AHRQ never clarified in the draft what qualifies a skin substitute versus a wound dressing. So then a question arises: would xenografts and placental products be considered dressings and not skin substitutes, since they do not contain enhanced wound healing properties?	PAGES 3-4, Background Section: Thank you for your comment, however, xenografts and placental products are composed of extracellular matrix (ECM) which is believed to contain enhanced wound healing properties. We have revised page 3 to read: "Growth factors and ECM components of the skin substitute may promote cell proliferation, reduce wound degradation caused by MMPs within the wound, and promote wound vascularization. These properties may enhance the wound healing potential of skin substitutes beyond that of standard of care."
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Introduction	Guiding Questions: 1. PAGE 4, Guiding Questions Section, AHRQ listed Guiding Question Number 2 as: "What classification systems have been developed to characterize skin substitutes?" and subsequently, "What are important skin substitute parameters and active components currently being used when classifying skin substitutes?" a. As previously noted, AHRQ never clarified in the Findings section of the draft what qualifies a skin substitute versus a wound dressing. As such, perhaps an additional question, "What differentiates a skin substitute from a wound dressing" should be added to the AHRQ report.	Guiding Questions: 1. PAGE 4: Under Guiding Question 1, page 9, we added the following text: "For this report, we have not created a definition for a skin substitute product. Instead, we used the products listed under the Centers for Medicare & Medicaid Services (CMS) codes Q4101 to Q4182 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. 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."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Introduction	Page ii: Key Messages • Third bullet point regarding pain relief, although pain relief should be a goal for treating any patient with any modality, for patients with neuropathic ulcers, as a result of peripheral neuropathy, generally indicate the absence of pain or sensation i.e. patients may not feel any pain, making this outcome challenging to monitor.	Page ii: Key Messages, third bullet point: Due to space limitations, we are unable to extend text to Key Messages. We have however revised text in Guiding Question 6 as follows: "KIs suggested that patients be evaluated for pain using a visual analog scale (1–10), for wound odor and exudate, and for activities of daily living using a standardized validated assessment tool. Measuring pain in patients with diabetes with neuropathy may be challenging"
Public Reviewer #6:	Introduction	• Fourth bullet point, regarding future studies and a 4-week run-in period prior to study enrollment, we question the rationale behind this recommendation. Published standard treatment protocols and	Fourth bullet point, run-in period: We revised Guiding Question 6 (best practices) to recommend that studies include a 2- to 4-week run-in period before study enrollment and randomization.

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Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation		guidelines recommend that standard of care be used for at least four weeks and show no improvement prior to the use of an advanced treatment modality such as the use of a skin substitute (Sheehan et al. 2003). Our study protocols adhere to that and have put in place a 2-week run in period to ensure patients with challenging wounds that needed an advanced treatment modality would be assessed appropriately, and potentially exclude wounds that are "easier to heal" or would heal with standard of care alone. To extend that from a 2-week to a 4-week run-in period only extends the patient's suffering from the DFU and puts the patient at greater risk.	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Introduction	Additionally, we question the rationale for the 6-month post-healing follow-up and would appreciate any references that point to this as being an acceptable follow-up time-point?	Fourth bullet point, 6-month followup: A 6-month followup was recommended by the subject matter experts or Key Informants (KIs) we consulted prior to and during the development of the technical brief. The KIs with expertise in chronic wound care helped to inform the clinical content of the brief such as recommendations on clinical followup. We agreed that for a chronic and potentially recurrent condition, 6-month followup made sense.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Introduction	Background: We believe the following statement requires context: Studies rarely reported clinical outcomes such as amputation, wound recurrence at least 2 weeks after treatment ended, and patient-related outcomes such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and -reported studies providing more clinically relevant data in this field is this Technical Brief's clearest implication.	Background: We appreciate your comments, but due to space limitations are unable to expand the Structured Abstract. We believe the context is provided throughout the report.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Introduction	The primary endpoint for treating chronic wounds is wound closure (100% re-epithelialization). We agree that all products should be studied and report clinically relevant information, wound closure is the goal of treatment. Payers and clinicians evaluate product effectiveness based on wound closure rates. Patients want wound closure as this reduces the risk of infection, odor, draining, and amputation and allows for return to function. Sustainability of wound closure is also important, and most studies follow patients for 4-12 weeks after the study period ends. The Key Findings section and the Background section seem to minimize the importance of wound closure as the primary endpoint. On page 4 the report points this out well.	We define completely closed/healed wounds as "skin closure with complete reepithelialization without drainage or dressing requirements versus failure to heal" under Methods. We note that FDA specifies that wound closure must be confirmed at two consecutive study visits 2 weeks apart. We also list complete wound closure as a primary endpoint in all discussions and listing of outcomes in the text and evidence tables in Appendix C.
Public Reviewer #7: Louis Savant	Introduction	The report also states that: We interviewed Key Informants with expertise in chronic wound care to help select a classification system to categorize the skin substitutes.... However, we found	We apologize for miscategorizing studies examining Grafix and GrafixPrime. We have made the appropriate revisions to

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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 evidence tables in Appendix C.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Introduction	Background: Osiris appreciates your description of chronic wounds and the physiology associated with wound healing. We believe there as a significant knowledge gap in the understanding of wound healing biology by clinicians, payers, and researchers impacting treatment decisions for chronic wounds. We believe AHRQ is lacking mention of the critical role mesenchymal stem cells play in wound healing. Mesenchymal stem cell (MSC), play a significant role in coordinating the repair response by recruiting other host cells and secreting growth factors and matrix proteins. Studies have shown that the number and function of MSCs in diabetics and the aged population are impaired, which may explain why diabetics and older people experience delayed healing. We believe an explanation of wound healing biology without mentioning the role of MSCs is incomplete and outdated. Below are a few references for your convenience. Ennis WJ, Sui A, Bartholomew A. Stem cells and healing: impact on inflammation. Adv Wound Care 2013;2:369–378. Cianfarani F, Toietta G, Di Rocco G, Cesareo E, Zambruno G, Odorisio T. Diabetes impairs adipose tissue-derived stem cell function and efficiency in promoting wound healing. Wound Repair Regen 2013;21:545–553. Rodriguez-Menocal L, Salgado M, Ford D, Van Badiavas E. Stimulation of skin and wound fibroblast migration by mesenchymal stem cells derived from normal donors and chronic wound patients. Stem Cells Transl Med 2012;1:221–229. Maxson S, Lopez EA, Yoo D, Danilkovitch-Miagkova A, Leroux MA. Concise review: role of mesenchymal stem cells in wound repair. Stem Cells Transl Med. 2012;1(2):142-149.	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." Background: Thank you for submitting references on the role of MSCs. We have added the following text to the Background section on Chronic Wounds: "Chronic wounds may also have deficient and defective mesenchymal stem cells (MSCs). MSCs synthesize growth factors and cytokines that affect the proliferation and remodeling phases of wound repair. Recruiting MSC into a wound may be an essential part of the wound healing process."
Public Reviewer #7: Louis Savant	Introduction	Good "Standard of Care" (SOC) for wounds is crucial. The information mentioned on SOC is good, but should also include proper nutrition, reduced use or elimination of tobacco products,	We agree with your comments that "good 'standard of care' [SOC] is crucial"; however the section of the report on

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Osiris Therapeutics, Inc.		patient hygiene, assessment of medications being taken, and management of all co-morbid conditions. Patient compliance with treatment is also an important factor in successful wound healing. We believe these additional elements of SOC should be included in AHRQ.	Standard of Care is only intended to describe the SOC applied to the wounds.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Introduction	Osiris would like to suggest that AHRQ change the title and terminology utilized throughout this Technology Assessment. The AHRQ refers to the products being assessed as "skin substitutes". The term "skin substitutes" is clinically inaccurate and does not correctly describe the technology. These products do not "substitute" for skin, they are temporary covers or barriers that provide biologic components to promote cell migration and proliferation. While the term "skin substitutes" is still frequently used, Osiris recommends that "skin substitutes" be replaced with a more current descriptor of "Cellular and/or Tissue Based Products for Skin wounds (CTPs)". CTPs is broad and is inclusive of both current and future technology, although Osiris favors creating a universal classification for CTPs to more accurately describe the differences in CTPs as the tissue sources, components and cellularity of the products varies considerably. By using CTPs, AHRQ would contribute to getting the industry to move away from skin substitutes to the move appropriate term of CTPs.	As noted in the report: "For this report, we have not created a definition for a skin substitute product. Instead, we used the products listed under the Centers for Medicare & Medicaid Services (CMS) codes Q4101 to Q4182[27] 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. 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."
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Introduction	Guiding Questions: Osiris believes the AHRQ guiding questions are very comprehensive. Guiding Questions: The guiding questions seem very thorough.	Thank you for your comment.
Public Reviewer #8 Anonymous	Introduction	Guiding Questions: comprehensive clear and robust	Thank you for your comments.
Peer Reviewer #1	Methods	Affirmative for all questions above.	Thank you for your comments.
Peer Reviewer #3	Methods	Hurrah for underscoring the importance of the Viswanathan bias tools. A second Hurrah for the Davison Kohler 2018 classification which again underscores the importance of viable living cells	Thank you for your comments.
Peer Reviewer #3	Methods	Absolutely clear might ask do living cells epithelium alone, dermis alone or combination facilitate wound healing as opposed to matrix	We didn't identify any evidence on this specific question, but agree it would be interesting to know whether the cells themselves without the ECM stimulate healing.

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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. The decision to use complete healing as the primary outcome is logical. I agree with the authors that better future studies would look at longer term outcomes like amputation, mobility, site of care.	Thank you for your comments.
Peer Reviewer #5	Methods	Inclusion and exclusion criteria are justified. The search strategy was clearly described and other methods described seem matched to the report purpose.	Thank you for your comments.
Peer Reviewer #6	Methods	c. Methods: 1) Section 1a (p. 5). It is unclear whether KIs from the United Kingdom are best positioned to comment on wound care in the United States. There are differences in healthcare practices (e.g., reimbursement), regulatory environment, and available products (including specific wound dressings or skin substitutes) in the two countries. Thus any clinical input from KIs from outside the U.S. may not be appropriate for or reflective of clinical considerations in the U.S. I recommend adding to this section to discuss how this issue was addressed.	Methods: Section 1a (p. 5): We did not ask KIs for their input on regulatory environments, and have added the following text: "We did not ask KIs for input on reimbursement, which is outside the scope of this report. We did not ask KIs to comment on specific skin substitute products to avoid biasing our assessment."
Peer Reviewer #6	Methods	2) p. 5, Section 1b. This literature search is missing data from FDA's public databases which provide summary information on clinical studies considered by FDA in the evaluation of cleared/approved medical products. While the databases are mentioned in Appendix A, it is unclear if data from the actual trials were extracted from the available information. This may overlook some publicly available information, although the number of studies eligible for conclusion may be small. One document that I did not see cited was the Summary of Safety and Effectiveness Data (SSED) for Integra Omnigraft, P900033/S042, available here: https://www.accessdata.fda.gov/cdrh_docs/pdf/P900033S042B.pdf The databases that would have this information (in SSEDs for PMA products and 510(k)Summaries for 510k products) are below: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm https://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm	Methods, p. 5, Section 1b: Thank you for these resources. We only included peer-reviewed publications for this report.
Peer Reviewer #6	Methods	2) p. 6, Table 7: Exclusion criteria include "inadequate standard of care". Standard of care varies from institution to institution, and may vary by country (US vs UK). Please provide detailed	Methods, p. 6, Table 7: When evaluating adequacy of the standard of care for included studies, we referenced common principles as described in Current Treatment for Chronic

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		information about what was acceptable standard of care and what was not, and why; it seems only one study was excluded on this basis with wet-to-dry dressing being considered as not standard of care (Appendix B, p. B-1). I note that SOC is described in tables in Appendix C, but discussion is not provided as to the variation in SOC and why these different, variable practices/products were all considered acceptable SOC. This still leaves quite a wide range of practices that could be considered standard of care, which means it may be difficult to compare the studies if there is extreme variance in the Standard of Care arms.	Wounds (page 3). In one instance we specifically asked for KI input regarding the adequacy of standard of care. The KIs agreed with our decision to exclude this study (Campitiello et al, 2017) due to inadequate standard of care.
Peer Reviewer #6	Methods	3) Reporting bias, p. 7: Note that the FDA's wound healing guidance recommends that wound closure should be evaluated for at least 3 months of followup following complete wound closure, to assess for recurrence. Complete wound closure is defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart. Thus a more robust assessment would consider the addition of the 3 month followup time point for assessment of wound recurrence. https://www.fda.gov/downloads/drugs/guidances/ucm071324.pdf	Methods, Reporting bias, p. 7: While we agree that studies should evaluate recurrence at 3 to 6 months after wound closure, we were more lenient in our risk-of-bias (ROB) tool with measuring recurrence at least 2-weeks after wound closure.
KI Reviewer #1	Methods	I like the way they did the review. The only thing to consider would be to include GRADE analysis for the RCTs. Right now, we make the assumption that all RCTs are of the same quality, when they actually differ in terms of methodology (particularly in terms of number of patients).	The EPC Program applies the GRADE approach when we do a full systematic review. Doing so is beyond the scope of a technical brief.
KI Reviewer #2	Methods	Search strategy well explained and defined and logical. Would suggest explicating stating the databases searched (the information is available in the additional materials) as not all readers will go to the additional materials to determine databases searched and a brief overview would be helpful. Good explanation of grey materials searched. Well defined criteria for study inclusion. Well defined criteria for rating bias in the studies. The criteria are specific for wound studies and this is a strength	We have revised the text to read: "For this project, ECRI searched the bibliographic databases listed in Appendix A, including EMBASE, MEDLINE, PubMed, and CINAHL."
KI Reviewer #3	Methods	Excellent table describing inclusion and exclusion criteria. Appreciated the fact that the studies that were reviewed included all care settings including home care.	Thank you for your comments.
KI Reviewer #4	Methods	The inclusion criteria are well-justified. While the exclusion of non-FDA regulated skin substitutes is reasonable, it might be interesting to know if anything was excluded on this basis, since so few studies overall were found. Otherwise the exclusion criteria are well-justified. The outcome measures are well-defined and appropriate. Statistical methods were essentially not used. The risk-of-bias questions are well-justified and appropriate.	A search of studies excluded at the abstract level did not indicate any studies were excluded for being non-FDA regulated skin substitutes.

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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.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Methods	Page 5: Method 1. Data Collection, (d) Risk-of-Bias Assessment, • Page 7, Risk-of-Bias Questions: o Selection Bias, Question 4 & 5: As an overall comment, we question the starting data point of a 15% difference, where does this data point originate and why has it been given such significant weight in your methodology to determine "Risk-of-Bias"	Selection Bias, Question 4 & 5: We chose 15 percent as a minimum beyond which the loss of patients would jeopardize the randomization process that distributes patients and patient characteristics equally between treatment groups. We chose a 15 percent difference as it was a commonly used threshold in other ROB tools. We believe 15 percent is not too severe a cut off for assessing attrition bias.
Public Reviewer #6:	Methods	i. Regarding the question, "Were the mean wound sizes at the start of treatment similar (no more than a 15 percent difference) between groups," this is hard to control down to such a small	These questions are designed to detect risk of selection bias and have not been used to exclude any studies (please see study inclusion criteria in Table 1). Using this ROB tool we

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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	Using this as a reference point, are the authors of the brief suggesting that if one were randomizing a study and had a greater than 15% difference, the study would have to be canceled or the randomization restarted?	We are not suggesting that studies be cancelled or randomization be restarted, only that there's a potential risk of these biases.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Methods	o Detection Bias, Question 7: "Was the wound assessor blinded to the patient's treatment group?" This question needs clarification i.e. Does this mean when the treatment is applied or when assessment was made post-treatment? This is impossible for the investigator administering the treatment but possible for a study's validator as in the DiDomenico et al (2018) AmnioBand RCT and the Zelen et al (2018) AlloPatch RCT. How can one be blinded if you have SOC vs. a Treatment Group?	Detection Bias, Question 7: The question regarding wound assessor blinding is referring to assessments made post-treatment.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Methods	Reporting Bias, Question 8: Did the study report wound recurrence as an outcome, and was it assessed at least 2 weeks after treatment ended?" What is the rational for this post-treatment time frame for recurrence to be tracked 2 weeks vs 6 months as suggested later in the paper? We believe 2 weeks would be sufficient to assess wound closure but not wound recurrence.	Reporting Bias, Question 8: While we agree that studies should evaluate recurrence at 3 to 6 months after confirmed wound closure, we were more lenient in our ROB tool with measuring recurrence at least 2-weeks after wound closure.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Methods	Additionally, we believe both per-protocol and intent-to-treat results should be reported in the manuscript, as reporting only per-protocol data could be misleading (i.e. falsely elevated).	We agree that reporting of both intent-to-treat analysis and per-protocol-analysis is important. We captured attrition and differential attrition in our assessment of risk of bias for this report.
Public Reviewer #7: Louis Savant	Methods	Osiris agrees with most of the questions posed in the Risk of Bias section. We agree that wound duration and the number of co-morbidities have the most impact on healing. These factors are	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

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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 findings and implications as a potential risk of bias. The source of funding can impact study design bias, but if AHRQ is going to cite this, we believe you need a valid reference that shows bias in studies referenced in AHRQ attributed to manufacturer funding. Otherwise, AHRQ is making an assumption that may be incorrect and the TA itself is biased.	Source of funding was not included in our ROB tool which is based on AHRQ EPC methods. Industry funding however is an important factor to consider since it raises concern about publication bias or selective outcome reporting in that poor results may not be published. We documented "source of funding" of included studies in the evidence tables in the Appendix.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Methods	Under your "Risk of Bias" questions there is no mention of the study sponsor as a bias, but the report later mentions a criticism that studies were funded by manufacturers.	We are not citing manufacturer funding as a source of bias in our ROB tool.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Methods	We applaud AHRQ for attempting to provide a classification for CTPs, however in the methods section we question how you arrived at using the Davison-Kolter system. What classification systems have been developed to categorize skin substitutes? a. What are important skin substitute parameters and active components currently being used when classifying skin substitutes?	The Davison-Kotler system was decided upon after a review of several published classification systems used for categorizing skin substitutes (including Kumar 2008, Ferreria 2011, and Nathoon 2014). Due to the limitations of these classification systems as described in the report, we chose the Davison-Kotler system. The KIs helped inform this decision.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Methods	We question why the 2018 Davison-Kolter system was the system chosen for classifying products? It is very new and is not widely accepted as the correct way to classify products. Osiris believes there is merit to the Davison-Kotler system, but it does not accurately classify all products. The FDA has its own classification system which is how the products are classified when they enter the marketplace, which Osiris also believes is flawed. However, the FDA will not accept the Davison-Kolter system. The question is: why would AHRQ choose a system which the FDA will not accept and has not gone through significant industry review and validation? Osiris believes this requires explanation and added context that this classification is not validated, nor is AHRQ implying this is the correct classification.	We were asked to identify classification systems that were developed to categorize skin substitutes. The FDA classification system is strictly a regulatory classification system. Categorizing products according to FDA categories has been removed from the report.

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Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Methods	Again, your KI's did not correctly identify our cellular amniotic membrane product Grafix.	We apologize for miscategorizing studies examining Grafix and GrafixPrime. We have made the appropriate revisions to Guiding Questions 3, Guiding Question 4, and all relevant evidence tables in Appendix C.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Methods	Why did you exclude data from registries and real-world retrospective trials? Real-world trials and registry data provide additional insight into the effectiveness of products in a clinical setting, and can validate RCT data.	While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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 #9: Antonio Montecalvo Organogenesis, Inc.	Methods	Methods: Published Literature Search We encourage AHRQ to add publications of comparative effectiveness research (CER) studies of clinical outcomes in real-world settings to the 2019 report. Randomized clinical trials (RCTs) demonstrate what a treatment can do in a protocol defined population of subjects that are treated under tightly controlled conditions. CER studies of real-world clinical treatment practices show what a treatment does do in a real-world setting that is more reflective of how patients are treated in the community rather than the narrow restrictions of a RCT. CER studies are performed on much larger patient populations at many more centers. Large sample sizes, regional diversity in clinical facilities, long follow-up times post-treatment are all significant strengths of CERs compared to RCTs. RCTs and CERs should be used as complimentary to each other to most completely and accurately assess patient response to clinical treatment. RCTs have high "internal validity" because randomization, careful selection of participants, and standardized treatment protocols help maximize the possibility of observing a treatment effect, if it exists. Although RCTs are considered the "gold standard" in determining if a product can work, there may be limitations in the generalizability or "external validity" of data generated. The strict criteria for patient inclusion (which may exclude "higher-risk" patients), rigorous monitoring, and adherence to treatment protocols may create a potentially artificial environment that is not representative of the full patient population	Thank you for your comments. While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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.

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		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.	

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Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	*Risk of Bias (page 7)* One of the areas the Alliance has significant concerns with this technology assessment lies in some of the questions posed in the Risk of Bias section and ultimately in the conclusions reached based on the analysis of those questions. Listed below are some of our concerns: • It appears that the reviewers chose a non-validated approach to assess bias, which does not seem to have been reported in the literature.	Thank you for your thorough review of the report. The potential for bias in each included primary study was assessed using our ROB instrument developed for this report, based on the criteria described by Viswanathan et al., and modified specifically for comparative studies of wound care interventions. We made three revisions to the ROB tool used in the 2012 AHRQ report "Skin Substitutes to Treat Chronic Wounds." We replaced a question on Performance Bias (Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?) with a question on Reporting Bias (Did the study report wound recurrence as an outcome, and was it assessed at least 2 weeks after treatment ended?). We also added a question under Selection Bias (Was the method of measuring wound condition at enrollment reported?).
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	• While some of the elements listed are certainly crucial, definitions of "yes", "no", or "not reported" are missing.	The definition of "Yes" and "No" is described in the Methods section. Our ROB assessment of the included RCTs is provided in Table C-31 "Risk-of-bias assessment for 21 included RCTs" in Appendix C.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	• What criteria did the reviewers use to judge that a study used appropriate randomization methods or concealment of treatment group allocation?	Our judgment of appropriate randomization methods or allocation concealment was based on criteria developed by the ECRI Institute-Penn Medicine Evidence-Based Practice Center (ECRI-Penn EPC), informed by the AHRQ EPC Methods Guide. Appropriate randomization is typically accomplished using a computer or table of random numbers to assign patients to groups. Allocation by date of birth, date of admission, hospital numbers, or alternation are not appropriate randomization methods. Adequate methods of allocation concealment include centralized randomization schemes; randomization schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes.

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Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	• 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 did they arrive at these specific criteria?	We acknowledge that these are not the only important baseline parameters for assessing selection bias, but these three parameters should be sufficient to detect selection bias. We chose 15 percent as a minimum beyond which the loss of patients would jeopardize the randomization process that distributes patients and patient characteristics equally between treatment groups. Important parameters to wound healing at baseline to table for all included RCTs were approved by individuals at AHRQ and the CMS with expertise in wound healing.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	In wound care studies it is important to list all relevant parameters to wound healing at baseline and adjust for them in such fashion through stratification or regression, or both. Numbers of comorbidities are not helpful because only specific comorbidities and lifestyle factors (e.g., BMI or smoking) have a direct impact on healing.	In Guiding Question 6 and Next Steps, we encourage the reporting of subgroup analysis according to comorbidities, HbA1c levels, influence of race and ethnicity, and adequate debridement.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	• There is also no reporting of how the reviewers judged these criteria, how they arrived at a consensus, or even kappa (inter- relater reliability) statistics.	We judged criteria for the ROB based on AHRQ EPC Methods Guidance.

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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 15% difference between groups?* This criteria does not seem to be based on any known standard and in itself will limit the population for clinical trials. It reduces the pool of results information that can be generalized to “real world” situations of chronic wounds. Most clinical trials in wound care select a size range of wounds for inclusion which is often broader than 15% difference to ensure randomization reflects as best as possible the wound sizes seen in clinical practice. This arbitrary selection introduces less “valuable” information for clinicians. This factor can be adjusted for in analysis as stated in the comment to Question 3. *Question 5 -Were the mean wound duration at the start of treatment similar (no more than a 15% difference) between groups?* This is also another artificial restriction for conducting clinical trials and is not validated in any known standard for clinical trials. Chronic wounds of longer duration have been already shown in the literature to respond differently to treatment, and should not be restricted to a 15% difference. Again, this factor can be adjusted for in analysis (see comment to Question 3).	Questions 3, 4, 5 “Risk of Bias” (page 7): These questions are designed to detect risk of selection bias but did not lead to exclusion of any studies. (Please see study inclusion criteria in Table 1). A 15% difference on important baseline characteristics is not an uncommon criterion in systematic reviews.

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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 Alliance of Wound Care Stakeholders	Methods	Question 7- *Was the wound assessor blinded to the patients treatment group?* It is important to have the patient be blinded, but AHRQ did not address this in the technology assessment. It would have been a more appropriate risk of bias question to have been posed rather than a question which automatically will incite bias as it is impossible to blind the wound assessor. The Alliance recommends a standard in which 2 blinded assessors agree to wound closure. This would eliminate investigator bias.	Question 7: We acknowledge the difficulty in performing blinded studies, therefore we selected wound assessor blinding to assess risk of detection bias. We agree that two blinded assessors would be preferable.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Methods	Question 10 - *Was there a 15 percent or less difference in completion rates in the study arms?* This criteria does not seem to be based on any known standard and is irrelevant. Dropout rates of > 20% are important and large differentials between groups are important, too, but we don't know the critical number. Most systematic review methods accept 20% as a break point. More importantly, the difference in censoring rates and loss of endpoint and variable data *between groups* is the more worrisome.	Question 10: We and others have selected 15% difference in completion rates to assess the risk of attrition bias. No studies were excluded based on this question. Using our ROB tool we determined that none of the included studies were at high risk of bias.
Public Reviewer #11: Manuel Pubillones, MD Noridian Helathcare Services	Methods	Reading	Thank you for your review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	Methods	Methods: None. Comments only.	Thank you for your review.
Public Reviewer #8 Anonymous	Methods	agree that real world populations should be studied, in so far as knowing what their response to skin substitute use is against control.	Thank you for your comments.
Peer Reviewer #1	Results	Is the amount of detail presented in the results section appropriate? Yes Are the characteristics of the studies clearly described? Yes Are the key messages explicit and applicable? Yes Are figures, tables and appendices adequate and descriptive? Yes Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? No	Thank you for your comments.
Peer Reviewer #2	Results	Summary?	Guiding Question 1 Overview: Our medical editor recommended the use of Overview.
Peer Reviewer #2	Results	Overview or summary?	Guiding Question 2 Overview: Our medical editor recommended the use of Overview.
Peer Reviewer #2	Results	I would remove and at least and make a hyphen and group references. 40-50% (references grouped)	Failure to Heal: We have revised the text as suggested. The text now reads: “Failure to heal during the treatment phase was described as not achieving a reduction in area by at least 40 percent to 50 percent.”
Peer Reviewer #2	Results	studies	Comment incomplete, no response necessary
Peer Reviewer #2	Results	delete [, with] and [53%] edit to read and 9 studies did not report blinding of outcome assessors	Assessor Blinding: The text has been revised as requested.
Peer Reviewer #2	Results	Is this the summary as the key points above. If so, this seems redundant. I would think the Questions 3 section should have a concluding paragraph and not sure overview makes sense??	Guiding Question 3 Overview: We were asked to add an overview at the end of each Guiding Question.

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 importance of data provided from national registries. We mention this in Guiding Question 6: "The ongoing trials include a registry study that may provide more data on patients outside the typical RCT (Table E-1). Data collected by the U.S. Wound Registry is intended to provide comparative-effectiveness data for patients with chronic wounds and ulcers being treated with cellular and/or tissue-based products that will include skin substitutes." In the Summary and Implications section: "While the bulk of evidence continues to focus on use in diabetic foot ulcers, ongoing trials will provide additional published data on treating venous leg ulcers and pressure ulcers. Two registry trials may provide additional effectiveness and harm data on use of skin substitutes for diabetic foot ulcers, venous leg ulcers, and pressure ulcers." An examination of the registry data is outside the scope of the report, however a future report may examine these databases.
Peer Reviewer #2	Results	Is <12 good control? Seems very high to me. In surgery we aim for <8	Guiding Question 6, Patient Inclusion: We agree that HbA1c should be significantly lower to be considered "good control." We have reworded the statement as follows: "Investigations of diabetic foot ulcers typically included only patients with 'HbA1c <12 percent).
Peer Reviewer #2	Results	Aha. Here's a registry. i haven't heard of it before. Also it seems to be run by Medicare? Is this the ideal registry??	Guiding Question 6, Patient Inclusion: The registry trial is included in our list of ongoing clinical trials. We believe this registry will collect real-world data in patients outside a typical RCT.
Peer Reviewer #2	Results	Isn't this what the NIH is supporting?? it would be helpful to analyze costs as this is a major concern of all stakeholders	Guiding Question 6, Study Design: We did not identify any registered ongoing trials sponsored by NIH. Analyzing cost is beyond the scope of this report.

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.
Peer Reviewer #3	Results	I am concerned about the implicit suggestion that living cells need to be rejected so healing is not impaired. The reason the most effective biological dressings with living cells are effective is that the cells are alive and influence the host to generate a healthy wound base. The living cells in the dressings presumably by: production of cytokines, growth factors, changes in microbial environment and lord know what, are presumed to talk to the host to make a more felicitous base. Epidermal cells talk to dermal cells and vice versa indeed this interaction is critical to development of hair buds, chicken feathers and multiple other morphologies such as sole skin etc. Just think of the interactions between the check point inhibitors and cancer.	Guiding Question 2: We agree with the reviewer's comments. We have removed several sentences on page 15 referring to tissue rejection.
Peer Reviewer #3	Results	The data suggests for Apligraf that it is efficacious in healing chronic old diabetic wounds We aggressively debride such a wound and then apply the Appligraf to generate a receptive healthy wound base	Guiding Question 2: Data in the Zelen 2016 study comparing Apligraf with EpiFix and standard of care suggest that Apligraf provided more effective wound healing and a shorter time to heal than standard of care.
Peer Reviewer #3	Results	This is very rich in detail and comparisons of the literature and that is the charge of the report.	Thank you for your comments.
Peer Reviewer #4	Results	I commend the authors on the thorough listing of methodologies, outcomes. I would have found a Forrest plot figure a useful complement to the tables.	A meta-analysis is beyond the scope of this report.
Peer Reviewer #4	Results	As a minor point, there is a typo on page 33 lines 5-10: sentence repeat.	Guiding Question 4: This duplicate sentence has been removed.
Peer Reviewer #5	Results	Presentation of information on the studies included is organized in a digestible way, with figures and tables providing detailed information. The text and points included supplement and do not duplicate the table and figure information, so as a package they are comprehensive. There is a duplicate sentence, page 33, Section on Guiding question 4, systematic review summary. "the authors noted that use of amniotic membranes...healed at a quicker rate."	Thank you for your comments. We have deleted the duplicate sentence.

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 identify additional products that may be considered skin substitutes according to the definition used in this manuscript. Some examples chosen at random that may have been missed include Polynovo's NovoSorb and BTM Wound Dressings (K172140, K142879) and Kerastat Gel (K162759 - https://www.accessdata.fda.gov/cdrh_docs/pdf16/K162759.pdf); however, it is unclear if they should be included as the definition/criteria for a skin substitute, for the purposes of this	2) We only considered skin substitute products listed by CMS. We now also include reference to the CMS codes Q4101 to Q4204 developed by CMS in 2019. We have also revised the FDA regulatory information. Products are no longer categorized or grouped according to FDA regulatory categories.

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 classification panel, at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/ucm518493.htm	
Peer Reviewer #6	Results	3) p. 13, Guiding Question 1 Overview, line 28-30: Note that for devices, FDA considers claims of promoting or accelerating wound healing to be Class III PMA claims; products regulated under 510(k) are not evaluated for these claims and are not permitted to make these claims. FDA's approach thus conflicts with the statement made in this section; please add a comment to acknowledge this conflict.	3) p. 13, Guiding Question 1 Overview, line 28-30: We have removed text referring to the promotion of wound healing by skin substitutes.
Peer Reviewer #6	Results	4) p. 15 lines 6-13, Tables 5-10; and p. 20 Guiding Question 2 Overview: It is unclear how the authors determined which layers of skin are being "replaced". Is it determined by the need to include a secondary dressing? Is it determined by the source of the cells/tissues? Is it based on the indications or claims (full or partial thickness wounds)? I might consider that the Integra Bilayer matrix could be considered to simulate both dermal and epidermal tissues, with the top silicone layer serving more like the epidermis/stratum corneum; however, it is classified in Table 9 as "dermal". I recommend that the authors clarify how they determined that a product "replaces" the epidermal or dermal layer (or both). Currently it is not clear how this was determined. It is unclear what the clinical utility of this portion of the classification system is, as it is not clear if the products are really used differently depending on if they are epidermal/dermal/both.	4) p. 15 lines 6-13, Tables 5-10; and p. 20 Guiding Question 2 Overview: We added the following text to address this: “The composition of the product determines which layers it is designed to replace.”
Peer Reviewer #6	Results	5) p. 28 line 12-14 " 5 studies had more than a 15 percent difference...reported at the start of the treatment"... This sentence should explain what are the 2 or more comparators that are showing a difference of 15 percent; i.e., a 15 percent difference compared to what?	5) p. 28 line 12-14: This sentence describes baseline study characteristics and is not related to treatment comparisons.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	6) p. 30 Successfully Healed Wound" Please add to this section that the KI recommendations/suggestions conflict with the FDA definition of complete wound closure. Note that complete wound closure is defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart. In addition, FDA's wound healing guidance recommends that wound closure should be evaluated for at least 3 months of followup following complete wound closure, to assess for recurrence. It is unclear which studies met this criterion. Thus a more robust assessment would consider the addition of the 3 month followup time point for assessment of wound recurrence. https://www.fda.gov/downloads/drugs/guidances/ucm071324.pdf	6) p. 30 Successfully Healed Wound": We have added the following text: "Two studies reassessed healing two weeks after initial wound healing, which agrees with FDA guidance of measuring confirming complete wound healing at two consecutive study visits 2 weeks apart."
KI Reviewer #1	Results	Would add GRADE criteria for the RCTs	A GRADE analysis is beyond the scope of a technical brief.
KI Reviewer #2	Results	There is sufficient detail in the results section. characteristics of the studies are well represented and provided. The figures and tables and appendices throughout are very helpful, thoughtfully developed and add to the report. The tables are clear and easily understandable. The only area that is not provided is the ethnicity/racial breakdown of subjects included in the reviewed studies. While not a major flaw, this information is becoming more important in terms of making adequate clinical decisions. Likewise, most the results show a preponderance of male versus female subjects. Some mention of how this might influence use of the data or insights regarding the gender differences would be beneficial. Early in the report it is mentioned that additional studies were searched for data on pressure ulcers as no RCTs existed, yet this data is not discussed at any later time in the report. This should at a minimum be explained both in the results area and later in the discussion section (perhaps as a limitation of existing science in the area or as part of the recommendations for future research?)	We have added ethnicity/race to the patient characteristics tables in Appendix C and added text to reflect this information. Gender is also reported. In Guiding Question 6 we note: "Four (19%) studies performed statistical analysis examining the influence of race and Hispanic ethnicity on healing of diabetic foot ulcers and venous leg ulcers. One study indicated that being Caucasian was significantly associated with healing within 12 weeks (hazard ratio, 3.01; 95% CI: 1.33 to 6.80; p=0.008). Future research is needed in this area as well as an analysis of gender differences. We did not identify any studies that did subgroup analysis by gender." We have added text to Guiding Question 6: "The majority of studies examined diabetic foot ulcers. More studies are needed on venous leg ulcers, pressure ulcers, and other chronic wounds to determine whether skin substitutes are an effective and practical therapy for these wounds." We have also added the following text to the Methods section: " Updated searches did not identify any nonrandomized comparative studies for pressure ulcers and arterial leg ulcers."
KI Reviewer #3	Results	Well defined.	Thank you for your comments.

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 justified by the results. I don't believe that studies were misclassified and do not know of any missed studies.	We identified three additional studies in the updated literature searches (Tettelbach 2019, Brown-Etris 2019, Cazzell 2019) and added 2 studies (Tettelbach 2019, DiDomenico 2018) missed in these searches.
Public Reviewer #2: Zack Bridges ACell Inc.	Results	Findings: On Page 17, the paragraph describing products derived from various animal sources lists one as being derived from "sheep bladder". We believe this is a typo and should be corrected to "sheep stomach".	We changed “sheep bladder” to “sheep tissue.”
Public Reviewer #2: Zack Bridges ACell Inc.	Results	Consider separation of human amniotic products within acellular category. Even though the cells are dead, they, and their components (DNA, cell membranes) are still present within the tissue and capable of eliciting a host response. Therefore, the term "acellular" for these products may be somewhat misleading compared to the other products that are specifically devoid of cells and cellular content (decellularized animal and human tissues and synthetic materials).	We have separated human placental products from other acellular products (see Table7).
Public Reviewer #2: Zack Bridges ACell Inc.	Results	We would request that the authors add the outcome "average cost per subject" as a consideration to the evaluation and analysis of primary studies comparing skin substitutes for guiding question 4. In one study cited in this technical brief (Frykberg et al. 2016) and summarized in Table 19, data on the average cost per subject for two skin substitutes was captured and reported in the results of the study. In primary studies whose results demonstrate no statistically significant differences in the clinical outcomes, information related to the cost of care may help a reader better assess two products from an economic standpoint. The data related to this outcome should be included in Table 19 for all primary studies that published this information.	The reporting and analysis of cost is beyond the scope of the report.
Public Reviewer #2: Zack Bridges ACell Inc.	Results	Within guiding question 6 under the discussion of study design outcomes (page 44) the authors indicate that very few studies include recurrence rates. We noted that in the discussion under guiding question 4, in the review of RCTs comparing skin substitutes with standard of care (SOC) in patient groups treated for DFUs, there is only one study (Alvarez et al. 2017) where the recurrence rate is noted as less frequent than in the SOC group. As the authors noted this outcome was a consideration (c. Wound recurrence, page 31) we would ask that in addition to this outcome being noted in Table 19 that this outcome and the primary study are cited in the section titled "Acellular Dermal Substitutes Versus Standard of Care" on page 34 of the technical brief. As the author is recommending that recurrence rates be captured in future	We added the reference to Alvarez on page 34.

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)."
Public Reviewer #2: Zack Bridges ACell Inc.	Results	Page 36, Table 18 Please add the following footnote at the bottom of the table: *Now marketed as CYTAL® Wound Matrix	Page 36, Table 18: We have revised Table 18 as requested.
Public Reviewer #2: Zack Bridges ACell Inc.	Results	Page 38, Table 19 Please add the following footnote at the bottom of the table: *Now marketed as CYTAL® Wound Matrix	Page 38, Table 19: We have revised Table 19 as requested.
Public Reviewer #13: Bud Brame LifeNet Health	Results		
Public Reviewer #13: Bud Brame LifeNet Health	Results	We would like to provide some clarity to the assignment of DermACELL AWM as listed in the January 28th, 2019 Draft Technical Brief on Skin Substitutes for Treating Chronic wounds. The clinical relevance of our RCT (Cazzell, et. al) was to design an intent to treat study comparing DermACELL AWM versus standard of care with a smaller third arm to obtain general comparisons against a similar product, GraftJacket. The study was powered against Standard of Care and not the GraftJacket cohort. Consequently, our DermACELL AWM study should also be listed on page 26, under Primary Studies as one of 12 and not 11 Primary Studies. DermACELL AWM should also be listed and compared on page 27 and page 34, under Acellular Dermal	We chose to group the Cazzell study with the five other head-to-head comparison studies, since it includes two skin substitutes. We now refer to the Cazzell study in the section, Acellular Dermal Substitutes versus Standard of Care. The text reads: "See results from a 3-arm study (Cazzell et al. 2017) that includes standard of care in Table C-25 and Table C-26 and the section Acellular Dermal Substitutes versus Acellular Dermal Substitutes below."

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. We greatly appreciate the mention on pages 28 and 36, Acellular Dermal Substitutes vs Acellular Dermal Substitutes and desire to keep the study specifically outlined in this section but we feel our RCT study should also be included in the SOC comparison section. The AHRQ report points out the intentionally underpowered GraftJacket arm but fails to mention the intention of the study, which was a comparison to SOC. The mention of an underpowered arm can inadvertently lead the reader to the wrong intent of the study, which specifically has been mentioned to me several times when discussing this report with fellow colleagues.	
Public Reviewer #13: Bud Brame LifeNet Health	Results	Several antidotal comments in general on the Technical Report. □ The new accepted terminology for Skin Substitutes is actually CTP's or Cellular and/or Tissue Based Products, please update the Technical report with this new terminology. To assist with defining a CTP, the AHRQ should use the definition as provided by the ASTM, CTPs are defined primarily by their composition and comprise cells and/or the extracellular components of tissue. CTPs may contain cells (viable or nonviable), tissues, proteins, and other materials for which there is a rationale for benefit beyond that achievable with conventional wound coverings. CTPs may additionally include synthetic components. Cellular components are differentiated by tissue of origin, species (for example, porcine, bovine), cell type, viability, processes employed (for example, primary cells, cultured cells), any genetic modification or other manipulation, and viability.*[1]*	As noted in the report: "For this report, we have not created a definition for a skin substitute product. Instead, we 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." We have also added a paragraph describing the ASTM International classification system for CTPs.
Public Reviewer #13: Bud Brame LifeNet Health	Results	□ Theraskin – On Page 19 of the document, the sentence starting, "The tissue is procured (not harvested) within 24-hours postmortem from an organ or tissue donor. "Harvested" is an insensitive term that should be removed from all literature which describes any HCT/P as these tissues are graciously consented	We replaced all mentions of "harvested" with "procured." We have revised the description of Theraskin in Appendix D.

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		donated human gifts. This information should be corrected to read, "TheraSkin (Table 13) is a cryopreserved human, living, split-thickness allograft that contains living cells, growth factors, and an architecturally-preserved human ECM scaffold that can be re-vascularized by the recipient. Around 7-14 days after application, the epidermal cells and any antigenic components are removed but the dermal scaffold and the matrix is retained. Living cells survive through procurement, cryopreservation, and thawing.	
Public Reviewer #13: Bud Brame LifeNet Health	Results	The US government does not sponsor clinical trials for any product, whether it a HCT/P, medical device, PLA, or 510(k). Until such a time this practice changes, if there is any coverage consideration from of 3rd party payer, it is solely up to the manufacturer to pay for such clinical studies and the AHRQ should at least acknowledge this statement of fact - so that it does not inadvertently subject the reader to bias because the study was funded by manufacturers. In LifeNet Health's case, we also use a third party adjudicator to ensure data interpretation was non-biased.	Source of funding was not included in our ROB tool which is based on AHRQ EPC methods. Industry funding however is an important factor to consider since it raises concerns about publication bias or selective outcome reporting since poor results may not be published. We documented "source of funding" of included studies in the evidence tables in the Appendix.
Public Reviewer #13: Bud Brame LifeNet Health	Results	AHRQ states that they consulted with 6 KIs as well as some peer reviewers who provided input into this TA but did not mentioned the identity of these informants and reviewers. For transparency, those names should have been provided in the draft document. We greatly appreciate those names being provided during final draft.	We include the list of KIs and Peer Reviewers in the final draft.
Public Reviewer #13: Bud Brame LifeNet Health	Results	Questions 3, 4 and 5 under the Risk-of-Bias questions on page 7 – what was the rationale behind applying a 15% difference in comorbidities, mean wound size, and mean wound duration? This criteria does not seem to be based on any known standard and limits the population for clinical trials. This approach also implies that all comorbidities have an equal weight in terms of the potential to affect wound healing, which is not accurate. Additionally, wounds that have been around for quite some time, have been shown in the literature to be difficult to heal.	We chose 15 percent as a minimum beyond which the loss of patients would jeopardize the randomization process that distributes patients and patient characteristics equally between treatment groups.
Public Reviewer #13: Bud Brame LifeNet Health	Results	Blinding is a good practice but not always achievable when comparing standard of care to a CTP. However, it should be recommended that at least 2 separate blinded adjudicators be utilized to decrease the chance of bias.	We acknowledge the difficulty in performing blinded studies, therefore we selected wound assessor blinding to assess risk of detection bias. We agree that two blinded assessors would be preferable.
Public Reviewer #13: Bud Brame LifeNet Health	Results	Guiding Question #2 – What was the genesis of using the 2018 Davison-Kolter method of classifying CTPs. This classification is new and not widely accepted, could the AHRQ utilize the ASTM standards for CTP classifications?	The Davison-Kotler system was decided upon after a review of several published classification systems used for categorizing skin substitutes (including Kumar 2008, Ferreria 2011, and Nathoon 2014). Due to the limitations of these classification systems as described in the report, we chose the Davison-Kotler system. The KIs helped inform this decision.

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	RCT data should not be the only source from which usable clinical data can be obtained. While not advocating small case study series, studies associated with product performance on patients where wound closure rates and size reduction are monitored by a well-designed, systematically controlled methodology (or evidence based practice – EBP) can provide payers and clinician with real like evidence when treating patients with chronic, non-healing wounds. AHRQ has recognized that studies that are more representative of clinical practice and the typical patient population utilizing CTPs should be included. In this document AHRQ states, "KIs suggested that patient inclusion criteria could be expanded to include patients more representative of clinical practice and of poorer health than typical patients included in RCTs." This supporting statement, in the Technical Assessment is exactly why real-world evidence (RWE) is so important and necessary in chronic wound care.	While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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 #13: Bud Brame LifeNet Health	Results	Run in periods – most payers require at least 4 weeks of conventional care prior to accepting the usage of CTP's. The industry study standards should not need an additional two weeks (totally 6 weeks) when performing a RCT. An additional two weeks further reduces the patient population and greatly improves the clinical results by excluding patients that would not have healed and harmed the final data analysis.	We appreciate your comment regarding the difficulty with run-in periods prior to starting a study.

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*. (b) *Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, et.al. Advances in skin regeneration using tissue engineering. Int J Mol Sci. 2017 Apr 7;18(4).*)	The number of grafts administered is captured in the Appendix when reported.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	Findings: 1. PAGE 13, Findings Section, AHRQ made the statement: "Cellularity is considered the most important discriminator among skin substitutes since the presence of cells increases the rejection risk and increases manufacturing complexity. In this system, skin substitute products are divided first into acellular and cellular groups." a. All allogenic technologies, including those with incomplete decellularization, will result in an immune response. This is different than rejection and is an important distinction in the case of skin substitutes because rejection implies that, like solid organ transplantation, the entire organ is rejected and dies. In the case of TheraSkin, for example, the living cells will produce non-immunogenic growth factors until they are identified as non-self; at that time, those cells are destroyed but the dermal scaffold remains and becomes vascularized or incorporated to promote healing.	Page 13: We agree that this is an important point. We have revised the description of Theraskin in Appendix D.

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Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	2. PAGE 15, Findings Section, AHRQ made the statement: "We have organized the 74 skin substitute products by the classification principles described by Davison-Kotler et al.22 and present them in this section. We used Acellular/Cellular, followed by Dermal and Epidermal/Dermal, and Source material (natural human, natural animal, and synthetic) in our organization scheme. We did not consider permanence since all the skin substitute products are biodegradable/temporary and contain no permanent nonbiodegradable components." a. Solsys Medical contends that in the case of living human skin allografts (HSAs), this statement is not always accurate and should be corrected. (See reference: Hoekstra MJ, Kreis RW, du Pont JS. History of the Euro Skin Bank: the innovation of preservation technologies. Burns 1994;20Suppl 1:S43-7.) Similar to experiences with HSA rejection described in the literature, we have had instances where the rejection phenomenon with TheraSkin did not occur due to due to host immunity or coincidental histocompatibility matching between donor and recipient. 3. PAGE 15, Findings Section, AHRQ made the statement: "Tissues obtained from human donors also have the risk of infectious disease transmission." a. Solsys Medical would like to urge AHRQ to include qualifiers to this statement, such as, "Tissues obtained from human donors may have the risk of infectious disease transmission; therefore, industry standards developed by the FDA and AATB are utilized to minimize and eliminate this risk."	Page 15: We agree with the reviewer's comments. We have removed several sentences on page 15 referring to tissue rejection. We have noted the FDA and AATB standards under Theraskin in Table D-9 of Appendix D.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	4. PAGE 15, Findings Section. AHRQ made the statement pertaining to Acellular Skin Substitutes: Acellular skin substitutes are described as having "…bioactive compounds including collagen and growth factors contained within the ECM." a. The concentration of growth factors is highly variable and often exist only in trace amounts due to various processing and sterilization techniques; growth factors are not the main mode of action in these products, but rather a human ECM collagen scaffold.	We removed "growth factors" from this sentence. The revised text reads: "Various manufacturers of acellular dermal skin substitutes compete based on their proprietary processing technique and maintenance of the ECM."
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A.	Results	5. PAGE 15, Findings Section, AHRQ made the statement: "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." a. As a practicing physician and Chief Medical Officer at Solsys Medical, it should be noted that this statement is accurate only if the intent is to implant the tissue inside the patient which is	We have removed the following sentence as requested: "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."

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Chief Medical Officer, Solsys Medical, LLC		contrary to the use of skin substitutes for topical application to repair and heal wounds. Within 72 hours, neovascularization through angiogenesis into the graft occurs. At about 7 to 14 days, the antigenic components (epidermal cells) are rejected but the remaining dermal components become incorporated. (See references: (a) Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005 Sep;25(3):587-605. (b) Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, et.al. Advances in skin regeneration using tissue engineering. Int J Mol Sci. 2017 Apr 7;18(4).)	
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	6. PAGE 15, Findings Section. AHRQ made the statement: "Natural human dermis must be sterilized to prevent potential disease transmission." a. As a practicing physician and Chief Medical Officer at Solsys Medical, it should be noted that this statement is inaccurate. Tissues obtained from human donors may have the risk of infectious disease transmission; however, industry standards developed by the FDA and AATB are utilized to minimize and eliminate this risk without requiring sterilization. (See reference: Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005 Sep;25(3):587-605.)	We removed the following sentence as requested: "Natural human dermis must be sterilized to prevent potential disease transmission."
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	7. PAGE 15, Findings Section. AHRQ made the statement: "Various manufacturers of acellular dermal skin substitutes compete based on their proprietary processing technique and maintenance of the ECM and its growth factors." a. As a practicing physician and Chief Medical Officer at Solsys Medical, it should be noted that this statement is inaccurate. These products are decellularized collagen with variable, often trace, amount of growth factors remaining after the processing; these tissues function as a scaffold and growth factors are not their primary mechanism of action.	We removed "growth factors" as noted above.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	8. PAGE 16, Findings Section. AHRQ made the statement: "Commercially available human placental membranes are a relatively new treatment for chronic wounds. An earlier AHRQ evidence report on skin substitutes did not consider amniotic membrane products.1 The amnion/chorion membranes or separate amnion are obtained from the placenta of screened donors after caesarean delivery. The membranes have an ECM rich in collagen as well as growth factors and lack immunologic markers.2" a. Solsys Medical contents that this statement is incorrect because though mesenchymal stem cells (MSC) are less immunogenic	Page 16: We have removed "lack of immunologic markers." The sentence now reads: "The membranes have an ECM rich in collagen as well as growth factors."

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		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 tissue is harvested within 24-hours postmortem from an organ donor. When harvested, the allograft is washed with antibiotics and cryopreserved. According to the manufacturer, living cells survive through harvesting, cryopreservation, and thawing.30 FDA regulates Theraskin as human tissue for transplantation." a. Solsys Medical would like to request the following corrections relating to TheraSkin: "TheraSkin (Table 13) is a cryopreserved human, living, split-thickness allograft 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. The donor criteria for TheraSkin surpass those required by the AATB and the FDA and TheraSkin maintains a proven track record of zero disease transmission. When procured, the allograft is washed with a series of antibiotics and cryopreserved using a proprietary cryopreservation process. According to a characterization study by Landsman (2016), living cells survive through procurement and thawing. FDA regulates TheraSkin as human tissue for transplantation." (See reference: 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).)	Page 19: We have revised the description of Theraskin in Table D-9 of Appendix D. We did not intend to provide extensive product descriptions in Table 13.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	10. PAGES 20-21, Findings Section. AHRQ made the statement: "We divided acellular and cellular skin substitute products according to whether they replaced just the dermis or the dermis and epidermis. No skin substitute products replace only the epidermis. We then grouped products according to their source (natural human, natural animal, and synthetic). We split Davison-Kolter's natural source group into natural human and natural animal. Using this modification to the Davison-Kotler et al. classification scheme, we identified human cadaver dermis (13 products), human amniotic membranes (26 products), animal tissue sources (22 products), synthetic sources (2 products), and a	Page 20-21: Theraskin is grouped with cellular products in the next paragraph.

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		combination of natural and synthetic materials (3 products) as acellular dermal substitutes." a. Solsys Medical requests in addition to "human cadaver dermis" that AHRQ add "human cadaver epidermis and dermis", which describes TheraSkin.	
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	b. Solsys Medical would like to request in addition to Figure 1 (Acellular portion of algorithm" that AHRQ also include a similar "Cellular Products" portion. Within the Bilayer>Epidermal and Dermal>Natural, Temporary or Permanent to properly describe TheraSkin.	Figure 1: Due to space constraints, the entire classification system will not legibly fit on one page. The pathway for cellular products is identical.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	11. PAGE 22, Findings Section, AHRQ made the statement: "…we excluded 73 articles at the abstract level for reasons including not addressing a guiding question, not a study design of interest (e.g. retrospective comparative), and a study protocol." a. Solsys Medical contends that exclusion of studies other than RCTs is inappropriate since there are numerous retrospective studies that meet all of the other criteria and are analyzed in a statistically rigorous manner. In fact, retrospective studies are a closer representation of true clinical treatments than the RCT because they include "real world" patients with exposed muscle, tendon and bone, include patients with elevated HbA1c, and include wounds larger than 10cm2. We believe it was unnecessarily restrictive, to exclude all non-RCT studies.	PAGE 22: While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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. Chief Medical Officer, Solsys Medical, LLC	Results	12. PAGE 23, Findings Section, AHRQ made the statement: "Studies excluded at full-text level (n=33)" which included both "Primary studies published before 2012 (n=8)" and "Included in 2012 AHRQ report Skin Substitutes for Treating Chronic Wounds (n=1)." a. Solsys Medical urges AHRQ to consider both of the following points: i. The overall knowledge of wound care and treatments available to address the standard of care (SOC) has improved significantly in the past two decades (offloading, compression, treatment of infection, debridement, moist wound care, etc). Updating dated clinical trials utilizing the current definition of SOC and best practices could be invaluable in better understanding the appropriate use of these technologies. ii. Given that the new AHRQ 2019 report on Skin Substitutes for Treating Chronic Wounds does not include "Update" in the title, it could easily be assumed that the medical community and policy	PAGE 23: The 2012 report "Skin Substitutes for Treating Chronic Wounds" is currently available on AHRQ.gov (2012 report Skin Substitutes for Treating Chronic Wounds). The study designs of the following studies (DiDomenico, Landsman, Budny, Wilson, Landsman) are not within the scope of our review as described in the Methods section.

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		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 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. Foot Ankle Spec. 2011 Feb;4(1):29-41. 13. PAGE 23, Findings Section, AHRQ made the statement: "PRISMA flow diagram of study screening>20 clinical studies>(3 systematic reviews, 17 randomized controlled trials." a. Solsys Medical urges AHRQ to consider also including the following TheraSkin studies, which we believe may have been an oversight that should be included in both the 2019 Technical Brief and the Appendices: i. Budny AM, Ley A. Cryopreserved allograft as an alternative option for closure of diabetic foot ulcers. Podiatry Management. 2013 Aug: 131-136. In this study, 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. ii. 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. In this study, 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. iii. Landsman A, Rosines E, Houch A, Murchison A, Jones A, Qin	

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		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	14. PAGE 24, Findings Section, AHRQ made the statement: "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." a. Solsys Medical would like to request the following typographical correction: "Eighty-two percent of studies enrolled fewer than 60 patients per arm. All studies, except for Towler, 2018, were manufacturer-funded, and most studies were conducted in U.S. wound care centers." Towler, 2018 was an independent study – not funded by a manufacturer.	PAGE 24: We have revised the sentence regarding manufacturer funding which now distinguishes the Towler study as reported no funding: "Most studies enrolled fewer than 60 patients per arm. Nineteen (90%) studies were manufacturer-funded (one study did not report funding, and one study reported no funding). Most studies were conducted in U.S. wound care centers.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	15. PAGE 29, Findings Section. AHRQ made the statement regarding Cellular Epidermal and Dermal Substitutes versus Cellular Epidermal and Dermal Substitutes: "One study compared two cellular epidermal and dermal substitutes in venous leg ulcers.30 Eligible patients had wounds greater than 30-days duration and area less than 40 cm2. Individuals with end-stage renal disease, severe malnutrition, or severe liver disease were excluded. Fifteen patients was the maximum enrollment in any study arm. Mean age was early 60s, with mostly males enrolled. Mean wound size was 6.3 cm2 in the intervention arm and 4.9 cm2 in the standard of care arm. Mean wound duration was not reported. Comorbidities included diabetes, obesity, peripheral vascular disease, smoking use, lymphedema, and neuropathy. This 20-week study used a 30-day run-in period, was conducted in a U.S. wound care center, and reported "no funding." For additional details, see Table C-15 to Table C-17 in Appendix C." a. As previously requested under a separate comment, Solsys Medical urges AHRQ to add the following TheraSkin studies (both to the 2019 Technical Brief and the Appendices), which we believe may have been an oversight: i. 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.	PAGE 29: The 2012 report "Skin Substitutes for Treating Chronic Wounds" is currently available on AHRQ.gov (2012 report Skin Substitutes for Treating Chronic Wounds). The study designs of the following studies (DiDomenico, Landsman, Budny, Wilson, Landsman) are not within the scope of our review as described in the Methods section.

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		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		

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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 regarding Cellular dermal substitutes versus cellular epidermal and dermal substitutes: "Statistically significant benefits to Theraskin over Dermagraft in diabetic foot ulcers at 12 weeks included more wounds healed in a shorter time with fewer grafts. No difference in wound healing was reported at 20 weeks. Patients had wounds <10 cm2, >30 days duration, with HbA1c <12 percent.33" a. Solsys Medical would like to request the following typographical change, "Statistically significant benefits to TheraSkin over Dermagraft in diabetic foot ulcers at 12 weeks included more wounds healed in a shorter time and with fewer TheraSkin grafts (4.36) compared to Dermagraft grafts (8.92). No difference in wound healing was reported at 20 weeks. Patients had wounds <10 cm2, >30 days duration, with HbA1c <12 percent.33"	PAGE 32: We revised the text on page 37, but do not include information on graft applications in the Key Points.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	17. PAGE 32, Findings Section. AHRQ made the statement regarding Cellular epidermal and dermal substitutes versus cellular epidermal and dermal substitutes: "No statistically significant difference was reported between Apligraf and Theraskin for venous leg ulcer healing (at 12 and 20 weeks) and number of grafts per subject. Recurrence did not occur at 26 weeks. Eligible patients had wounds greater than 30-days duration and area less than 40 cm2.30" a. Solsys Medical would like to request the following changes be made: i. Towler, 201830 was designed to be an inferiority study; therefore, it should be clearly noted that since no statistical difference existed between Apligraf and TheraSkin groups in VLU healing rates (TheraSkin VLU healing rates at both 12 and 20 Weeks were 93.3% compared to Apligraf 75% (12 weeks) and 83.3% (20 weeks)) met the study's null hypothesis which was: TheraSkin is non-inferior to Apligraf.	PAGE 32: A review of the manuscript indicated that the Towler study was designed as a pilot study to provide data for a larger non-inferiority RCT. As such, we are just reporting the data as presented in the publication.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	ii. AHRQ, did, however, fail to include the statistically significant conclusion of this study30: TheraSkin ($2,495) is more cost-effective than Apligraf ($4,317) in the treatment of VLUs.	Cost was outside the scope of the report.
Public Reviewer #5:	Results	18. PAGE 38 Table 19, Findings Section, AHRQ includes a table of overviews of the 6 head-to-head studies reviewed for the 2019 report. a. Solsys Medical requests that the following changes be made to	PAGE 38: A review of the manuscript indicated that the Towler study was designed as a pilot study to provide data for a larger non-inferiority RCT. As such, we are just reporting the data as

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Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC		Table 19 based on submitted comments above. i. Update the Overview for Towler, 201830 to state: "Authors reported TheraSkin (n=15) for VLU healing (at 12 and 20 weeks) was not inferior to Apligraf (n=12). Wounds remained healed through week 26. Significant findings included that TheraSkin ($2,495) is more cost-effective than Apligraf ($4,317) in the treatment of VLUs. ii. Add the additional requested head-to-head references requested above, including: 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. 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. b. 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.	presented in the publication. We are not including cost data in the report (see Methods). The study designs of the following studies (DiDomenico, Landsman, Budny, Wilson, Landsman) are not within the scope of our review as described in the Methods section.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Results	19. PAGE 39, Findings Section, AHRQ made the statement "Our search of ClinicalTrials.gov identified 29 ongoing clinical trials examining skin substitutes in chronic wounds of interest." a. Solsys Medical plans to add its on-going clinical trials to ClinicalTrials.gov, as our clinical process allows. Until that process is complete and ClinicalTrials.gov can be updated, we ask that AHRQ add Solsys Medical's following list of future studies and publication plan both to the 2019 Technical Brief and the Appendices: i. Large registry study of 1,556 DFU patients with matched cohorts comparing TheraSkin (n=778) vs. SOC (n=778): submitted for publication, anticipated publication Q2 2019. a. Intent-to-treat healing rates were significantly higher for DFUs treated with TheraSkin® compared to matched Standard of Care wounds (p = 0.0045). b. DFUs treated with TheraSkin® were significantly more likely to complete treatment than matched SOC wounds (p <0.0001) and significantly less likely to quit (p=0.0119) or be transferred (p=0.0119).	Page 39: Our search of ongoing clinical trials was limited to clinicaltrials.gov. We provide a direct link to each ongoing clinical trial in Appendix E to provide the reader with additional details of each trial.

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		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 HC, Harkless LB, Bouton AJ. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. Diabetes Care 2001 Jan;24(1):84-88.) e. Additionally, TheraSkin® use resulted in decreased times to heal for wounds that remained stagnant or increased in size over the first four weeks of standard care (p = 0.0001 and 0.0027, respectively). ii. Large registry study of 3,994 patients with wounds below the knee of all etiologies using matched cohorts comparing TheraSkin (n=1997) vs. SOC (n=1997): anticipate submission and publication Q2 2019. a. Study included patients with venous, arterial, diabetic, surgical, and pressure wounds. b. Wounds below the knee were significantly more likely to heal given the application of TheraSkin® versus Standard of Care (p < 0.0001). c. Reduced amputations: Amputation rates differed significantly (p = 0.0017) with the control group having 2.75 times more amputations than then the TheraSkin® cohort. iii. Registry study of 174 patients with matched cohorts comparing TheraSkin (n=87) vs. Apligraf (n=87) in the most difficult to heal VLU: anticipate submission and publication Q2 2019. a. Demonstrates non-inferiority between Apligraf and TheraSkin in treating VLU (p=0.01) iv. TheraSkin vs. SOC Randomized Controlled Trial in VLU: anticipate submission and publication end of 2020. v. Unfunded head to head Randomized Controlled Trial comparing TheraSkin vs. Apligraf in VLU: anticipate submission and publication Q4 2019. a. Expanding the Towler pilot study to additional sites	
Public Reviewer #5:	Results	20. PAGE 40, Findings Section, AHRQ made the statement regarding Guiding Question 6: “KIs suggested that patient inclusion criteria could be expanded to include patients more	While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs

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Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC		representative of clinical practice and of poorer health than typical patients included in RCTs." a. Solsys Medical urges AHRQ to consider that this is nearly impossible to accomplish in an RCT, which is why most studies are DFU and have strict exclusion/inclusion criteria. Once complex patients are added to such an RCT, it is nearly impossible to appropriately match cohorts. For these reasons, real-world evidence (RWE) is so important and necessary in chronic wound populations. b. Solsys Medical urges AHRQ to consider inclusion of RWE to the Technical Brief, without limiting data strictly to RCTs. i. Although it is the goal to provide evidence-based medicine in the routine care of patients (typically through long-term large n RCTs), primary reliance on this method poses an inherent challenge for chronic wound care patients as 81.3% of all trials include exclusion criteria related to patient co-morbidities. RCTs in chronic wound care, therefore, are limited in generalizability in the average real-world wound care population given that 50-99% of real-world patients would have been excluded from wound care RCTs due to co-morbidities. (See reference: Carter MJ, Fife CE, Walker D, Thompson B. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. Adv Skin Wound Care 2009 Jul;22(7):316-324.) ii. A systematic review and meta-analysis of skin substitute RCTs concluded that the body of evidence on effectiveness in the long-term, including lower limb salvage and recurrence, is currently lacking and cost-effectiveness is unclear. (See reference: Santema TB, Poyck PC, Ubbink DT. Systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers: highlights of a Cochrane systematic review. Wound Rep Reg. 2016;24:737-744.) iii. Given the overall lacking body of evidence for and challenges associated with studying a wound care population, Solsys Medical is planning a number of future clinical studies (provided above in a separate comment) to continue to build evidence, with particular emphasis on well-designed, matched cohorts, real-world evidence, in support of TheraSkin.	except for wound types for which insufficient 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:	Results	21. PAGES 42-43, Findings Section, AHRQ made the statement regarding Patient Inclusion: "Several KIs suggested that studies could include a broader selection of patients with comorbidities and poorer health that are more representative of the patient	PAGES 42-43: While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient

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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. Chief Medical Officer, Solsys Medical, LLC	Results	22. PAGE 43, Findings Section, AHRQ also made the statement regarding Patient Inclusion: "…only two of the included studies reported a subgroup analysis by wound size and/or wound duration." a. Solsys Medical contends that wound depth is an important patient factor to consider in determining best practices in study design for skin substitutes. Solsys Medical urges AHRQ to include wound depth as a factor in the final report.	PAGE 43: We consider wound depth as part of our consideration of "wound size."
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	Findings: 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]? We urge AHRQ to recognize the difference in evaluation and review involved with the different regulatory pathways for skin substitute products. PMA products such as Apligraf and Dermagraft are approved by FDA following rigorous pre-market evaluation as Class III devices. PMA approval requires applicants to conduct of an investigational trial which allows the FDA to evaluate the safety and effectiveness of the product based on scientific and clinical evidence. An FDA Advisory Committee of Clinical, Medical, Science, Statistical, and Industry experts then vote in an open public hearing to recommend the product for approval or non-approval based on the totality of data presented. FDA review of Apligraf and Dermagraft pivotal studies included multiple analyses of raw data performed by FDA statisticians and classification of all wound photographs as "Healed" or "Not Healed". All analyses were prospectively defined, and the analyses were performed on the intent to treat (ITT) population. The pivotal Apligraf and Dermagraft prospective, multi-center, parallel group RCTs remain as landmark studies with the largest	Guiding Question 1: We have revised the section on FDA Regulations and most of the information on FDA regulations and classifications has been removed. Products are no longer categorized or grouped according to FDA regulatory categories.

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		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. Products that are regulated through other pathways are subject to far less rigorous review than PMA products. Products that have been cleared for marketing as Class II devices through the 510(k) process have shown that the candidate device is substantially equivalent to another predicate device that is cleared for marketing in the US. Clinical trials may or may not be required in the 510(k) application. Products that are regulated as human cell tissue products (HCT/Ps) do not require pre-market evaluation. Clinical trials to demonstrate safety and effectiveness are not required and if the sponsor decides to conduct clinical trials, then there are no FDA approvals or reviews of trial protocols, informed consent, study design, data entry and verification, statistical methods and analyses, and the final study reports. FDA pre-market approvals assures extensive clinical trial oversight of study design and evaluation of results. When there is no third party oversight of clinical data, then publications should be carefully scrutinized. AHRQ should adopt a policy of identifying FDA approved studies as primary source information of clinical publications of skin substitutes for the treatment of chronic wounds.	
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	Guiding Question 4: What are the outcomes of treatment strategies, including skin substitutes alone and/or in addition to other wound care modalities compared to other wound care modalities in patients with different types of chronic wounds, for patient oriented outcomes?	Guiding Question 4: The protocol including the ROB tool discussed in the Methods section were reviewed and approved by the KIs. The protocol was also posted on AHRQ's website for public review. Our ROB tool (based on AHRQ EPC methods) was used to detect study biases and was not used to exclude any studies.
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	In evaluating the evidence to answer question 4, AHRQ assessed the risk-of-bias using a 10-item risk-of-bias tool. AHRQ found that the 17 studies evaluated had low or moderate risk of bias. We are concerned that the classification system that AHRQ uses to assess the risk-of-bias has significant limitations. The 10 questions that make up the assessment are not sufficiently specific and additional questions should be included, such as • Did the study identify dropped patients? • Did the trial sponsor perform the final review of study results?	We do not weigh individual questions. Instead if we believed that a particular bias should be emphasized, we ask more questions in that area. Therefore, our tool has six questions addressing selection bias, and two questions assessing attrition bias. One question each addressed detection bias and reporting bias. We did not rate any studies as high ROB. Sample size is a component of our inclusion criteria (see Table 1).

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		• Did a blinded panel of reviewers assess photographs of all wounds studied to determine healing? In addition, the assessment gives each question the same weight and certain elements, specifically attrition bias, should be given more weight than other measures. We recommend applying a weight for the attrition bias questions that is twice the weight of other questions. We also recommend probing further on the statistical methodology used in the study. For example, the method of determining sample size can substantially bias study results. Retrospective use of interim sequential interim analyses to determine sample size in a post hoc manner cannot be justified. Small sample sizes lead to results where no clinically meaningful results can be drawn. As currently structured, the scale assigns different risk levels based on the raw number of "no" responses. While this method may appropriately distinguish between studies on different ends of the spectrum (for example, studies that have 2 "no" responses vs 10 "no" responses), the differences between the categories is ill-defined. There is no justification as to why a study with 7 "no" responses is considered to have "moderate" risk of bias but a study with just one more "no" response is considered "high" risk.	We have designed our cutoffs so studies poorly designed and conducted would have a high risk of bias (8-10 No).
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	We are also concerned that the current risk-of-bias classification system has been misapplied and evidence that has a high risk-of-bias has been mis-identified as low or moderate risk. The report appendix lists the responses to the 10 risk of bias elements but does not explain how the authors came to those conclusions. For example, AHRQ concludes that a study comparing EpiFix to Apligraf to standard wound care treatment (Zellen, 2016) had a "no" response to only three of the ten questions (questions # 3, 5, and 8) and therefore determined that the study has a "low" risk of bias. We disagree with this assessment. Our review of the same study found that five additional questions (questions #4, 6, 7, 9, and 10) were appropriately answered "no" for a total of eight "no" answers and the study should have been identified as having a "high" risk of bias. Specifically, we found that: • mean wound sizes at the start of treatment were not similar (more than a 15 percent difference in the Intent To Treat patient populations) between treatment and control groups (question #4); • the method of measuring wound size was not defined and no statements were made regarding intra- or inter- site standardization (question #6);	Zelen 2016 ROB assessment: Question 4: mean wound size is 2.7 Apligraft vs. 2.6 Epifix, a 4% difference. Data presented are based on an intent-to-treat population. Question 6: Authors reported "photos and tracings" as methods of measuring wound size on enrollment (see page 274 of the study). Question 7: Authors note "study adjudicators and validators were blinded about group assignment when examining photographic images of the entire study population to confirm the appropriateness of wounds enrolled and confirmation of healing on completion of the study." See page 274 of the study. Question 9: Per Figure 1, 97% Apligraf and 91% EpiFix were completers, a 6% difference in completion. Since we evaluated the study as a head-to-head comparison we did not include data from the SOC arm in our ROB analysis.

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		• different site personnel assessed the wound status and the study included no evidence of any effort to ensure assessor blinding to the product administered to a specific patient and did not include use of a blinded panel of unbiased reviewers of photographs to determine healing status (question #7); • 85% or more of patients did not provide data at the end of 12 week study. In fact, only 83 of the 104 patients (79.6%) randomized were analyzed. The authors state that an intent to treat (ITT) analysis was performed on all randomized patients but it was not. At best, the analysis presented is a modified per protocol (MPP) analysis which is NOT accepted by FDA. (question #9) • There was not a 15% or less difference in completion rates in the study arms. Epifix reported 0 patients lost to follow-up or 100% completion rate while the standard of wound care group had 13 patients lost to follow-up (and counted as treatment failures) for a completion rate of 62.8% (22/35)	
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	We strongly recommend that AHRQ review the risk of bias analysis to better reflect limitations of the studies included in the report. Our review found that, in addition to the Zellen study, three other studies also had eight or more “no” answers to the risk-of-bias questions and should be classified as “high” risk. The list below summarizes our findings: • Ananian (2018) – 8 no answers: Questions 2, 3, 4, 5, 6, 7, 8, 9	Ananian 2018: As noted on Table C-31, we agree with your assessment of questions 2, 4, 5, 6, 7, and 8. Question 3: a review of patients with heart disease and diabetes in Table 1 indicates less than a 15% difference in arms. Question 9, a review of figure 1 indicates a completion rate of 86.8% GrafixPrime arm, and 83.7% Dermagraft arm, less than a 15% difference in completion.
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	• Sanders (2014) – 9 no answers: Questions 2, 3, 4, 5, 6, 7, 8, 9, 10	Sanders 2014: As noted on Table C-31, we agree with your assessment of questions 3, 4, 5, 7, and 8. Question 2: sealed envelopes were used to conceal allocation. Question 6: photos were used to measure wounds at enrollment. Question 9: 100% of patients provided data at week 12. Question 10: 100% of patients were reported at 12 weeks, therefore no difference in completion rates.
Public Reviewer #9: Antonio Montecalvo Organogenesis, Inc.	Results	• Towler (2018) – 9 no answers: Questions 2, 3, 4, 5, 6, 7, 8, 9, 10 We ask that AHRQ revise the risk-of-bias rating for these studies (Zellen (2016), Ananian (2018), Sanders (2014) and Towler (2018)) from “moderate” to “high” .	Towler 2018: As noted on Table C-31, we agree with your assessment of questions 3, 4, 5, 7, and 8. Question 2: sealed envelopes were used to conceal allocation Question 6: photos were used to measure wound condition Question 9: 100% of patients provided data at week 12 and week 20 Question 10: 100% of patients provided data at week 12 and week 20, therefore no difference in completion rates Ratings will remain as noted in the report.

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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 classification system is based on patient risk, not on effectiveness. The much higher complexity of the regulatory process associated with the higher risk Class III devices has no relationship to their effectiveness. Lower risk devices (Class I and II) often have the same or higher effectiveness than Class III products. This fact is borne out by examining published clinical studies. Only a well-run clinical study can demonstrate effectiveness. Many people make the false assumption that clinical studies are only required and performed for Class III devices. High quality clinical studies can be, and are, conducted on Class II devices. In fact, the FDA requires clinical studies for 10-15% of Class II devices as a condition of approval. Risk-based classification does not provide a reliable gauge of whether effectiveness has been shown in a clinical study. Furthermore, the quality of the study does not correlate with the device classification. For example, a study published in the Journal of Vascular Surgery in late 2006 reviewed and ranked sixty-eight potentially relevant randomized clinical trials (RCTs) previously published in the treatment of venous leg ulcers. Included were clinical studies of Class II and Class III products. In the final analysis, only 2 RCTs contained all 7 elements of a quality	Guiding Question 1: The focus of this guiding question has been revised and no longer divides the skin substitute products by the three FDA regulatory pathways. While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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.

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		study, and both showed statistically significant benefit for healing chronic venous ulcers. Those two RCTs were for OASIS Wound Matrix (a Class II device) and Apligraf (a Class III device). There is also an assumption that within Class II, all devices with the same 3-letter FDA product code (or PRO code) are equally effective. This is not true. Some devices within a particular PRO code undergo extensive clinical testing to demonstrate effectiveness, while others do not. The PRO code is simply an internal "bucket" into which FDA sorts devices by intended use, composition, etc. It is not intended to indicate relative effectiveness or safety. In direct communication with high ranking officials in CDRH, we have been told categorically that the PRO code classification is for "FDA administrative purposes only" and is not intended to be used for reimbursement decisions. There are good reasons for the FDA to make such a statement. Different devices within the same code have different technologies and vastly different levels of clinical data to support their claims of effectiveness. This leads to the conclusion that the most effective device with the greatest proven clinical utility may also be the one with the lowest cost and lowest risk. In the FDA device classification system, Class III (highest risk) does not necessarily equate with increased effectiveness; in fact, it may be quite the opposite. As such, the Alliance recommends that AHRQ should include all studies on CTPs that FDA permits to be marketed in the U.S. and guiding question should be changed to reflect this.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*Guiding Question 2: What classification systems have been developed to categorize skin substitutes? What are important skin substitute parameters and active components currently being used when classifying skin substitutes?* AHRQ has used in its document the 2018 Davison-Kolter method of classifying CTPs. The Alliance questions why this classification system was chosen? First of all, we have concerns that since it is so new, it has not been widely accepted or validated. Secondly, we question the reason for the classification or its usefulness. There are many classifications that exist already. For instance, if the intent was for the FDA to adopt this classification, this probably would not happen since the FDA has	Guiding Question 2: We were tasked to review the literature for classification systems used for skin substitutes and to define the important skin substitute parameters and active components used when classifying skin substitutes. Our literature search identified several peer-reviewed published articles discussing classification systems used for skin substitutes including Davison-Kotler 2018, Kumar 2008, Ferreria 2011, and Nathoon 2014. Our searches did not identify nor did any of the KIs suggest using the ASTM standard guide on CTPs. After a comparison of the identified systems, we selected the Davison-Kotler classification system because it was organized according to skin substitute parameters (e.g., cellularity, source, etc.) as directed in Guiding Question 2. The KIs helped inform this decision. There

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		its own classification system which is how the products are classified when they enter the marketplace. AHRQ provides a lengthy discussion on the Davison-Kolter system and grouped products accordingly but the real question is why go through this type of exercise to group/classify the products and then do nothing with the classification? The Alliance would like to know what AHRQ and other entities will ultimately do with the groupings of products based on this classification system. We were surprised that AHRQ had not included the classification system from the ASTM standard guide on CTPs. The Alliance recommends that AHRQ use instead the classification that is included in the ASTM International Standard Guide: F3163-16 Classification of Cellular and/or Tissue-Based Products (CTPs) for Skin Wounds. The ASTM classification[2] of CTPs includes the following groupings based also on their composition: 6.1.1 *Biosynthetic* 6.1.2 *Biosynthetic and Animal Based* 6.1.3 *Non-Living Tissue Based* 6.1.3.1 *Non-Living Tissue Based – Human Based* 6.1.3.2 *Non-Living Tissue Based – Animal Based* 6.1.4 *Living Cells Biological* 6.1.4.1 *Living Cells Biological – Minimally Processed* 6.1.4.2 *Living Cells Biological – Cultured* 6.1.4.3 *Living Cells Biological – Cultured and Animal* *Products Listed as CTPs which are Surgical Dressings* In both Questions 1 and 2 there are charts that list the CTPs. Unfortunately, there are products listed which even though they have collagen in them and have gone through the 510(k) process, they are not classified as CTPs by the Centers for Medicare and Medicaid Services. Instead they are coded, covered and paid as surgical dressings and therefore, do not belong in these tables.	was no intention of having the classification system adopted by the FDA or any other organization. We have added the following paragraph describing the ASTM International classification system for CTPs: "ASTM International published a "Standard Guide for Classification of Cellular and/or Tissue-Based Products (CTPs) for Skin Wounds" in 2016. According to the guide, "CTPs are defined primarily by their composition and comprise cells and/or the extracellular components of tissue. CTPs may contain cells (viable or nonviable), tissues, proteins, and other materials for which there is a rationale for benefit beyond that achievable with conventional wound coverings. CTPs may additionally include synthetic components." The guide also has a classification system for CTPs based on four composition categories: biosynthetic, biosynthetic and animal based, non-living tissue based, and living cells biological. The non-living tissue based category is further divided by source (human or animal), and the living cells biological category is divided by processing (minimal, cultured, and cultured and animal). Living cells are presumed to be human." We have also added a new table (Table 5) that compares the ASTM and Davison-Kotler systems. In an effort to be inclusive in our listing of skin substitute products, we used the products listed under the 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. As noted several of these animal collagen-based products are designed more for exudate absorption and maintaining a moist wound environment than interaction with the wound healing process. We have removed Colla-Pad, CollaSorb, and Collexa. The other Collagen Wound Dressings included in our report are promoted as having an interaction with the healing process. We did not include or exclude products based on their coding alone.

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		The following are examples but are not all inclusive: CollaSorb® collagen dressing, Endoform™ dermal template and Puracol® and Puracol Plus® Collagen Wound Dressings. A simple check of the PDAC website would have allowed AHRQ to confirm that these products were surgical dressings not CTPs.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*Inconsistencies* Within the AHRQ technology assessment, there are inconsistencies and inaccurate information contained in the assessment which need to be rectified prior to being published in final. With respect to inconsistent or inaccurate information related to a particular product, since the AHRQ TA may be used by CMS and other payers to define products, possibly for coverage or reimbursement purposes, it is critical that the AHRQ TA be corrected to accurately describe all products. The Alliance has highlighted several of those areas for AHRQ so the document can be revised prior to being finalized. Examples include: • Grafix is correctly listed as a "cellular" product in some parts of the document, and incorrectly listed as an "acellular" product in other parts of the document. (Page 20, Table 11 – Grafix is listed as a cellular product (correct), Pages 26, 27, 31, 32, 33, 34, 38 Grafix is listed as acellular (incorrect), 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.) • "Theraskin (Table 13) is a cryopreserved human, living, split-thickness allograft that contains fibroblasts and keratinocytes. The tissue is procured within 24-hours postmortem from an organ donor. When procured, the allograft is washed with antibiotics and cryopreserved. According to the manufacturer, living cells survive through harvesting, cryopreservation, and thawing. FDA regulates Theraskin as human tissue for transplantation." This information should be corrected to read, "TheraSkin (Table 13) is a cryopreserved human, living, split-thickness allograft	Appropriate revisions have been made for all mentions of Grafix and GrafixPrime as per the manufacturer's request. We have also updated the description of Theraskin in Appendix D as per the manufacturer's request.

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		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 regulates Theraskin as human tissue for transplantation."	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	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 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.[3] If this statement is edited to "Animal tissues must be sterilized to prevent potential disease transmission." then the statement would be accurate.	We have removed the sentence "Natural human dermis must be sterilized to prevent potential disease transmission."
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	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 is not accurate since in the context of chronic wounds, these tissues are intended to be used externally rather than for implantation. In the context of chronic wounds, the antigenic components are removed by the host but the remaining dermal components become incorporated." 4	We have removed the sentence "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."
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*Guiding Question 3: What are the study design characteristics (such as those listed below) in each included investigation for each chronic wound type?)* *Evidence* In this AHRQ analysis, RCT studies limit the population that can be included in the studies to limit the variability between the	Guiding Question 3, Evidence: We agree with your assessment regarding the value of RCTs. While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient evidence (<5 RCTs) had been identified (see Methods). The approach and the inclusion criteria used in this technical brief were reviewed and

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		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 excluded because they can unpredictably impact the clinical outcomes and make appropriate patient matching nearly impossible. RCTs are conducted to remove the variables that can artificially impact the outcome and mask the "effect" of the study product. At the same time, they have inclusion criteria that includes wounds that have not responded to standard usual treatment to be evaluated. As AHRQ noted, this can result in a more healthy population in the RCT studies than in real world situations.	approved by the KIs. The protocol was also posted on AHRQ's website for public review.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	It is important to note the following information from the US Wound Registry (USWR) which illustrates the shortcomings of RCTs especially for the wound care patients who have multiple comorbidities. An analysis of 2014 Medicare cost data demonstrated that chronic wounds affect nearly 15% of Medicare beneficiaries and that Medicare's annual spend to treat them could reach $96.8 billion.[5] This national Medicare dataset revealed that patients generally have more than one ulceration and they remain unhealed for at least a year. In fact, chronic wounds are not a disease but a symptom of disease. The average Hierarchical Condition Category (HCC) score of physicians participating in the USWR is 2.9, and the prevalence of only some major comorbid diseases (based on Medicare data from physician NPI) is as follows: 1. Hypertension 73.5% 2. Chronic kidney disease 52.5% 4. Diabetes 47.8 5. Heart Failure 38.6 6. Ischemic Heart disease 49.7 7. RA and osteoarthrotis 49.7	We agree that the data from the U.S. Wound Registry will be quite valuable for assessing the effectiveness of commercially available skin substitutes. Specifically, we note in Guiding Question 6: "The ongoing trials include a registry study that may provide more data on patients outside the typical RCT (Table E-1). Data collected by the U.S. Wound Registry is intended to provide comparative-effectiveness data for patients with chronic wounds and ulcers being treated with cellular and/or tissue-based products that will include skin substitutes."

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		8. Afib 19.9 9. Alzheimer's 22 10. Asthma 30 11. COPD 27 12. Depression 34 13. Cancer 13 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. All prospective trials involving diabetic foot ulcers (DFUs) and venous leg ulcers (VLU) used virtually identical exclusion criteria which were: [6] · For DFU studies, no DFUs > Wagner Grade II (most enrolled only Wagner 1) · Diabetes as a co-morbid condition for any study other than DFU · Venous stasis except in VSU trials · Alcohol/drug abuse · Anticoagulant treatment · Cellulitis or local wound infection · Cancer or recent cancer treatment · Collagen vascular disease/connective tissue disease · Rheumatoid arthritis/autoimmune disease, any type · Scleroderma/lupus, any autoimmune disease · Charcot foot changes in DFU · Corticosteroid treatment any reason · Deep venous thrombosis/pulmonary embolus · Gastrointestinal disease of any kind /any Liver disease/Hepatitis	

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		· 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 ulcers but dehisced surgical wounds. Surgical wound dehiscence, also the most expensive wound, only occurs because patients have some underlying medical problem which prevented normal healing. Nearly 20% of wounds are simply classified as "chronic ulcers" because they don't fit into any specific wound category. Thus, RCTs in wound care do not address the most common chronic wound types. Besides excluding all the patients with serious co-morbid diseases which are not only common among chronic wound patients but are in fact, the cause of the chronic wound, RCTs also select only very small and superficial wounds.	Dehisced surgical wounds are outside the scope of the report.
Public Reviewer # 10: Marcia Nusgart	Results	RCTs have failed to enroll representative patients because in the past, there was no way to risk stratify patients and/or serious wounds based on their likelihood of healing given the numerous	As mentioned above, studies with retrospective designs are not within the scope of our reviews as described in the Methods section.

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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 terms of this AHRQ TA, wound care experts have therefore conducted evidence-based studies to allow for more diverse groups of patients with longer duration wounds and more complex or larger wounds to understand effectiveness in a 'real world' application. Unfortunately, AHRQ has not identified these studies in their review or included them in their analysis. We would like to urge AHRQ to include studies other than RCT information in this report, and in fact, it should apply the same tools (risk of bias, consistency, directness and precision) to give a more realistic picture of clinical evidence available for CTPs. Additionally, AHRQ should consider obtaining real world evidence from some of the wound registries (e.g. U.S. Wound Registry, Net Health) that are available.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*Real World Evidence* AHRQ has recognized that studies that are more representative of clinical practice and the typical patient population utilizing CTPs should be included. In the findings section AHRQ states, "KIs suggested that patient inclusion criteria could be expanded to include patients more representative of clinical practice and of poorer health than typical patients included in RCTs." We strongly support this statement which is why real- world evidence (RWE) is so important and necessary in chronic wound care. While randomized controlled trials (RCTs) represent the highest level of evidence regarding individual studies, such studies only provide evidence for efficacy of a treatment in relatively healthy patients and typically exclude vulnerable populations and wounds that are more severe in terms of their characteristics.11 The percentage of "real world" patients excluded in such studies in wound care can be high.12 RCTs are appropriate for establishing an effect under controlled conditions but are problematic when solely used to translate outcomes to "real-world" patients with	Real World Evidence: While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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. The study designs of the following studies (Budny, Desman, Landsman, Landsman, O'Donnell, Raspovic and Wilson) are not within the scope of our review as described in the Methods section. The DiDomenico 2011 study was included in the 2012 report, and does not meet inclusion criteria for this report due to publication date.

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		chronic wounds because many patients do not fit the populations used in RCTs.13 A good example of why some promising wound care products do not work well in all populations despite having reasonable successful outcomes in RCTs is that wound care RCTs are of limited duration to keep trial costs down, which limits the size/depth, and type of wound that can be treated and expected to heal within the trial time frame. This is one reason why evidence-based practice (EBP) came into being. It can be defined as "an approach to decision making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits the patient best"14 or as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.15 In other words, the approach does not only consider RCTs. In this regard, Tunis observed that "There is an urgent need to increase the capacity to conduct simple, real-world, prospective clinical studies to efficiently provide reliable data on the risk, benefits, and costs of new and emerging technologies."16 As it is difficult to conduct prospective, real-world clinical studies due to the high number of variables which would make data analysis extremely complicated, using data from a number of wound registries and EHR systems would be advantageous. Because the authors of this systematic review chose only to examine RCTs published in the peer-reviewed literature, much of the evidence on CTPs is missing, and thus, the conclusions in terms of coverage of these products are skewed. Additionally, as the search excludes RCTs published prior to 2012, many CTPs with valid RCT results are excluded from the conclusions drawn in this TA. This, as well as the inaccessibility of the previous AHRQ TA from 2012, implies that those CTPs are no longer effective, which is not true. Since RCTs may not treat the same patients treated in clinical practice, as has been recognized by AHRQ in this TA, evidence from RCTs may have limited value in predicting clinical outcomes in the real-world. However, there are a few real-world trials for CTPs published prior to September 2018 and they could have been included in this TA if for nothing else to provide context. These real-world trials have in some	

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		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 include (but are not limited to) the following: • *Budny AM, Ley A. Cryopreserved allograft as an alternative option for closure of diabetic foot ulcers. Podiatry Management. 2013 Aug:131-136.* • *Desman E, Bartow W, Anderson LH. Human skin allograft for patients with diabetic foot ulcers, venous leg ulcers, or surgical/traumatic wounds: a retrospective, descriptive study. Ostomy Wound Manage. 2015 Jul;61(7):16-22.* • *DiDomenico L et al, "A Prospective Comparison of Diabetic Foot Ulcers Treated with Either a Cryopreserved Skin Allograft or a Bioengineered Skin Substitute." WOUNDS 2011;23(7);184-189* • *Landsman A, Roukis TS, DeFronzo DJ et al. Living cells or collagen matrix: which is more beneficial in the treatment of diabetic foot ulcers? Wounds 2008 20:111-6.* • *Landsman AS, Cook J, Cook E, Landsman AR, Garrett P, Yoon J, Kirkwood A, Desman E. 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. Foot Ankle Spec. 2011 Feb;4(1):29-41.* • *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).* • *O'Donnell TF Jr, Lau J. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. J Vasc Surg 2006;44:1118-25.) This study should have been included as should any other systematic review that the authors have dismissed merely for the fact that it is a review. As*	

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		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. • *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.* • *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.*	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*Grading* The Alliance has concerns with the grading system identified in this TA. It is too inflexible and does not have specific risk of bias.	Grading: Specific ROB are listed in the Methods section and include selection bias, detection bias, reporting bias, and attrition bias.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*Guiding Question 6: What best practices in study design could be used to produce high quality evidence on skin substitutes?* *Study Design- Run In Period* As part of the Key Messages, in the section on Study Design under Question 6 and on page 46 regarding "What should future study designs have in common?", AHRQ states, "future studies may be improved by using a 4- week run-in period before study enrollment and at least a 12-week study period. They should also report whether wounds recur during 6-month follow up." The Alliance is concerned regarding the recommendation of a 4 week run in period as that time frame is too long for a patient with a chronic wound. If AHRQ is going to make this recommendation, the run in period should only be 2 weeks. In trials, patients have already failed at least 4 weeks of standard wound care (SOC). The 2-week run in period means that patients will receive a minimum of 6 weeks of SOC prior to enrollment in the trial and showed little to no improvement. All published clinical guidelines recommend using adjunctive advanced therapy after 4-weeks of failed	Guiding Question 6: We revised Guiding Question 6 (best practices) to recommend that studies include a 2- to 4-week run-in period before study enrollment and randomization.

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		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 20 weeks is 30%. There is no need to extend the run-in period for trials.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	However, reporting PAR during failed SOC and standardizing the inclusion/exclusion criteria for SOC and PAR would allow for a better comparison of data between RCTs. In the 17 published RCTs for CTPs there are trials where the 12-week healing rate in the SOC group is much higher than the 24% reported by Margolis. The Alliance recommends using "relative improvement" (the percentage difference between the healing rates of the treatment and control group) as a standardized method to compare trials. Relative improvement provides a more accurate picture of the product effectiveness vs SOC, and accounts for the differences in study populations treated in different trials.	Thank you for your comments regarding use of "relative improvement" which would be appropriate for meta-analysis, however a meta-analysis is outside the scope of the report.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	As different chronic wounds are significantly variable, it is incredibly difficult to have a standardized study designs that include standardized run-in periods. Should AHRQ determine a need to move forward with the standardized run-in period, currently we have found that when appropriately structured, 2 weeks is sufficient to bring all wounds to the same level with 2 weeks of good wound care, which is the real point of having a screening phase in the first place. In addition, it is sufficient time to eliminate fast healers, which dilutes the clinical responders of each group, as well as being enough time to properly apply inclusion and exclusion criteria. Finally, 4 weeks would mean higher screening failure rates for trials, which makes the trial longer, put more patients at risk, and make the trial more expensive and at higher risk for not being completed, all of which are undesirable.	Guiding Question 6: We revised Guiding Question 6 (best practices) to recommend that studies include a 2- to 4-week run-in period before study enrollment and randomization.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Results	*Evidence Gaps* The TA states: Industry funds the large majority of published studies, which raises concern about publication bias or selective outcome reporting in that poor results may not be published. Independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely. The evidence gaps will be only partially	We agree with your comments regarding industry funding of healthcare research, however the possibility of publication bias still remains. We address this issue in Next Steps: "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

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		addressed by currently registered ongoing trials, which are largely funded by industry. Only four of the ongoing RCTs are comparing two skin substitutes. Alliance response: Unrelated to the questions posed with respect to bias, there is an undertone to the assessment in which AHRQ implies a critical slant that all CTP evidence was funded by manufacturers. This is misleading because nearly all research conducted across the entire health care industry is funded by manufacturers. Reputable manufacturers invest in evidence for their products to ensure coverage for their products and for commercialization purposes. The fact reported in the AHRQ that only 13 products out of 74 included in the analysis (18% of brands) have published evidence is proof that no outside source of funding is conducting studies for products. AHRQ should qualify the comments to provide the context that across the entire health care industry there is very little funding of clinical trials, and manufacturers are relied upon to fund research on their products. Furthermore, the source of investment for a clinical study is not an automatic cause of bias or concern for the integrity of data generated. The Alliance believes that there is no bias to a study funded by the manufacturer as long as the investigators have no financial conflict of interest with the manufacturer. Across the healthcare spectrum, one must also question, where will the studies come from if they are not financed by the manufacturer? The types of studies that CMS and FDA either require now or in the future for commercialization in the marketplace are not the subject of those studies currently or perhaps in the future funded by NIH, PCORI or AHRQ. Similarly, as the federal and state governments are limited in the funds that they can provide to conduct randomized controlled trials and academic institutions are limited in the funds that they receive from government entities and non-for-profit organizations for conducting randomized controlled trials, it is often device or drug manufacturers that have to fund these studies in order to obtain the clinical evidence that is needed to obtain approval/clearance to market the products. All of these studies have to be reviewed by institutional review boards at each clinical study site and are subject to scrutiny by the FDA.	"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 completed before March 2017…We are unsure whether or not the lack of publications for these five trials is due to publication bias, but independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely. The evidence gaps will be only partially addressed by currently registered ongoing trials, which are largely funded by industry. Only four of the ongoing RCTs are comparing two skin substitutes."

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		As stated, the source of investment for a clinical study is not an automatic cause of bias or concern for the integrity of data generated. 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. Standard Guide for Classification of Cellular and/or Tissue Based Products (CTPs) for Skin Wounds. ASTM International. February 2016 DOI:10.1520/F3163-16 3. (See reference: Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005 Sep;25(3):587-605.) 4. (See references: (a) Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005 Sep;25(3):587-605. (b) Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, et.al. Advances in skin regeneration using tissue engineering. Int J Mol Sci. 2017 Apr 7;18(4).) 5. Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haught R, Nusgart M. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds., Value in Health, 2018, Vol.21, Issue 1, P27-32. http://www.valueinhealthjournal.com/article/S10983015(17)30329-7/pdf http://dx.doi.org/10.1016/j.jval.2017.07.007 6. Carter M, Fife CE, Walker D, Thomson B. Estimating the Applicability of Wound-care Randomized Controlled Trials to General Wound Care Populations by Estimating the Percentage of Individuals Excluded from a Typical Wound Care Population in Such Trials: 2009, 22: 316-24. 7. Horn SD, Fife CE, Smout RJ, Barrett RS, Thomson B. Development of a Wound Healing Index for Patients with Chronic Wounds. Wound Rep Reg. 21; 823-832, 2013. 8. Fife CE, Horn Susan D, Smout RJ, Barrett RS, Thomson B. A Predictive Model for Diabetic Foot Ulcer Outcome: The Wound Healing Index. Adv Wound Care. 5(7): 279-287, 2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4900227/ 9. Horn S, Fife CE, Barret R, Thomson B. A Predictive Model for Pressure Ulcer Outcome: The Wound Healing Index.	

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		Adv Skin Wound Care. 28(12): 560-572, 2015. 10. Carter MJ, Fife CE. Clinic Visit Frequency in Wound Care Matters: Data from the US Wound Registry. J Wound Care. 26(Sup1): S4-S10, 2017. 11. Serena T, B, Carter MJ, et al. Consensus principles for wound care research Obtained using a Delphi process. Wound Repair Regen 2012; 20:284-93. 12. Carter MJ, Fife CE, Thomson B, Walker D. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. Adv Skin Wound Care 2009;22:316-24. 13. van Rijswijk L, Gray M. Evidence, research, and clinical practice: a patient-centered framework for progress in wound care. Ostomy Wound Manage 2011;57:26-38. 14. Gray JA. Evidence-based Health Care: How to Make Health Policy and Management Decisions. London: Churchill Livingstone, 1997. 15. Institute of Medicine (2001). Crossing the Quality Chasm: A New Health System for the 21st Century, Washington, DC: National Academy Press. 16. Tunis SR. A clinical research strategy to support shared decision making. Health Aff (Millwood) 2005;24:180-4.	
Public Reviewer #11: Manuel Pubillones, MD Noridian Helathcare Services	Results	Pg. 05; Missing the word “Project” after Technical Brief on the first sentence: Purpose. This Technical Brief describes…	Page 5: We do not believe the mention of “project” has been an omission.
Public Reviewer #11: Manuel Pubillones, MD Noridian Helathcare Services	Results	Pg. 11; Typo on the last “signal” the “a” should be separate. …weeks of standard of care without achieving a 50 percent reduction in wound size may signala…	Pg. 11: We have removed this typographical error.
Public Reviewer #11:	Results	Pg. 39; Which are the second “wound care modalities? May need to be paraphrased. Guiding Question 4: What are the outcomes of treatment strategies, including skin substitutes alone and/or in	Pg. 39: We accepted any wound care modalities except wet to dry gauze (see Methods).

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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 Corporation	Results	Guiding Questions: Question 1: The definition of AmnioMatrix (page 11 of document, 19 of .pdf) goes into great length on the Warning Letter issues and how the authors had not heard back from Integra. The Integra Response to this issue is "According to the FDA's Final Guidance entitled: 'Regulatory Considerations for Human Cell, Tissues and Human Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use', the FDA has announced that they will exercise enforcement discretion until November 2020 for low-risk products they consider more-than-minimally-manipulated. Integra is working with the FDA to pursue acceptable approvals for their morselized amniotic tissue products."	Guiding Questions: Question 1: Mention of the Warning Letter has been removed from Table 4 and does not appear anywhere in the report.
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	Results	Question 2: AHRQ provides a lengthy discussion on the Davison-Kolter system and grouped products accordingly. Integra believes that products should be classified according to one of the FDA approved classification systems as Davison-Kolter is not well known.	Question 2: We were tasked to review the literature for classification systems used for skin substitutes and to define important skin substitute parameters and active components used when classifying skin substitutes. The FDA regulatory classifications do not supply this information. After reviewing several published classification systems (including Kumar 2008, Ferreria 2011, and Nathoon 2014) and their limitations, we selected the Davison-Kotler classification system because it was organized according to skin substitute parameters (e.g., cellularity, source, etc.). The KIs helped inform this decision. We have also added a paragraph describing the ASTM International classification system for CTPs.
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	Results	Integra Flowable should not be in Table 9 since it does not contain a synthetic component (i.e. silicone)	Integra Flowable is now listed in Table 7.
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	Results	Question 4: Tables providing clinical summaries should also include the average number of applications. We ask that AHRQ consider including mean wound area reduction as a potential endpoint in addition to incidence of wound closure as total wound closure is often not achievable in the population that has chromic wounds - often elderly and/or with multiple co-morbidities. The	Question 4: Table 18 and Table 19 are provided as a brief overview of included RCTs. Number of applications and other wound-related outcomes are included in the Appendices. While we agree that wound area reduction is an important wound-healing outcome, we did not include it as an outcome of interest for this report.

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		rate of wound closure is often a more meaningful endpoint in wound studies.	
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	Results	A clinical summary table can capture key pieces of information as shown below; the overview column (as an example, see Table 19) contains too much information that is difficult to review. Only the important and relevant information should be reported in a table format. The details can be provided in the text. Study Skin Substitute Control Incidence of wound closure (12 weeks) Mean area wound reduction (12 weeks) # of applications	We were tasked with providing a summary statement of included RCTs and chose to display the information in Table 18 and Table 19.
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	Results	Question 5: We believe that once an RCT is published, real world evidence (RWE) and real world data (RWD) that reinforces the RCT should be accepted in technology assessment studies. We believe there is a decreasing number of RCTs being conducted on chronic wound types (diabetic, venous, pressure, etc.) due to the high cost, ethics of treatment comparison to "standard of care" which is often no longer the treatment standard, and short lifecycles of medical devices not justifying the investment. In addition, most RCTs have significant exclusion criteria that results in the an intent-to-treat population that has little resemblance to the patients actually treated with skin substitutes in the real world.	Question 5: While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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 #14: Kara Gainer American Physical therapy Association	Results	Within the report, AHRQ states that studies which discuss skin substitutes rarely reported patient-related outcomes such as return to function or pain. We agree more studies are necessary. However, we have highlighted below several studies related to function and wounds that may be of interest to AHRQ in the future. J Burn Care Res. 2014 Sep-Oct;35(5):431-6. Results of a prospective randomized controlled trial of early ambulation for patients with lower extremity autografts. Lorello DJ1, Peck M, Albrecht M, Richey KJ, Pressman MA. J Phys Ther Sci. 2017 Dec;29(12):2201-2205. Effect of aquatic versus land based exercise programs on physical performance in severely burned patients: a randomized controlled trial. Zoheiry IM1, Ashem HN2, Ahmed HAH3, Abbas R4. J Burn Care Res. 2017 Jan/Feb;38(1):e70-e78. An Intervention Bundle to Facilitate Return to Work for Burn-Injured Workers: Report From a Burn Model System Investigation. Carrougher GJ1, Brych SB, Pham TN, Mandell SP, Gibran NS. Burns. 2012 Dec;38(8):1165-73.	We appreciate your insight and references provided; however, these topics (e.g. burns) are not within the scope of the report.

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		Exercise training to improve health related quality of life in long term survivors of major burn injury: a matched controlled study. Grisbrook TL1, Reid SL, Edgar DW, Wallman KE, Wood FM, Elliott CM.	
Public Reviewer #15: Jason Hodde Cook	Results	Findings: 1. Table 9 includes Integra Flowable Wound Matrix, but this product does not have a silicone layer and should therefore be presented in Table 7 instead.	Findings: We moved Integra Flowable Wound Matrix from Table 9 to Table 7.
Public Reviewer #16: Alisha Oropallo Northwell Health	Results	Grafix is no longer a living skin equivalent in reference to page 19.	Grafix is correctly categorized on page 19 as a cellular dermal replacement from human placental membrane as per manufacturer's comments.
Public Reviewer #16: Alisha Oropallo Northwell Health	Results	Which categories do skin substitutes with PHMB and hylauronic acid define?	Hyalomatrix® tissue reconstruction matrix was categorized as acellular/dermal replacement for synthetic materials.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page v: Findings • We do not believe the Davison-Kotler classification system accurately classifies placental tissue (i.e. "human amniotic membranes") by including them under the category of acellular dermal substitutes. Because of the inherent properties of placental tissue along with non-immunogenic properties, the body readily adsorbing and incorporating it, it does not need to be decellularized - a process that most dermal allografts undergo (e.g. Acellular Dermal Matrices or ADMs). In describing "human amniotic membrane" uses as skin substitutes, we believe a separate category is required i.e. "placental tissue" with a subcategory to include "amnion membrane only" and "amnion and chorion membrane," which more accurately describes these tissues based on their composition.	Page v, Findings: We have categorized and separated human placental membranes from human dermis as shown in Table 5 and Table 6. The human placental membranes listed in Table 6 were considered in the acellular category because they did not claim to have viable cells involved in wound treatment. In contrast, four human placental membrane products claiming to have viable cells were categorized as cellular dermal replacements from human placental membranes and listed in Table 11.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Regarding the reporting of "wound recurrence at least 2 weeks after treatment ended" we question the rationale for the 2-week reporting and would appreciate any references that point to this as being an acceptable follow-up time-point?	FDA's "Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment" recommends confirming complete wound healing at two consecutive study visits 2 weeks apart.
Public Reviewer #6:	Results	Page 1: Background • Page 1, Normal Skin: First paragraph, 12th line starting with the sentence, "The dermis is composed…" as the dermal layer also	Page 1: Background: The text now reads: "This skin layer provides mechanical strength and a substrate for water and nutrient diffusion; it contains blood vessels, nerves, sweat

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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. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 1, Chronic Wounds: First paragraph, 5th line regarding the sentence "A wound may be considered chronic if it has not entered the cellular migration and proliferation phase after 4 weeks," we would a reference for the bases of the "4 weeks" period.	Page 1, Chronic Wounds: We have added a reference for the basis of the "4 weeks" period.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page 3: Current Treatments for Chronic Wounds • Page 3, Advanced Therapies: Third line: Typographical error, spelling i.e. "signala" to "signals"	Page 3: Current Treatments for Chronic Wounds: We have fixed the typographical error.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 3, Advanced Therapies: We believe that the term "advanced therapies" needs to be better defined i.e. What is an advanced therapy for wound care?	Page 3, Advanced Therapies: We have removed the header "advanced therapy."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 3, Skin Substitutes: First paragraph, starting with 4th line, "Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient's skin. Skin substitutes should have functional and structural characteristics that closely match autologous skin" we disagree with these statements. Skin substitutes should support the host tissue to regenerate or facilitate functional capabilities. They do not necessarily need to have the same structure. Furthermore, we disagree with the notion that "The ideal skin substitute would be durable, completely autologous, and endothelialized and contain adnexal structures and adult stem cells, but such a construct does not yet exist." A	Page 3, Skin Substitutes: We have revised the text to read: "The ideal skin substitute would be durable, completely autologous, and endothelialized. It would contain adnexal structures and adult stem cells."

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		skin substitute should provide key matrix components which help host cell function (cell attachment, infiltration and remodeling of the graft).	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page 4: Guiding Questions • Regarding guiding question 3(f) i.e. "Basic study design and conduct information including at least method of patient enrollment, care setting, and use of run-in period," the Zelen et al. (2018) AlloPatch RCT and the DiDomenico et al. (2018) AmnioBand RCT both included a 2-week "run-in" period where weekly treatment with SOC was performed prior to randomization, and the index wound was assessed each week and its area calculated; if the area had not reduced by more than 20%, and all inclusion and exclusion criteria continued to be met 2-weeks after screening, the patient was then randomized. We believe this 2-week "run-in" period provides a better assessment of the patient and their wounds in terms of the medical necessity for a more advance treatment modality such as AmnioBand and AlloPatch and provides a higher quality trial data by way of excluding potentially "better healers" within the studies populations without putting them at any greater risk by extending the run-in period to 4-weeks.	Page 4: Guiding Questions: We revised the recommendations for run-in periods to "a 2- to 4-week run-in period before study enrollment and randomization." We also added the following text to Next Steps: "Studies should document prior treatment with appropriate standard of care for at least 4 weeks prior to the run-in period to confirm the chronicity of the wound."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Regarding guiding question 4(c) i.e. "Wound recurrence (reoccurrence) (include time when initial wound healing was measured, and follow-up to assess durability of healed wounds)" please know that both the Zelen (2018) AlloPatch RCT and the DiDomenico (2018) AmnioBand RCT index wounds were determined by the site investigator as healed if complete (100%) epithelialization occurred without drainage and need for dressing. A follow-up validation visit was scheduled one week after initial wound closure to assess durable closure. The principal investigator was responsible for approving protocol pathway decisions regarding wound closure or individual patient continuation in the study based on photographic review. 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; they included a vascular surgeon, two plastic surgeons, a general surgeon, and a podiatrist. The panel reviewed decisions made by site investigators regarding patient enrolment, healing, and study continuation. Patients were fitted for and dispensed diabetic shoes and molded insoles, provided complimentary by the sponsor at study exit.	Regarding guiding question 4(c): We agree with the reviewer's comments. Data on AlloPatch and AmnioBand are reported In Table 18.

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Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page 8: Findings 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]? • Page 8: Key Points: Second bullet point, 5th line, again, 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. Additionally, we commend the use of the term "human placental membranes" stated in that same line as opposed to "amniotic membrane."	Page 8, Findings: We replaced all mentions of "cadaver skin" with "donated human dermis."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 9: FDA Regulations for Skin Substitute Products: Third paragraph, please change the word "manufacture" to "process" as most establishments are not manufacturing human dermal tissue or human placental membrane but rather processing the tissue.	Page 9: We have changed "manufacture" to "process."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 11, Table 4, Products regulated by FDA as human tissue for transplantation in accordance with FDA's requirements for banked human tissue: Second and 3rd rows, as requested previously, in referring to our acellular dermal matrix allograft, AlloPatch®, we request that only the registered trademarked name be used throughout the brief (i.e. AlloPatch®) and any reference to "AlloPatch HD Acellular Dermal Matrix" and "AlloPatch HD" be deleted and replaced with only "AlloPatch®. Furthermore, regarding any reference to the product description, we ask that it read "AlloPatch is an aseptically processed human reticular dermal tissue for use as a chronic or acute wound covering." Additionally, we ask the same for our placental tissue, AmnioBand® (see row 9 of Table 4). That is, please use the registered trademark "AmnioBand®" throughout the document; and that 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 covering." Device Manufacturer Product Description AlloPatch® Musculoskeletal Transplant Foundation (dba MTF	Page 11, Table 4: We have updated the text to read "AlloPatch®". We have added the description of AlloPatch as requested.

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		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: We replaced all mentions of "cadaver skin" with "donated human dermis."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page 13, Guiding Question 2: What classification systems have been developed to categorize skin substitutes? What are important skin substitute parameters and active components currently being used when classifying substitutes? • Page 13: Key Points: First bullet point: In terms of classification systems and cellularity, it should be noted that some of the tissues have non-viable cells as opposed to those that have viable cells while others have had their cells removed completely (i.e. acellular). Tissue type should be the first criteria (dermal allograft, placental membrane, xenograft, manufactured), followed by cellularity (cellular or acellular).	Page 13: Key Points: In dividing products according to cellularity, we only included products claiming viable cells in the cellular classification under cellular skin substitutes.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 14: Key Points: Third bullet point: We do not believe human amniotic membranes should be grouped categorically with Acellular Dermal Substitutes as they are not acellular. This is not an appropriate categorization of these tissues. • Page 14: Key Points: Fourth paragraph: In that we still do not believe the 2018 Davison-Kotler et al. classification system corrected the 2014 Nathoo et al. shortcomings and whereas placental tissue can contain cells, they should not be categorized as acellular, at a minimum, in describing "human amniotic membrane" used as skin substitutes, we believe a separate category is required i.e. "placental tissue" with a subcategory to include "amnion membrane only" and "amnion and chorion membrane," which more accurately describes these tissues based	Page 14: Key Points, third bullet point and fourth paragraph: We have categorized and separated human placental membranes from human dermis as shown in Table 5 and Table 6. The human placental membranes listed in Table 6 were considered in the acellular category because they did not claim to have viable cells involved in wound treatment. In contrast, four human placental membrane products claiming to have viable cells were categorized as cellular dermal replacements from human placental membranes and listed in Table 11.

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		on their composition. Additionally, they can be further classified as hydrated or dehydrated, aseptically processed or gamma radiated.	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 15: Acellular Skin Substitutes o First paragraph, 3rd line: Once again, 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 also request the term "human placental membranes (amnion or amnion/chorion membranes)" be used.	Page 15: Acellular Skin Substitutes: We have replaced the text "human cadaver" with "donated human dermis."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o Second paragraph, regarding the "risk rejection": It should be noted in the document that risk of rejection (or immunogenicity) is not an issue with placental tissue; and that dermal allografts need to be acellular, as cell remnants of adult cells may be immunogenic. That is, the need for effective cell removal does not apply to immune-privileged amniotic cells.	Text has been added to read: "Rejection is not a risk with placental tissue. Antibacterial and pain-reduction properties have also been reported."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o Third paragraph, 3rd line: Once again, in deference to the donor and donor families, we respectfully request that you refrain from using the word "cadaver" and re-write the sentence to adjust for that e.g. "Donated human dermal allografts provide a structurally intact natural three-dimensional ECM."	Third paragraph, 3rd line: We have replaced the text "human cadaver" with "donated human dermis."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o Third paragraph, lines 6-9; clarification needs to be added to differentiate between xenografts and allografts. Xenografts provide a sacrificial substrate for excess MMPs to degrade. Human dermal substitutes (allografts) provide a similar scaffold for host cell attachment and infiltration and remodeling (breakdown and synthesis of new matrix proteins).	Third paragraph, lines 6-9: This section is a brief overview of Acellular Skin Substitutes. Details regarding xenografts being degraded by access MMPs are details not necessary for this paragraph.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o Third paragraph, lines 10-13; we agree "Harsh processing and gamma-irradiation" does induce structural changes – damaging or destroying the extracellular structure. That is why MTF aseptically processes its tissues, to preserve the natural structure and integrity of the tissues. Please refer to the following papers: § Cell Tissue Bank. 2017 Dec;18(4):573-584. doi: 10.1007/s10561-017-9647-0. Epub 2017 Aug 10. Chemical sterilization of allograft dermal tissues. Phipps A, Vaynshteyn E,	Third paragraph, lines 10-13: Thank you for your comment. We have added the Nilsen reference.

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		Kowalski JB, Ngo MD, Merritt K, Osborne J, Chnari E. § Plast Reconstr Surg Glob Open. 2016 Oct 4;4(10): e1065. eCollection 2016 Oct. A Novel Reticular Dermal Graft Leverages Architectural and Biological Properties to Support Wound Repair. Dasgupta A, Orgill D, Galiano RD, Zelen CM, Huang YC, Chnari E, Li WW. § Aesthet Surg J. 2016 Nov;36(suppl 2): S7-S22. Epub 2016 Oct 3. Do Processing Methods Make a Difference in Acellular Dermal Matrix Properties? Nilsen TJ, Dasgupta A, Huang YC, Wilson H, Chnari E.	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o Third paragraph, line 15, and once again, 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).	Third paragraph, line 15: We have replaced the text "human cadaver" with "donated human dermis."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 16, Table 5. Acellular/Dermal replacement from human cadaver dermis o Again, in deference to the donor and donor families, we respectfully request that you refrain from using the term "human cadaver dermis" and replace it with "donated human dermis."	Page 16, Table 5: We have replaced the text "human cadaver" with "donated human dermis."
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o As on Page 11, Table 4, we ask that the registered trademark "AlloPatch®" be the referenced device name and all references to "AlloPatch HD Acellular Dermal Matrix" be deleted. Furthermore, we ask that the "Manufacturer" information be changed to read so that the row within Table 5 now reads: Device Manufacturer Regulatory Information AlloPatch® Musculoskeletal Transplant Foundation (dba MTF Biologics), Edison, NJ, USA HCT/P	Page 11, Table 4: We have updated the text to read "AlloPatch®".
Public Reviewer #6: Daniel G. Papadopoulos, MPA	Results	o We appreciate the correct nomenclature being used in the paragraph following Table 5 i.e. the use of the term "human placental membranes" as well as the terms "amnion/chorion membranes" as well as the term "separate amnion membrane." This establishes the correct sub-categories of placental tissues. o In the paragraph following Table 5, we agree with the statement regarding harsh processing damaging the biological activity of	Nomenclature following Table 5: Thank you for your comment. We have replaced the text "human cadaver" with "donated human dermis."

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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: This chart is quite confusing as one of our tissue forms, AlloPatch is a single layer and replaces the epidermal and dermal layers.	Figure 1: As a single layer, AlloPatch only replaces the dermal extracellular matrix (ECM) in this classification.
Public Reviewer #6:	Results	Page 22: Guiding Question 3: What are the study design characteristics (such as those listed below) in each included investigation for each chronic wound type? • Page 22, regarding statement (f) “Basic study design and	Page 22: Guiding Question 3: We agree with your comments regarding these two statements.

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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 substitutes.	Page 24, Key Points, 6th bullet point: "60 patients per arm" was a convenient cutoff that we arrived at after reviewing the number of patients enrolled per arm described in all included RCTs.
Public Reviewer #6: Daniel G. Papadopoulos, MPA	Results	• Page 24, Key Points, 7th bullet point, "Our risk-of-bias analysis indicated that 47 percent and 64 percent of included studies had more than a 15 percent difference between study arms in baseline mean wound size (range up to 53.5 cm2) and baseline mean wound duration (range up to 479 weeks)." Regarding this point, this should not be about a hard number (e.g. a 15% difference) but	Page 24, Key Points, 7th bullet point: We chose 15 percent as a minimum beyond which the loss of patients would jeopardize the randomization process that distributes patients and patient characteristics equally between treatment groups.

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Musculoskeletal Transplant Foundation		rather about the wound sizes being statistically different. Wound sizes per arm differentiate is especially hard to control in a randomized study. In the Zelen et al. (2018) AlloPatch RCT, the study average wound size was greater than the SOC arm average wound size arm but still having far greater healing rates than the SOC arm.	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o 8th bullet point, regarding successful wound closures and KIs suggesting that 40 to 50% wound closure in 4 weeks as a good predictor of successful wound closure, both the Zelen et al. (2018) AlloPatch RCT and DiDomenico et al. (2018) AmnioBand RCT includes this data with 50% and 48% wounds healed at 4 weeks respectively.	8th bullet point: Thank you for pointing this out. A 12-week followup was the primary outcome listed in Appendix C for included studies.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page 24: Systematic Reviews • Page 24, System Reviews: please spell AmnioBand with a capital “B.” It is spelled with a lower case “b” i.e. AmnioBand not Amnioband.	Page 24: Systematic Reviews: AmnioBand has been changed as requested.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 25, 1st paragraph, 1st sentence regarding the Paggiaro et al 2018 meta-analysis: As mentioned in our General Comments, this study is statistically flawed and should not be used as a reference in this brief (or any other document).	Page 25, 1st paragraph, 1st sentence: We reached out to the authors after identifying the reporting error in the publication. We note in Table C-1: “We replicated the meta-analyses, finding the same results for risk ratio/relative risk and mean difference as stated in the paper. Both outcomes are statistically significant and clinically important. In the text, the authors reference the p-values for the tests of heterogeneity, which have no bearing on the statistical significance of the difference between groups. We contacted the authors, who are now submitting an erratum to the journal.”
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o Within this paragraph please spell AmnioBand with a capital “B.” It is spelled with a lower case “b” i.e. AmnioBand not Amnioband.	AmnioBand has been revised as suggested.

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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 significant and should be highlighted within this paper.	Page 25, 3rd paragraph: The Guo et al. 2017 systematic review met study inclusion criteria (see Table 1).
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	Page 26: Primary Studies • Page 26, 2nd paragraph, 3rd line: Please correct the spelling and brand name of "Allopatch" to capitalize the "P and delete the "HD" as requested previously so that it reads "AlloPatch" and not "Allopatch HD®." Additionally, please spell Amnioband with a capital "B" as previously discussed so that it reads "AmnioBand" not "Amnioband." • Page 26, regarding, Table 16, Skin Substitutes compared with standard of care in 11 RCT o As in our previous comments, please change the Skin Substitute name Allopatch HD® Acellular Dermal Matrix" to "AlloPatch®" listed in the 1st column and capitalize the "P" in AlloPatch. o As in our previous comments, please change the Skin Substitute name "AmnioBand® Allograft Placental Matrix" to AmnioBand®" listed in the 1st column. o As in our previous comments, we disagree with the categorization of placental tissues as being "Acellular dermal." It is more accurate to refer to them as "Placental Tissue" and subcategorize them as being either being an "amnion membrane" only or "amnion & chorion membranes"	Page 26: Primary Studies: Revised text for AlloPatch, AmnioBand, and the categorization of placental tissue have been completed.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	o The AmnioBand study listed in this table is not the most recent study. We ask the most recent study be included i.e. DiDomenico et al. 2018 as part of this technical brief.	DiDomenico 2018 has been included
Public Reviewer #6: Daniel G. Papadopoulos, MPA	Results	Page 27: Acellular Dermal Substitutes versus Standard of Care • Page 27, 1st paragraph, 2nd line, as in our previous comments, please change the name Allopatch HD® to "AlloPatch®" and capitalize the letter "P" in AlloPatch. Additionally, as in our	Page 27: Revisions to AlloPatch and AmnioBand have been updated as requested.

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Musculoskeletal Transplant Foundation		previous comments, please change the name “Amnioband” to AmnioBand,” capitalizing the letter “B.”	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	Results	• Page 27, 2nd paragraph, 5th line regarding classification of wounds, both the Zelen et al. (2018) AlloPatch RCT and DiDomenico et al. (2018) RCT wound eligibility included only those that were classified as	Page 27, 2nd paragraph: We believe this sentence has been inadvertently cutoff.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	Findings: 1. Page 12: Suggest the description of Grafix and GrafixPL be updated as follows: Grafix®, Osiris Therapeutics, Inc., Columbia, MD, USA, Grafix is a cryopreserved cellular placental membrane stored at -80C. GrafixPL Prime, Osiris Therapeutics. GrafixPL Prime is a lyopreserved cellular placental amniotic membrane stored at room temperature.	Findings, Page 12: We revised the text in Table 4 as requested.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	2. Page 13: Cellularity is considered the most important discriminator among skin substitutes since the presence of cells increases the rejection risk and increases manufacturing complexity.	Page 13: Thank you for your comment. We have added the following sentence to page 16: “Rejection is not a risk with placental tissue. Antibacterial and pain-reduction properties have also been reported.”
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	On page 13 there is a statement that “cellularity” is important because the presence of viable cells increases the risk of rejection. While this is a factual statement based on the theoretical risk of immune system reactions to foreign cells, Osiris believes this statement requires additional clarification or context. First, two products with viable cells (Apligraf and Dermagraft) have been on the market for nearly 20 years with no evidence in published clinical trials or reported clinical experience of immunogenic reactions to the products. Grafix has been on the market for 7 years and with more than 20 published studies and clinical use there are no reports of immunogenic reactions to the viable cells or the amniotic tissue. Second, since chronic wound patients are known to have deficient or dysfunctional cells, products with viable cells may provide clinical benefits that acellular products do not provide. We think the AHRQ should include this additional information.	On Page 13 under Guiding Question #2: We have added this text: “Tissues obtained from human donors also have the risk of infectious disease transmission; therefore, industry standards developed by FDA and the American Association of Tissue Banks are used to minimize and eliminate this risk.” We also removed two sentences regarding rejection risk.
Public Reviewer #7: Louis Savant	Results	3. The AHRQ contains inaccurate and conflicting information for Grafix and GrafixPL Prime products. Specifically, Grafix is correctly listed as a “cellular” product in some parts of the	We apologize for miscategorizing studies examining Grafix and GrafixPrime. We have made the appropriate revisions to

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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	Guiding Questions 3, Guiding Question 4, and all relevant evidence tables in Appendix C.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	On Table 19, Page 38, we suggest clarifying the statement regarding more patients with osteomyelitis and cellulitis. It should state this was at baseline, these conditions did not occur during treatment. This is misleading as someone may think more complications occurred in the Grafix arm, which is not the case.	On Table 19, Page 38: We have made the corrections as noted.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	Page 39: The statement below on page 39 should be revised due to the data leading to this finding is false. When Grafix is included with cellular products, no longer is this statement true. 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.	Page 39: The statement is still true despite recategorizing Lavery 2014 with studies comparing “Cellular dermal substitutes versus standard of care.”
Public Reviewer #7: Louis Savant	Results	Page 40: This statement should be revised to reflect the correct number of cellular and acellular products. Based on the modified Davison-Kolter classification system, these 19 skin substitutes can	Page 40: All statements have been revised after recategorizing Grafix and GrafixPrime.

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Osiris Therapeutics, Inc.		be classified as acellular dermal, cellular dermal, and cellular epidermal and dermal substitutes.	
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	Page 43: There are at least 3 real-world trials reporting on registry data or outcomes from EHR data. Perhaps you should include these? The ongoing trials include a registry study that may provide more data on patients outside the typical RCT (Table E-1). Data collected by the U.S. Wound Registry is intended to provide comparative-effectiveness data for patients with chronic wounds and ulcers being treated with cellular and/or tissue-based products that will include skin substitutes.	Page 43: While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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 #7: Louis Savant Osiris Therapeutics, Inc.	Results	Page 43: KIs recommended that studies include a 4-week run-in period before study enrollment and randomization. In all studies, patients failed 4 weeks of standard of care prior to having a 1-2 week run-in period. To require a 4-week run-in after failing 4-weeks of SOC would be unethical and not reduce study bias. This would cause more patients to decline participation.	We revised Guiding Question 6 (best practices) to recommend that studies include a 2- to 4-week run-in period before study enrollment and randomization.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	Findings: There are significant inconsistencies and inaccuracies with how our product GRAFIX is classified throughout the TA which need to be corrected. Osiris appreciates the opportunity to have those inaccuracies corrected for the final AHRQ publication, along with other recommendations we believe need further review and consideration. On Page 12, please update the product descriptions for Grafix and GrafixPL Prime as follows: GRAFIX (cryopreserved placental membrane) is a cryopreserved amnion or chorion matrix retaining the extracellular matrix, growth factors, and endogenous neonatal mesenchymal stem cells, fibroblasts and epithelial cells of the native tissue. Only Grafix PRIME contains epithelial cells, Grafix CORE (chorion) does not. GrafixPL PRIME (lyopreserved placental membrane) is a lyopreserved amnion matrix retaining the extracellular matrix, growth factors, and endogenous mesenchymal stem cells, fibroblasts and epithelial cells of the native tissue. The AHRQ contains inaccurate and conflicting information for Grafix and GrafixPL Prime products. Specifically, Grafix products are correctly listed as a "cellular" product in some parts of the 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	We apologize for miscategorizing studies examining Grafix and GrafixPrime. We have made the appropriate revisions to Guiding Questions 3, Guiding Question 4, and all relevant evidence tables in Appendix C.

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		reimbursement purposes, it is critical that the AHRC be corrected to accurately describe all products, including Grafix. Additionally, this TA will need several other changes throughout the document to correctly reclassify comparative studies to other products and standard of care as a result of Grafix being listed as "cellular". Inconsistencies and inaccuracies identified in the AHRQ regarding cellularity of Grafix 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. Grafix and GrafixPL Prime are correctly described as cellular. • Page 20, Table 11 – Grafix is listed as a cellular product (correct) • On page 24, Systematic Reviews, AHRQ incorrectly calculates studies. You need to update your numbers to reflect that Grafix is a cellular product, and we have one RCT vs. SOC and 1 RCT vs. another cellular product, Dermagraft • Page 25, Table 15 incorrectly lists Grafix as acellular dermal for the Lavery study. • The same error is repeated on Pages 26, 27, 31, 32, 33, 34, 35, 36, 37, 38, Grafix is listed as acellular in multiple locations (incorrect). Please correct these errors. • On Page 28, Grafix studies below under: Cellular Dermal Substitutes versus Standard of Care • On Page 29, the Grafix vs Dermagraft RCT (Annanian 2018) should be listed under: Cellular Dermal Substitutes versus Cellular Epidermal and Dermal Substitutes • 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.)	
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	In Table 19, Page 38, in describing the Overview if the Annanian trial we believe the following statement is misleading: Osteomyelitis and cellulitis occurred in more patients receiving Grafix Prime (13.1% vs. 5.4%). This is inaccurate and not how the study reports adverse events because there were more AEs and SAEs in the Dermagraft group vs Grafix including more osteo and cellulitis, and not all SAE's in the Grafix group we ulcer related. There was one report of osteomyelitis and one report of cellulitis for Grafix vs. 5 reports of osteo and cellulitis for Dermagraft, all ulcer related. The summary of AEs is presented in Table 5 of the	In Table 19, Page 38: Revisions have been made as requested.

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		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. Only two of these involved the index ulcer: 1 osteomyelitis and 1 cellulitis event. Please correct the AHRQ to reflect that the Dermagraft group has more ulcer related AEs and SAE's than Grafix.	
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	On Page 13 under Guiding Question #2, Osiris disagrees with part of the statement: Cellularity is considered the most important discriminator among skin substitutes since the presence of cells increases the rejection risk and increases manufacturing complexity. It's the second part of the statement we have an issue with. While this is a factual statement based on the theoretical risk of immune system reactions to foreign cells, Osiris believes this statement requires additional clarification and context. First, two products with viable cells (Apligraf and Dermagraft) have been on the market for nearly 20 years with no evidence in published clinical trials or reported clinical experience of immunogenic reactions to the products. Grafix is a cellular product on the market for 7 years, and with more than 20 published studies and broad clinical use there are no reports of immunogenic reactions to the viable cells or the amniotic tissue. Second, since chronic wound patients are known to have deficient or dysfunctional cells, products with viable cells may provide clinical benefits that acellular products do not provide. We think the AHRQ should include this additional information.	On Page 13 under Guiding Question #2: We have added this text: "Tissues obtained from human donors also have the risk of infectious disease transmission; therefore, industry standards developed by FDA and the American Association of Tissue Banks are used to minimize and eliminate this risk." We also removed two sentences regarding rejection risk.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	Page 40, AHRQ will need to revised the following statement to correctly calculate the classification of products: Based on the modified Davison-Kolter classification system, these 19 skin substitutes can be classified as acellular dermal, cellular dermal, and cellular epidermal and dermal substitutes.	Page 40: This statement has been revised.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	Page 43: Why did AHRQ not include currently published registry trials and RWE trials? There are well done RWE trials to supplement RCTs and provide data on patients treated in the clinical setting. One such trial includes: Raspovic KM, Wukich DK, Naiman DQ, et al. Effectiveness of viable cryopreserved placental membranes for management of	Page 43: While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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.

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		diabetic foot ulcers in a real world setting. Wound Repair Regen. doi: 101111/wrr12635. Accessed 27 July 2018.	The Raspovic study did not meet our study inclusion criteria (see Methods).
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Results	Under Study Design on Page 43 AHRQ KI's recommend a 4-week "run-in" period versus the 1-2 weeks in current trials. Osiris believes 4-weeks is unnecessary and contradicts evidence. In trials, patients have already failed at least 4 weeks of standard wound care (SOC). The 2-week run in period means that patients will receive a minimum of 6 weeks of SOC prior to enrollment in the trial and showed little to no improvement. All published clinical guidelines recommend using adjuvant advanced therapy after 4-weeks of failed 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 20 weeks is 30%. There is no need to extend the run-in period for trials. However, reporting PAR during failed SOC and standardizing the inclusion/exclusion criteria for SOC and PAR would allow for a better comparison of data between RCTs. In the 17 published RCTs for CTPs there are trials where the 12-week healing rate in the SOC group is much higher than the 24% reported by Margolis. Osiris recommends using "relative improvement" (the percentage difference between the healing rates of the treatment and control group) as a standardized method to compare trials. Relative improvement provides a more accurate picture of the product effectiveness vs SOC, and accounts for the differences in study populations treated in different trials.	Under Study Design on Page 43: Real World Evidence: While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of RCTs or individual RCTs except for wound types for which insufficient 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. Thank you for your comments regarding use of "relative improvement" which would be appropriate for meta-analysis. A meta-analysis is outside the scope of the report.
Public Reviewer #18: William H. Tettelbach, MD, FACP, FIDSA, FUHM, CWS MiMedx Group, Inc.	Results	Our four comments in this section relate to: • Guiding Question 3: What are the study design characteristics…(for each chronic wound type?) Subsection f. Basic study design and conduct information including at least method of patient enrollment, care setting, and use of run-in period, and • Guiding Question 6: What best practices in study design could be used to produce high quality evidence on skin substitutes? 1) Length of Run-in Period and Impact on Research In regards to the suggestion by key informants of a 4-week run-in period versus a 2-week run-in period for future trials evaluating	Length of Run-in Period and Impact on Research: We revised Guiding Question 6 (best practices) to recommend that studies include a 2- to 4-week run-in period before study enrollment and randomization.

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		chronic wounds, which by definition have already been persisting for ≥ 30 days and in the majority of instances have been treated during those 30 days, would create an environment where enrollment of prospective study candidates would become much more arduous while at the same time drive up the overall cost to perform such desired studies. The end result would be the placement of additional barriers that would disincentivize potential sponsoring organizations or interested research institutions from conducting the trials. If not already appreciated, approximately 40% to 50% of potential candidates initially enrolled for a chronic DFU study are not ever randomized to a treatment or control group due to the fact that their wounds typically experience a ≥ 25% wound area reduction within the prescribed 2-week run-in period. To date there is no comparative evidence or trial demonstrating that a 4-week run-in period is superior to a 2-week run-in period in determining the refractoriness of a chronic wound to healing. Today's SOC is defined by the use of a simple alginate, foam or equivalent dressing plus appropriate debridement, moisture control and offloading where indicated. The often-referenced Sheehan study, which noted that a < 53% reduction in a DFU at 4 weeks of treatment implies the wound has a < 9% chance of healing by 12 weeks, exhibits a major shortcoming in that the control group in this study was treated with moistened gauze.(1) Therefore, via criteria established by this document, the 2003 Sheehan paper straightaway falls short of inclusion or of being referenced since any studies that used saline wet-to-dry gauze were excluded from this analysis. An updated analysis using modern SOC techniques to confirm or redefine the pivotal clinical decision point would be beneficial. The bottom line is the 2-week run-in period is a well-established study protocol metric that would confound results when compared against future studies using the suggested 4-weeks run-in period.	
Public Reviewer #18: William H. Tettelbach, MD, FACP, FIDSA, FUHM, CWS	Results	2) Reliance on Surrogate End Points Can Increase Detection Bias Noted several times in this review by a key informant is the suggestion "40% to 50% percent wound closure in 4 weeks was a good predictor of successful wound healing." We should keep in mind surrogate endpoints cannot be relied upon solely. Although surrogate endpoints are important for feasibility studies and afford	Reliance on Surrogate End Points Can Increase Detection Bias: We agree with your comments on surrogate endpoints. Grading evidence or synthesizing data is beyond the scope of a technical brief.

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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: William H. Tettelbach, MD, FACP, FIDSA, FUHM, CWS MiMedx Group, Inc.	Results	3) Exploration of "Appropriate criteria for discontinuing use of a skin substitute and switching to another advanced therapy option" Not Supported by Current Evidence The rationale behind the suggestion that "failure to heal after 6 weeks of treatment with a skin substitute may be an appropriate criteria for discontinuing use of a skin substitute and switching to another advanced therapy option" is intriguing since there again is no strong evidence to support such a claim. In fact, there are at least 3 level one RCTs that demonstrate the probability of healing a chronic DFU or venous leg ulcer more than doubles at 12 weeks compared to 6 weeks.(3)(4)(5) In the process of healing a chronic wound with advanced therapies, a 6 week hard stop does not take into account the wound's healing trajectory that should not be disrupted by a set time point alone, especially if a hard to heal wound is demonstrating signs of size reduction after every application of a skin substitute. Please keep in mind that the 21st Century Cures Act stresses that all policy decisions affecting patient care and expenses should be supported by evidence that is made transparent to those the policy decisions impact. (6)	Exploration of "Appropriate criteria for discontinuing use of a skin substitute and switching to another advanced therapy option": KIs are important in technical briefs, because the technologies in question are generally fairly new and relatively little written data may be available. Therefore KIs can contribute to an understanding of how the technology/intervention works, where it might fit into clinical care, and potential advantages or concerns. Therefore, we include KI suggestions even though there may be little clinical evidence at this time to support these suggestions.
Public Reviewer #18: William H. Tettelbach, MD, FACP, FIDSA, FUHM, CWS MiMedx Group, Inc.	Results	4) Statement of Support toward Diversified Studies and Report Outcomes We agree moving forward studies investigating the use of skin substitutes to treat pressure ulcers and arterial leg ulcers should be initiated. We also concur that the specialty of Wound Care may be better served if future chronic wound trials were able to better standardize the approach to study design as well as report outcomes such as wound recurrence, return to baseline activities of daily living and pain relief.	Statement of Support toward Diversified Studies and Report Outcomes: We apologize for the omission of these two studies from the draft report. One Tettelbach 2019 study ("A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers") was identified in the updated searches during the peer review process.

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		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 literature was performed in preparation for the analytical portion of the skin substitute assessment. However, when checking the completeness of references contained within the documents as well as the selection of RCTs comparing skin substitutes with standard of care (SOC), it became apparent that a key multicenter RCT with significant positive impact had not been included in this review. The article titled “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” was electronically published on August 22, 2018 in the indexed International Wound Journal.1 This publication became available before the PubMed set date limit of September 13, 2018. The possible explanation for this omission includes the fact that keywords found in the Appendix A. Search Strategies section, which were used to query the medical literature archives, did not contain the topic-specific search terms: • EpiFix, • dehydrated human amnion chorion membrane or • dHACM As a result, a noteworthy DFU study, in which 14 wound centers located across the United States participated and enrolled 110 patients, was excluded from the final analysis. We respectfully request that the following statistically significant study be included in this systematic review – “Skin Substitutes for Treating Chronic Wounds” (Tettelbach W et al. Int Wound J. Epub 2018 Aug 22. PMID: 30136445). (3)	Thank you for your insight on why the other Tettelbach study may have been missed. We have passed this information along to our staff. Both studies are now included in the final report.

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		2) Additional Recommendation for Improvement To make the Tech Assessment even more robust, we ask your consideration of including another meaningful multicenter RCT, which involved 11 wound care centers and enrolled 155 patients, with the goal of evaluating the efficacy of dehydrated human umbilical cord (EpiCord) in the treatment of DFUs. The article "A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers" which was electronically published just 11 days after the PubMed set date limit of September 13, 2018. (4) 3) Benefits to Inclusion The inclusion of these two additional multicenter RCTs would increase the statistical weight of the comparative analysis to SOC since the number of RCTs comparing skin substitutes to SOC would increase by 18% from 11 to 13. The inclusion of any other relevant manuscripts published within the extended set date limit, if allowed, would be welcomed. Additionally, we submit that the AHRQ Tech Assessment Brief is intended to be a long-standing document. With that goal, it makes sense to be as inclusive as is reasonably in line with the spirit and overall methodology of the rest of the Tech Assessment. We maintain that including the two studies referenced above will bring the Assessment to a most current status possible prior to final publication. Lastly—also in line with the spirit and methodology of the rest of the brief---the studies themselves are well-designed Level 1 evidence. Their inclusion only broadens the understanding of skin substitutes for chronic wounds and enhances the durability of the AHRQ Tech Assessment. Both studies include Intent-to-Treat analysis. Additionally, both studies examine (via blinded adjudicators) the role of adequate debridement in wound healing. We contend that this also advances the goals of the assessment: to broaden research outside of what has been traditionally performed in wound care studies. Key Findings:	

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		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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		• Per-Protocol EpiCord Treated Patients = 81% vs Control 54%, (p=0.0013) Intent-To-Treat • 70% of patients who received dHUC plus SOC had complete healing by 12 weeks. • 48% of patients who received Alginate plus SOC had complete healing in 12 weeks. • Intent-To-Treat EpiCord Treated Patients = 70% vs Control 48%, (p=0.0089) • Intent-to-Treat with adequate debridement with EpiCord & SOC – 96% healed at 12 weeks (p<0.001) • Intent-to-Treat with adequate debridement with SOC alone – 65% healed at 12 weeks (p<0.001) Findings: We submit the findings of the Tech Assessment can be improved by including the two studies identified in our comments under the Methods section. Please note that inclusion within the Tech Assessment will correct a perceived error in the search criteria within the Data Collection, Grey Literature Search and Published Literature Search. Please note that the findings of the overall AHRQ Tech Assessment Brief will be improved by including these studies, for the beneficial reasons outlined in the Methods section. Again, 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. Correcting the identified omission and being inclusive during the draft stages of this document helps to accomplish this goal.	

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Peer Reviewer #1	Discussion	Are the implications of the major findings clearly stated? Yes, however it takes a long time to get there which is certainly needful, however a statement earlier in the paper might be helpful to the reader so that the content has perspective. Are the limitations of the review/studies described adequately? Yes quite clearly done. In the discussion, did the investigators omit any important literature? I do not believe so as the 148 original papers we pared down to the those that fit the criteria and the reviewed in detail Is the future research section clear and easily translated into new research? Yes, but here again it takes a long time to get there which is certainly needful, however a statement earlier in the paper might be helpful to the reader so that the content has perspective.	Due to size constraints, we can only provide the Key Messages and Structured Abstract to highlight our findings. We do however provide Key Points and Overviews for each Guiding Question to highlight each section.
Peer Reviewer #2	Discussion	All feasible with registries and long term f/u data points like 6, 12, and 24 months	Next Steps: We have added text to reflect this: “Clinicians would benefit from having additional clinical evidence of effectiveness in patients resembling those in clinical practice. Patients with cardiovascular disease, kidney disease, and poor glucose control or those who smoke could be included in studies large enough to allow subgroup analysis of these patient populations. Clinicians will also benefit from information on race, ethnicity, and gender. Long-term followup of patients may be particularly important to judge not only recurrence, but also potential toxic or other harmful effects. This information may become available in wound care registries and in studies with long-term followup (e.g., 6 to 24 months).”
Peer Reviewer #3	Discussion	Please see above and include suggestion of competency of investigators and reproducibility is essential. That is what are the minimal requirements to be an investigator? Consider a cooperative group be formed with standards for competency.	The purpose of this technical brief is to describe skin substitute products commercially available in the United States used to treat chronic wounds, examine systems used to classify skin substitutes, identify and assess RCTs, and suggest best practices for future studies. While we agree that appropriate knowledge and training of investigators is extremely important in clinical trial research, we were not tasked to determine the minimal competencies of clinical researchers in this field.
Peer Reviewer #3	Discussion	yes but strengthen summary and consider adding a succinct conclusion with bullet points	Bulleted or key points are provided for each Guiding Question including Guiding Question 6 focused on best practices.

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Peer Reviewer #4	Discussion	I do agree with the future direction suggestions - clinicians (and payers) desperately need information about the effectiveness of these products in real patients with comorbidities and common wounds (including pressure ulcers)	Thank you for your comments.
Peer Reviewer #5	Discussion	I found the major findings to be very clearly presented, with sufficient detail, and not overstated. I think the future research recommendations is particularly relevant and interesting. The authors have identified specific areas where studies can be improved in design. If adopted this could make an impact on the quality of information gained from research on skin substitutes.	Thank you for your comments.
Peer Reviewer #6	Discussion	1) p. 24, Key points, line 37-38: "KIs suggested that 40 percent to 50 percent wound closure in 4 weeks was a good predictor of successful wound closure". This statement seems out of place; it is unclear if this suggestion was supported by the data in the studies. If so, please describe what data support this statement. If there is no data in these studies included in this review, then please remove this statement.	p. 24, Key points, line 37-38: We have moved this statement to Guiding Question 6 and added the following: “Evidence indicates that 50 percent reduction for diabetic foot ulcers at 4 weeks was a strong predictor of wound healing by 12 weeks when standard of care was used, while percent change in wound area for venous leg ulcers after 4 weeks was predictive of complete wound healing by 24 weeks.”
Peer Reviewer #6	Discussion	2) p. 30, Guiding Question 3 Overview. This section should note that Standard of Care varied significantly across the studies.	p. 30, Guiding Question 3 Overview: We have added text noting the variability in SOC. The text now reads: “Standard of care was the most common comparator in the included studies but varied considerably. Few studies reported infection surveillance and diabetic control as key components of standard of care.”
Peer Reviewer #6	Discussion	3) p. 30, Guiding Question 3 Overview, line 52-54, "KIs suggested that 40 percent to 50 percent wound closure in 4 weeks was a good predictor of successful wound closure". This statement should be removed as it is unrelated to the guiding question and it was not evaluated in the studies. No data is provided or discussed which supports this statement.	We have moved this statement to Guiding Question 6 and added the following: “Evidence indicates that 50 percent reduction for diabetic foot ulcers at 4 weeks was a strong predictor of wound healing by 12 weeks when standard of care was used, while percent change in wound area for venous leg ulcers after 4 weeks was predictive of complete wound healing by 24 weeks.”
Peer Reviewer #6	Discussion	4) p. 30 line 56 - p. 31 line 3: "Recurrence was lower with Dermagraft". Please revise this sentence to state the duration of followup for which recurrence was assessed.	p. 30 line 56 - p. 31 line 3: We have added followup of 24 weeks to these two statements.
Peer Reviewer #6	Discussion	5) Table 18, p. 35-36; Table 19, p. 38-39: The Overview column should include the duration of the study/followup when recurrence, and the time point at which wound closure/healing, was assessed. This is present for some but not all studies	Table 18, p. 35-36; Table 19, p. 38-39: We have revised Table 19 as suggested.

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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 #6	Discussion	7) p. 40 Lines 47-53. There are two Key Points which include KI suggestions. It is unclear whether these key suggestions are supported by the data or whether these are the conclusions of the authors. In addition, the last Key Point suggesting the criteria for discontinuing use of a skin substitute is unrelated to the Guiding question; this suggestion does not address best practices in study design and instead makes a clinical care/guideline recommendation. These Key Points which begin "KIs suggested..." should be removed.	p. 40 Lines 47-53: KIs are important in technical briefs, because the technologies in question are generally fairly new and relatively little written data may be available. Therefore KIs can contribute to an understanding of how the technology/intervention works, where it might fit into clinical care, and potential advantages or concerns. Therefore, we include KI suggestions even though there may be little clinical evidence at this time to support these suggestions.
Peer Reviewer #6	Discussion	8) p. 42 Patient Inclusion: KI suggestions are discussed. It is unclear whether the authors concur with these suggestions.	p. 42 Patient Inclusion: The purpose of engaging the KIs was to help inform our report because these individuals have a breadth of expertise in the topics area. The authors felt that their collective recommendations were practical and implementable, and addressed the issues of most relevance to stakeholders.

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Peer Reviewer #6	Discussion	Additionally, while registries may include more diverse patients, are there study design considerations for how registry data may be used or queried to answer research questions? Please comment on this.	We note in the Summary and Implications section: "The ongoing trials include a registry study that may provide more data on patients outside the typical RCT (Table E-1). Data collected by the U.S. Wound Registry is intended to provide comparative-effectiveness data for patients with chronic wounds and ulcers being treated with cellular and/or tissue-based products that will include skin substitutes. Registry data may be used for sub-analysis of key patient- (e.g., gender, race, comorbidities) and wound-related characteristics (e.g., severity, wound duration) that may not be available in typical RCTs. This information may help direct specific product use for different wound conditions." Delineating methods for registry studies is beyond the scope of this report. Please see the 3rd edition of AHRQ's publication "Registries for Evaluating Patient Outcomes: A User's Guide", a reference handbook with practical information on the design, operation, and analysis of patient registries. According to AHRQ, "properly designed and executed, patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness."
Peer Reviewer #6	Discussion	9) p. 43 Study Design: KI suggestions are discussed. It is unclear whether the authors concur with these suggestions. It is unclear on what basis or analysis of the specific data reviewed these suggestions are made. Recommend providing discussion of what data support these statements (such as the discussion provided in the Patient Inclusion section, p. 42-43), or remove unsupported statements.	p. 43 Study Design: KIs are important in technical briefs, because the technologies in question are generally fairly new and relatively little written data may be available. Therefore KIs can contribute to an understanding of how the technology/intervention works, where it might fit into clinical care, and potential advantages or concerns. Therefore, we include KI suggestions even though there may be little clinical evidence at this time to support these suggestions.

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 discussed as to why they may or may not be appropriate outcome measures for future studies.	p. 43 Outcomes line 52-55: We have added text noting the FDAs suggestion of measuring cosmesis to this section. The importance of other endpoints are discussed in the report except for the facilitation of surgical wound closure which is out of scope.
Peer Reviewer #6	Discussion	12) 8) p. 43 Outcomes: KI suggestions are discussed. It is unclear whether the authors concur with these suggestions.	p. 43 Outcomes: The purpose of engaging the KIs was to help inform our report because these individuals have a breadth of expertise in the topics area. The authors felt that their collective recommendations were practical and implementable, and addressed the issues of most relevance to stakeholders.

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 trials from the 2012 report. The text now reads: "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 completed before March 2017…We are unsure whether or not the lack of publications for these five trials is due to publication bias, but independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely. The evidence gaps will be only partially addressed by currently registered ongoing trials, which are largely funded by industry. Only four of the ongoing RCTs are comparing two skin substitutes."
KI Reviewer #2	Discussion	The implications of the major findings are clearly stated and adequate. Limitations are explained throughout the report sufficiently, clearly and appropriately. The future research section is clear and provides direction for future research. As noted earlier, the only omission detected is lack of any presentation/discussion of ethnicity/racial groups for subjects in the reviewed studies and gender.	As mentioned above, we have added ethnicity/race to the evidence tables and added text to reflect this information. Gender is also reported.
KI Reviewer #3	Discussion	Agree with the KI's that we need studies that follow patients 6 months after wound closure to determine wound closure.	Thank you for your comments.
KI Reviewer #4	Discussion	The implications of major findings are clearly stated. The limitations are described adequately. I do not know of any omitted studies that would change the conclusions. The Evidence Gaps and Next Steps sections are clear and easily translated into new research.	Thank you for your comments.
Public Reviewer #2: Zack Bridges ACell Inc.	Discussion	Summary and Implications: No comment	Thank you
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A.	Discussion	Summary and Implications: 1. PAGES 44-46, Summary and Implications Section, AHRQ summarizes (1) Skin Substitutes Being Examined in Clinical Trials, (2) Findings (from the 17 current RCTs evaluated), and (3) Evidence Gaps. a. Solsys Medical urges AHRQ to review all the comments submitted herein and re-consider how these new concepts affect the Summary and Implications section in the FINAL published	PAGES 44-46: We agree with the author's comments that more studies should report on patient compliance and recidivism.

Commentator & Affiliation	Section	Comment	Response
Chief Medical Officer, Solsys Medical, LLC		document. 2. PAGES 44-46, Summary and Implications Section, AHRQ questions what future study designs should have in common. a. Solsys Medical urges AHRQ that the connection with recidivism and the biologic used is unclear to us because recidivism is dependent on patient factors. An example would be a patient with a pressure ulcer on the heel that reoccurs regardless of which biologic was used.	
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Discussion	3. PAGE 46, Summary and Implications Section, AHRQ made the statement regarding evidence gaps, "Industry funds the large majority of published studies, which raises concern about publication bias or selective outcome reporting in that poor results may not be published. Independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely." a. Solsys Medical agrees that, ideally, future studies in wound care would not be industry sponsored. However, the FDA does not sponsor these studies and there is no other avenue to conduct this type of research today, without manufacturer funding, with the sole exception of Towler, 2018.	PAGE 46: We have added text to the Evidence Gaps section after our review of ongoing trials from the 2012 report. The text now reads: "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 completed before March 2017…We are unsure whether or not the lack of publications for these five trials is due to publication bias, but independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely. The evidence gaps will be only partially addressed by currently registered ongoing trials, which are largely funded by industry. Only four of the ongoing RCTs are comparing two skin substitutes."
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Discussion	Summary and Implications: On page 45 there is discussion regarding trials being limited to DFU and VLU. This is factual and perhaps worthy of mentioning that many patients with chronic wounds would fail inclusion/exclusion criteria for studies outside of DFU and VLU because they have multiple co-morbidities. It would be very difficult to match cohorts in a controlled trial when the patient population is not well-defined. This is a challenge for wound care related studies.	Thank you for your comments.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Discussion	Page 46 incorrectly states there is only one study comparing cellular dermal substitutes to SOC. Grafix, Apligraf and Dermagraft are all cellular products and have been compared to SOC in RCTs. Again, the entire AHRQ must be revised to correct for the inaccurate classification of Grafix as acellular.	We have made all revisions to Grafix and GrafixPrime as requested.
Public Reviewer #7: Louis Savant	Discussion	Summary and Implications: Osiris applauds the AHRQ for pointing out on Page 45 the need for published clinical evidence for all products so that clinicians and payers can make informed	Thank you for your comments.

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 two studies comparing cellular dermal substitutes with standard of care."	Grafix is now classified as a cellular product throughout the document.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Discussion	On Page 46 AHRQ implies a critical slant that all evidence was funded by manufacturers. Osiris believes this is misleading because nearly all research conducted across the entire health care industry is funded by manufacturers. Good manufacturers invest in evidence for their products. The fact reported in the AHRQ that only 13 products out of 74 included in the analysis (18% of brands) have published evidence is proof that no outside source of funding is conducting studies for products. Osiris believes the AHRQ should qualify the comments to provide context that across the entire health care industry there is very little funding of clinical trials, and manufacturers are relied upon to fund research on their products. Also, the peer-review process is in place to point out poorly conducted studies and identify bias in studies.	We have added text to the Evidence Gaps section after our review of ongoing trials from the 2012 report. The text now reads: "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"[1] 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 completed before March 2017…We are unsure whether or not the lack of publications for these five trials is due to publication bias, but independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely. The evidence gaps will be only partially addressed by currently registered ongoing trials, which are largely funded by industry. Only four of the ongoing RCTs are comparing two skin substitutes."
Public Reviewer #11: Manuel Pubillones, MD Noridian Helathcare Services	Discussion	Summary and Implications: Some corrections needed...	Thank you.
Public Reviewer #16: Alisha Oropallo Northwell Health	Discussion	Summary and Implications: Few comparative trials between skin substitutes exist. It is difficult for the clinician to choose amongst different skin substitutes. Most skin substitutes are determined by insurance reimbursement.	Thank you for your comments.

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 studies summarized in this literature search (Figure 3), it would be valuable information to highlight whether effectiveness of a given skin substitute is based on the ability to close a 1 cm2 wound versus a 15 cm2 wound. Information from the KIs on a clinically meaningful wound size for evaluation may also be valuable.	Next Steps: We mention the need for studies to report sub-analysis of several important wound and patient characteristics including wound size.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Conclusion	Next Steps: N/A, Solsys Medical has no additional comments to make relating to pages 46-52 of the AHRQ draft.	Thank you for your review of the report.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Conclusion	Next Steps: AHRQ points out on Page 47 that RCTs may not treat the same patients treated in clinical practice, and therefore evidence from RCTs may have limited value in predicting clinical outcomes in the real-world. However, there are a few real-world trials for CTPs published prior to September 2018 and they could have been included in the TA for context. These real-world trials have in some cases shown outcomes similar to that seen in RCTs. It would have been valuable to point these out and include them in the AHRQ. Osiris believes the following RWE trial provides relevant outcomes information in a DFU population without excluding patients with co-morbidities. 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.	While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of randomized controlled trials (RCTs) or individual RCTs except for wound types for which insufficient 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 #8 Anonymous	Conclusion	there should be trials done to compare results in particular populations with high risk behaviors and their response to particular product types,	We mention the need for studies to report sub-analysis of several important wound and patient characteristics such as smoking and alcohol use.
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Conclusion	In this AHRQ TA, even with the key questions and guiding questions posed as answered, the Alliance has questions regarding the actual findings. There should have been a detailed summary based on the statistics which included what is known, what is missing and what are gaps that need to be filled with respect to CTPs. The Alliance does not have a clear	The focus of a technical brief is three-fold. First, technical briefs are done on emerging technologies or topics where there is little available evidence. Secondly, they provide an overview of the state of the science, identifying ongoing research, gaps in evidence, and are used to inform future research needs Last, unlike a systematic review, technical briefs do not include grading of evidence or data synthesis.

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 evidence would be beneficial. Yet, AHRQ either eliminated or did not review any studies which would provide real world data and help to answer some of the questions posed in this TA. Until AHRQ reviews real world evidence for CTPs, the Alliance believes that this TA is incomplete.	While we agree that publications with real-world evidence are valuable, a decision was made at the study protocol stage to only include systematic reviews of randomized controlled trials (RCTs) or individual RCTs except for wound types for which insufficient 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 # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	Conclusion	The Alliance appreciates the opportunity to provide you with our comments and feedback on this TA. We would appreciate the opportunity to meet with your staff responsible for this TA and the ECRI authors of the study.	Thank you for your thorough review of the report.
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	Conclusion	Integra LifeSciences welcomes the opportunity to provide these comments on the draft technical brief. We would welcome the opportunity to engage with the research team further and answer any questions you may have.	Thank you for your comments.
Public Reviewer #16: Alisha Oropallo Northwell Health	Conclusion	Next Steps: Require post marketing analysis on skin substitutes before reimbursement is given.	Thank you for your comment. Requiring post-market analysis of skin substitute products is beyond the scope of the report.
Peer Reviewer #6	Appendix	2) In Appendix D, I see that product description and manufacturer claims are tabulated along with regulatory information. However, it is unclear in many cases where the information for product description/manufacturer claims came from. Ideally the manufacturer claims/commercial descriptions would align with the FDA regulatory documentation (e.g., 510(k) Summary, SSED), but sometimes that is not the case. I recommend that information be added to the Tables in Appendix D to identify where the information was sourced (this could be done with superscripts/footnotes). I recommend that the product description for each PMA or 510k device be compared to the cleared/approved device description available on the public FDA	2) In Appendix D: We provide links to the manufacturer's website where this information was sourced. Comparing this information to the FDA product descriptions is beyond the scope of the technical brief.

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 product description should be compared to literature/other information and discrepancies identified; I see that this was does for Amniomatrix in Table 4 which is appropriate. If no discrepancies need to be pointed out, it may be helpful to add a comment to page 9 or Appendix D to explain that this analysis was conducted.	
Peer Reviewer #6	Appendix	4) p. 22, Guiding Question 3, and Appendix C: Length of study/followup should be listed under Guiding Question 3f on p. 20.	p. 22, Guiding Question 3, and Appendix C: While we are unable to revise the Guiding Questions, we do capture length of study for all included studies in the evidence tables in Appendix C.
Peer Reviewer #6	Appendix	5) In Appendix C, Tables C21, C23, C25, C27 C29. Consider adding separate rows/entries to delineate safety endpoints, effectiveness endpoints, and primary, secondary, and exploratory endpoints if this information is present.	Appendix C, Tables C21, C23, C25, C27 C29: Due to meeting 508 compliance requirements, we are unable to add separate subcategories to delineate safety endpoints and effectiveness endpoints.
Public Reviewer #2: Zack Bridges ACell Inc.	Appendix	Appendixes: No comment	Thank you for your review of the report.
Public Reviewer #3: Marc Goldberg, BONAPEDA Enterprises LLC	Appendix	Appendixes: Wu et al, Diabetes Care, Vol 31, November 2008 Fife CE, et al; "Why is it so hard to do the right thing in wound care" Wound Rep Reg : 18 p 154-158 2010 Caroline Fife, Advances in Skin & Wound Care, July 2014, Vol 27 - Issue 7 - pp 310–316 McGuire et al, Lower Extremity Review, June 2018, Advances and alternatives in diabetic ulcer offloading Greer N, Foman N, Dorrian J, Fitzgerald P, MacDonald R, Rutks I, Wilt T. Advanced Wound Care Therapies for Non-Healing Diabetic, Venous, and Arterial Ulcers: A Systematic Review. VA-ESP Project #09-009; 2012. https://lermagazine.com/editor_memo/the-dfu-dilemma-is-the-total-contact-cast-a-true-gold-standard	Thank you forwarding these references, however the articles do not meet our inclusion criteria for publication (see Methods).
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A.	Appendix	Appendixes: 1. Table C-29, Page C-49: Solsys Medical notes that the Table is missing significant outcomes for Sanders 201433. It should be updated to include the following significant finding that TheraSkin ($2,495) is more cost-effective than Apligraf ($4,317) in the treatment of VLUs.	Appendixes: 1. Table C-29, Page C-49: We are not including cost data in the report (see Methods).

Commentator & Affiliation	Section	Comment	Response
Chief Medical Officer, Solsys Medical, LLC			
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	Appendix	2. Table C-29, Pages C-49-C-50: Solsys Medical notes that the Table is missing significant head-to head studies for TheraSkin (as previously commented). We request that it be updated to include: 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. 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. b. 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. c. 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.	Table C-29, Pages C-49-C-50: The designs of the following studies (DiDomenico, Landsman, Budny, Wilson, Landsman) are not within the scope of our review as described in the Methods section.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Appendix	Appendixes: • 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 requested changes to Grafix and GrafixPrime have been completed.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	Appendix	Appendixes: Please correct all sections where Grafix is incorrectly classified as "acellular" and revise the tables and information to correctly report that Grafix is a cellular product. • In the Appendix, Grafix is listed as acellular in the evidence tables on pages C-9, C-12, C-16. • Grafix data belongs on Page C-18, Table 6 comparing cellular	All requested changes to Grafix and GrafixPrime have been completed.

Commentator & Affiliation	Section	Comment	Response
		dermal substitutes with SOC. • One Pages C-21, Table C-12, Page C-23, Table C-13, and Page C-24, Table C-14, all information for the Annanian Grafix vs. Dermagraft RCT compares cellular products to each other. This is incorrectly reported as acellular vs cellular. This is important because it impacts other findings reported in the AHRQ. This trial should be listed beginning on Page C-26, Table C-15 under Cellular vs Cellular trials. • On Page C-45, Table C-23 comparing cellular dermal skin substitutes to SOC, Grafix is incorrectly not included. Please revise to place the Lavery 2014 trial in this section. • On Page C47, Table 27, the Annanian 2018 trial for Grafix is incorrectly listed as comparing an acellular product to a cellular product. This trial belongs on with evidence reported beginning on Page C-49, Table C-29 comparing cellular products to cellular products. • In Appendix D, Table D-7, on Page D-23 Grafix is correctly listed as a Cellular/Dermal replacement from human amniotic membrane (4 products in this category). Again, Osiris wants to point out the significant errors made in reporting Grafix as acellular throughout the AHRQ TA and requests all errors be corrected and findings revised to reflect these corrections. • On Page D-23 in Table D-7, the product description for GrafixPL PRIME does not correctly describe the product according to the product insert. Please revised as listed below for Grafix PRIME and GrafixPL PRIME: • Grafix PRIME (cryopreserved placental membrane) is a cryopreserved amnion matrix retaining the extracellular matrix, growth factors, and endogenous neonatal mesenchymal stem cells, fibroblasts and epithelial cells of the native tissue and is suitable for a wide variety of hard-to-treat acute and chronic wounds. • GrafixPL PRIME (lyopreserved placental membrane) is a lyopreserved amnion matrix retaining the extracellular matrix, growth factors, and endogenous neonatal mesenchymal stem cells, fibroblasts and epithelial cells of the native tissue and is suitable for a wide variety of hard-to-treat acute and chronic wounds.	
Public Reviewer #11: Manuel Pubillones, MD	Appendix	N/A	Thank you for your comment.

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
		(6) 21st Century Cures Act. H.R. 34, 114th Congress. 2016. https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf. Accessed February 1, 2019.	
Peer Reviewer #1	General	Generally this is a thorough review of the studies to date and a relevant attempt to direct future studies to ensure actionable data.	Thank you for your comments.
Peer Reviewer #2	General	Difficult topic. Job well done, a few minor comments and thoughts for consideration. Thanks for including me.	Thank you for your comments.
Peer Reviewer #3	General	The report is superb and an appropriate follow up to our 3 AHRQ reports on wound healing in 2014. It is an appropriate analysis of the multiple (74) skin substitutes and is well done. You make the point that there is a need for standardized protocols for advanced and often expensive wound skin substitutes. I am offering general considerations for this report	Thank you for your comments.
Peer Reviewer #4	General	I found this review to be very current and relevant to practice where many wound care consultants are recommending these products to my patients. The target audience is well defined. I found guiding question #3 to be quite broad, with 10 subclasses. For a clinician reading this report, much of this data is not relevant. I found an aspect of the "Risk of Bias" determination quite problematic. I do not see a category related to funding source in their 10 question assessment. I did find a statement in the review that every study was funded by the industry. This would be a major problem for groups evaluating this data for guideline development. Many groups would downgrade the quality of evidence based on this source information. I do not see source of study funding in Appendix table C-31 either. I feel the exclusion of funding information from the risk of bias determination is a major problem.	We appreciate your concern about the potential for bias related to funding source. Source of funding is included in a series of tables in Appendix C on "Basic study design and conduct information for studies." According to the AHRQ EPC Program Methods Guide, we do not consider funding source in evaluation of individual study risk of bias or overall study limitations. In full systematic reviews, we consider the potential impact of the funding source on publication or reporting bias when determining the overall strength of the evidence for a particular outcome. This step (grading evidence) is not a part of the Technical Brief process.

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 completed before March 2017…We are unsure whether or not the lack of publications for these five trials is due to publication bias, but independent funding of skin substitute research would reduce potential for bias and make comparisons of products more likely. The evidence gaps will be only partially addressed by currently registered ongoing trials, which are largely funded by industry. Only four of the ongoing RCTs are comparing two skin substitutes.”
Peer Reviewer #5	General	This is a very well written technical brief that evaluates and updates the previous AHRQ report on Skin Substitutes for Treating Chronic Wounds. The methods and findings are clearly described. The conclusions are supported by the findings and are highly relevant, particularly in regard to advising future studies in this area to strengthen the science as well as producing evidence that is translatable to practice.	Thank you for your comments.
Peer Reviewer #5	General	I found the major findings to be very clearly presented, with sufficient detail, and not overstated. I think the future research recommendations is particularly relevant and interesting. The authors have identified specific areas where studies can be improved in design. If adopted this could make an impact on the quality of information gained from research on skin substitutes.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	General	It is unclear how skin substitutes are defined and differentiated from wound dressings. Note that from an FDA regulatory perspective, all of the devices approved or cleared under PMA and 510(k) are also considered wound dressings. PMA approved products are considered interactive wound and burn dressings and may also include skin substitutes. However, the 510(k) cleared wound dressings are not evaluated as 'skin substitutes' and are not able to make a claim to be a skin substitute (such an evaluation would need to be made under a PMA). 510(k) cleared wound dressings are only evaluated for their ability to cover a wound and keep it moist; some of these may absorb into the wound over time. Thus there is a concern that the report overall may not be appropriately categorizing the products assessed and grouping together disparate products with different intended uses. It is possible that clinically, not much differentiation is made between how and when the different products are used. However, the difference in the cleared/approved intended uses of the products, compared to the clinical use, should be analyzed as a possible confounding factor in the methods and results.	Skin Substitutes section, p. 3. As mentioned above, please see revisions to Guiding Question 1, which now asks only for a list of potential skin substitutes commercially available in the United States. FDA regulatory information about each product has been removed. Due to the limited evidence for most skin substitute categories, we are unable to make any comparison across skin substitutes. We did however add text to Summary and Implication, Patient Inclusion: “The ongoing trials include a registry study that may provide more data on patients outside the typical RCT (Table E-1). Data collected by the U.S. Wound Registry is intended to provide comparative-effectiveness data for patients with chronic wounds and ulcers being treated with cellular and/or tissue-based products that will include skin substitutes. Registry data may be used for subanalysis of key patient- (e.g., gender, race, comorbidities) and wound-related characteristics (e.g., severity, wound duration) that may not be available in typical RCTs. This information may help direct specific product use for different wound conditions.”
Peer Reviewer #6	General	If skin substitutes are adequately defined, the report provides a useful, thorough overview of the clinical studies available on a subset of wound care products. The attempt at categorization is still somewhat confusing and unclear, in particular with respect to how a product is determined to replace the epidermis, dermis, or both. It is unclear if the different categories of products are used differently clinically. The target population, audience, and key questions are generally appropriate.	p. 15 lines 6-13, Tables 5-10; and p. 20 Guiding Question 2 Overview: We added the following text addressing the categorization: “The composition of the product determines which layers it is designed to replace.”

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	General	The report is well structured and organized. There is however lack of clarity regarding what is considered a skin substitute and how these products are distinguished from Standard of Care or Advanced Therapies; without clarity on this, the report is difficult to analyze and is of limited utility. The classification scheme proposed is a bit cumbersome, and it needs to be further clarified regarding how something is determined to replace epidermis/dermis/both. The methods were generally rigorous, but I have pointed out considerations that are missing throughout which should be added to complete the assessment. The analysis of the studies was appropriate, but limited by the variability among the studies themselves which makes it difficult to draw conclusions. The conclusions regarding how to improve studies are certainly appropriate.	The Davison-Kotler system was decided upon after a review of several published classification systems used for categorizing skin substitutes (including Kumar 2008, Ferreria 2011, and Nathoon 2014). Due to the limitations of these classification systems as described in the report, we chose the Davison-Kotler system. The KIs helped inform this decision. The report says the following about layers in the Davison-Kotler system: "Layering is either single or bilayer, with bilayer generally replacing both dermis and epidermis. Replaced region refers to whether the product is intended to replace dermis, epidermis, or both. The product's composition determines which layers it is designed to replace." We found no product that was intended to replace only the epidermis.
KI Reviewer #1	General	The authors did a very nice job reviewing a very complicated subject and making it evidence based. I will list below some ideas for improvement that the authors could consider	Thank you for your comments.
KI Reviewer #2	General	Target population and audience clearly defined. Key guiding questions clearly stated and used to organize the report. The report is clinically meaningful and offers well defined and data driven recommendations. Writing is clear and logical. Organization is well structured and meaningful.	Thank you for your comments.
KI Reviewer #2	General	The report is complex and dense, but this is directly related to the complicated nature of skin substitutes (the myriad of types and composition, etc.). Using the framework as presented in the introduction makes the work easier to navigate. The conclusions are very relevant to both policy and clinical practice, although due to the limitations in the studies we are still left with many unanswered questions.	We agree that we only addressed the set of questions proposed by AHRQ specific to this technical brief, but hope the information presented in the technical brief advances the field.
KI Reviewer #3	General	Report is well organized, comprehensive and easy to read.	Thank you for your comments.
KI Reviewer #3	General	I learned a great deal from this technology assessment. Great job!!	Thank you for your comments.
KI Reviewer #4	General	The report has a well-defined target population and audience. The key questions are appropriate and stated well.	Thank you for your comments.
KI Reviewer #4	General	The organization is suitable and useful. While the conclusions are known, the thorough demonstration is very helpful and indicates the scope of the research gaps. Those conclusions are relevant to policy and indicate a major gap for clinical decision-making.	Thank you for your comments.
Public Reviewer #2: Zack Bridges ACell Inc.	General	No comment	Thank you for reviewing the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3: Marc Goldberg BONAPEDA Enterprises LLC	General	General Comments: A key problem in the treatment of plantar diabetic foot ulcers is that there is no broadly accepted "Gold Standard" standard for offloading. (see commentary: https://lermagazine.com/editor_memo/the-dfu-dilemma-is-the-total-contact-cast-a-true-gold-standard). If the issue of offloading was addressed, healing rates for plantar DFUs may well increase independent of the use of advanced wound care therapies.	We thank you for your comments but addressing the standardization of offloading is beyond the scope of the report.
Public Reviewer #5: Dr. Arti Masturzo, M.D., M.B.A. Chief Medical Officer, Solsys Medical, LLC	General	General Comments: On Page 3 of the Background Section, AHRQ made the statement: “Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient’s skin [emphasis added].” Solsys Medical could not agree more with this statement by AHRQ and it forms the basis of why Solsys Medical brought TheraSkin® to market in 2010. In 2010, Apligraf® and Dermagraft®, both bioengineered attempts to approximate human skin, but NOT human skin, were the two dominate products in the U.S. wound care market and had secured the broadest insurance coverage of any skin substitute in the market. This broad insurance coverage was due in large part as a result of both products’ need to conduct large n RCTs to show safety and efficacy to secure FDA PMA approval before these products (that are NOT human skin) could be marketed for specific indications (diabetic foot ulcers and venous leg ulcers - consistent with the PMA studies). Again, consistent with AHRQ statement above, Solsys Medical hypothesized in 2010 that if manufactured approximations of human skin (Apligraf® and Dermagraft®), but NOT human skin, heals at X%, then a state-of-the-art cryopreserved human skin allograft - TheraSkin® - that contains ALL the relevant characteristics of human skin needed to heal human skin - growth factors, cytokines, collagen and living cells - would heal at X+%. Our clinical data has shown our hypothesis to have been correct and while the head-to-head RCTs that we have done, and another done independently, are smaller n RCTs, the results of these RCTs (for TheraSkin®, Apligraf® and Dermagraft®) are consistent with the large n pivotal studies for the respective products. In a cluttered market with over 100 products comprised of various bioengineered constructs, acellular xenografts, acellular dermal only allografts, acellular and cellular amniotic allografts, one skin substitute stands apart from the rest to be the greatest possible similarity with the patient’s skin - TheraSkin®.	Background, page 3: This statement was referenced from the Ferreira et al. 2011 article “Skin substitutes: current concepts and a new classification system” and is used as general background material as to what characteristics skin substitutes should contain. Thank you for your comments on Theraskin.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	General	General Comments: The Musculoskeletal Transplant Foundation March 8, 2019 Comments Agency for Healthcare Research and Quality Technology Assessment Program "Skin Substitutes for Treating Chronic Wounds" Draft Technical Brief Project ID 039-015-334 January 28, 2019 On behalf of the Musculoskeletal Transplant Foundation (MTF), thank you for the opportunity to comment on draft technical brief, "Skin Substitutes for Treating Chronic Wounds," Project ID 039-015-334 (further referred to herein as "the brief"). If you are not familiar with MTF, we are a non-profit organization, the world's largest tissue bank, and for three decades have served as our nation's leading tissue bank dedicated to processing and developing high quality and cost-effective allografts for clinical use -- providing over ten million allografts to facilities and physicians for transplantation. We were established by surgeons and continue to be directed by surgeons including a medical board of trustees and a donation board of trustees with donor families also serving as members. The work we do is both life-changing and life-saving. We honor the donor gift of donation by dedicating ourselves to research, actively advancing the science of allograft tissue transplantation, so we can continue to help others heal. MTF's breakthrough advancements, many of which have set industry benchmarks, are represented in a wide range of specialties including orthopedics, plastic and reconstruction, and wound care. As our wound care division offers two tissues forms, AlloPatch® and AmnioBand® that have been included in this technical brief, the purpose of our comments is three-fold: 1. To provide the agency with more accurate and current information regarding our tissues referenced herein; 2. To correct any misrepresentation or understanding of our tissue forms and the clinical and scientific data supporting them for treating chronic wounds; and 3. In doing so, present a better manuscript for public dissemination.	We reached out to the primary author of Paggiaro et al. 2018 after identifying the reporting error in the publication. We note in Table C-1: "We replicated the meta-analyses, finding the same results for risk ratio/relative risk and mean difference as stated in the paper. Both outcomes are statistically significant and clinically important. In the text, the authors reference the p-values for the tests of heterogeneity, which have no bearing on the statistical significance of the difference between groups. We contacted the authors, who are now submitting an erratum to the journal." The final report includes DiDomenico 2018 study which replaces the DiDomenico 2016 study included in the draft report.

Commentator & Affiliation	Section	Comment	Response
		GENERAL COMMENTS Although we have included specific comments in detail for each section and subsection of the brief with page reference, the following comments are general observations we ask the agency to consider. • We vehemently believe the Paggiaro et al 2018 meta-analysis referenced throughout the brief as part of the "Systematic Review" be removed as a reference document. The study is statistically flawed and should not be used as a reference in this (or any other document). If not, by continuing to use it as a reference it will question the validity of this brief, casting a shadow on the agency's credibility. Furthermore, the journal's editorial staff has noted the errors in the paper as referenced in Appendix C, Clinical Evidence, Table C-1, Characteristics of Systematic Reviews, column "Author's Conclusion" (i.e. "The authors drew an erroneous conclusion based on the data they provide…"). Until the erratum to the journal has been published all references to the Paggiaro et al. 2018 meta-analysis and its findings should be stricken from this brief. Additionally, the Paggiaro study did not include the most recent AmnioBand peer-reviewed, PubMed-indexed, 80-patient, multicenter, prospective Randomized Control Trial (DiDomenico et al 2018) and therefore is not update-to-date.	
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	General	• We believe this paper should include the aforementioned most recent AmnioBand peer-reviewed, PubMed-indexed, 80-patient, multicenter, prospective Randomized Control Trial, DiDomenico et al 2018 (Epub 2018, July 17) which is missing from this brief. This study, one of the strongest studies to date regarding the use an amnion & chorion membrane-based tissue form for the treatment of diabetic foot ulcers, for some unknown reason was not included in this brief. We request that it be included as part of this review.	The final report includes DiDomenico 2018 study which replaces the DiDomenico 2016 study included in the draft report.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	General	• Regarding the use of a 15% data point for a number of metrics, including comorbidities and wound sizes, this seems to be an arbitrary number that is not based on any standard that appears in literature. We question the use of the use of this 15% marker and request that it be removed as a criterion for use as part an assessment tool.	We chose 15 percent as a minimum beyond which the loss of patients would jeopardize the randomization process that distributes patients and patient characteristics equally between treatment groups.

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Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	General	• 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.	All reference to “human cadaver” have been replaced with “donated human dermis.”
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	General	• We do not believe the Davison-Kotler classification system accurately classifies placental tissue (i.e. “human amniotic membranes”) by including them under the category of acellular dermal substitutes. Because of the inherent properties of placental tissue along with non-immunogenic properties, the body readily adsorbing and incorporating it, it does not need to be decellularized - a process that most dermal allografts undergo (e.g. Acellular Dermal Matrices or ADMs). At a minimum, in describing “human amniotic membrane” used as skin substitutes, we believe a separate category is required i.e. “placental tissue” with a subcategory to include “amnion membrane only” and “amnion and chorion membrane,” which more accurately describes these tissues based on their composition.	We have categorized and separated human placental membranes from human dermis as shown in Table 5 and Table 6. The human placental membranes listed in Table 6 were considered in the acellular category because they did not claim to have viable cells involved in wound treatment. In contrast, four human placental membrane products claiming to have viable cells were categorized as cellular dermal replacements from human placental membranes and listed in Table 11.
Public Reviewer #6: Daniel G. Papadopoulos, MPA Musculoskeletal Transplant Foundation	General	• Regarding adverse events (AEs), we caution the authors of the brief with the wording used therein to describe AEs, as the way it is now written gives the impression that infections (AEs) were related to the grafts. We ask that statements regarding AEs be carefully worded and not be generalized to give the impression that it includes all studies and every tissue form. Throughout this assessment, statements are being made that can leave the reader with the impression that AEs are attributed to the graft placement when in fact many, if not all, were not found to be graft-related. Furthermore, statements are being made that give the impression that AEs are an indicator of graft safety – this may be true but only for those AEs found to be graft-related. In our studies, (Zelen et al. 2018, AlloPatch RCT and DiDomenico et al. 2018, AmnioBand RCT), AEs were reported and, most importantly, none were graft-related.	We noted all serious adverse events in the evidence tables in Appendix C and noted whether the events were product-related if reported.
Public Reviewer #6: Daniel G. Papadopoulos, MPA	General	• In referring to our acellular dermal matrix allograft, AlloPatch®, we request that only the registered trademarked name be used throughout the brief (i.e. AlloPatch®) and any reference to “AlloPatch HD Acellular Dermal Matrix” and “AlloPatch HD” be deleted and replaced with only “AlloPatch®. Furthermore, regarding any reference to the product description, we ask that it read “AlloPatch is an aseptically processed human reticular dermal	We have made the requested changes to AlloPatch and AmnioBand as noted above.

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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 covering."	
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	General	General Comments: Please correct this report to accurately reflect that Grafix products are cellular. if you need additional documentation to support this classification of Grafix, please contact me at: lsavant@osiris.com or 610-248-4459. Thank you	All Grafix- and GrafixPrime-related revisions have been completed as requested.
Public Reviewer #7: Louis Savant Osiris Therapeutics, Inc.	General	General Comments: Osiris appreciates the time, expert review, and value of this AHRQ Technology Assessment. We agree with most of the critical review and findings in the TA. However, there are significant inconsistencies and inaccuracies with how our product GRAFIX is classified throughout the TA. Osiris appreciates the opportunity to have those inaccuracies corrected for the final AHRQ publication, along with other recommendations we believe need further review and consideration. Please correct the AHRQ to accurately report that Grafix and GrafixPL Prime are cellular products; and correct all associated data in the body, tables and graphs, including findings that may be skewed due to incorrectly including Grafix evidence with acellular products. If you need information about Grafix and GrafixPL Prime please contact me at: LSavant@osiris.com or 610-248-4459. 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.	All Grafix- and GrafixPrime-related revisions have been completed as requested.
Public Reviewer #8 Anonymous	General	General Comments: excellent review of all available products, with I believe, realistic comparative results again confirming that products in a particular class are very comparable.	Thank you for your review of the report.

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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 is a nonprofit multidisciplinary trade association of physician specialty societies, clinical and patient associations whose mission is to promote evidence-based quality care and access to products and services for people with chronic wounds (diabetic foot ulcers, venous stasis ulcers, pressure ulcers and arterial ulcers) through effective advocacy and educational outreach in the regulatory, legislative, and public arenas. We appreciate the opportunity to comment on the AHRQ Draft Technology Assessment (TA) Report on "Skin Substitutes for Treating Chronic Wounds". These comments were written with the advice of Alliance clinical specialty societies and organizations who not only possess expert knowledge in treating complex chronic wounds, but also in wound care research. A list of our members can be found on our website. As stated both in our general and specific comments, we have severe concerns regarding this AHRQ TA. Many of these concerns were expressed in our 2012 comments; however, many of these same issues are again in the 2019 version. Therefore, we would appreciate the opportunity to again meet with AHRQ staff and ECRI authors to address our concerns and recommendations. General: We would like to commend AHRQ for this very detailed analysis since it is very difficult to perform. However, the Alliance has some significant concerns with portions of the Technology Assessment (TA) which impact its findings and have provided specific comments on the areas in which we disagree with the assessment as well as areas in which we have identified inconsistencies. *Short Turnaround o Respond to the AHRQ TA* As a general matter, while we appreciate the opportunity to offer our comments, we are very disappointed in the short amount of time that the AHRQ allowed for a deadline to respond to this very dense and complex document that is so critical to wound care	Thank you for your review of the report. Please see our comments above regarding the inconsistencies noted in the report. We are unable to comment on the turnaround time allowed to respond to the report. I hope you find the link to the 2012 report in working order using this link: 2012 report Skin Substitutes for Treating Chronic Wounds which we have also provided to other commenters interested in AHRQ's previous findings.

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		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 and offer valuable and meaningful comments to these assessments. *Assumption that Reader is Familiar with 2012 AHRQ TA* In addition, while the Alliance commented on the draft AHRQ 2012 TA on "Skin Substitutes for Treating Chronic Wounds (Dec 2012) and met with staff to explain our comments, we have concerns that the authors assume that the reader is familiar with the concepts and issues addressed in the Dec 2012 document since they referenced it in the 2019 TA. When we attempted to access it from the link on the AHRQ website, we discovered that the link was broken. Thus, we recommend that AHRQ fix this in the future.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	General	*Use the Clinically Accurate Term "Cellular and/or Tissue Based Products for Skin Wounds (CTPs)" Instead of "Skin Substitutes"* Moreover, the Alliance would like to request that AHRQ change the title and terminology utilized throughout this TA. The AHRQ refers to the products being assessed as "skin substitutes". The term "skin substitutes" is clinically inaccurate and does not describe the technology. The Alliance recommends that "skin substitutes" be replaced with a more inclusive descriptor "Cellular and/or Tissue Based Products for Skin Wounds (CTPs)". CTPs accurately describes all technologies in this sector, is broad and is inclusive of both current and future technology. This term was created and adopted by an Alliance workgroup of scientists, clinical associations and business entities in 2012 and used the following criteria to determine the new term of CTPs: • be based on science • be inclusive of all products in marketplace today with eye towards what is in the "pipeline" • be neutral in regards to FDA--- nothing that would be offensive and not allow manufacturers to get their products approved in the future if needed • ensure that all products are eligible for Medicare coverage as drugs and biologicals consistent with their USP monographs • easily understood by clinicians	As noted in the report: For this report, we have not created a definition for a skin substitute product. Instead, we 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. The FDA does not use the term skin substitutes in any of their product descriptions, but instead groups these products according to their regulatory pathways. CMS still uses the term skin substitutes as noted in their 2018 and 2019 listing of Q codes for individual products. The term "skin substitutes" is still widely used in the clinical literature. We have added a paragraph describing the ASTM International classification system for CTPs.

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		• easily linked to the existing CPT codes for the application of the products	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	General	The Alliance believes that the term "skin substitute" is misleading and inaccurate to describe the products that are the subject of this assessment for the following reasons: 1. The FDA does not allow these products to be called "skin substitutes'' because they do not actually substitute for skin. 2. Both CMS and AHRQ have concerns with the terms and did the following: ▪ AHRQ in its 2012 final technology assessment on skin substitutes inferred that these products were not "skin substitutes" since *"A true "skin substitute" would act like an autologous skin graft in adhering to the wound bed while providing the physiological and mechanical functions of normal skin.* ▪ CMS abandoned the term in the code descriptors for these products in 2010 when the Agency agreed that these products are not skin substitutes and instead issued Q codes for each individual product by its brand name. 3. ASTM, the international standard setting organizations thought so highly of this new terminology that in February 2016 it published a definitive standard (F3163-16) devoted to the nomenclature for these products titled "Standard Guide for Classification of Cellular and/or Tissue-Based Products for Skin Wounds." The workgroup that created this standard included FDA (who agreed with the term), scientists, engineers and clinicians who worked collaboratively to ensure that the standard is inclusive of all the products in this space. It is now not only used by them but by those who do wound care research. We are using parts of this standard throughout our comments as noted below. 4. Payers in their LCDs are using this term. Of the four Medicare Administrative Contractors who have a	We found no reference to the ASTM standard guide or any recommendations to use the term CTP instead of skin substitutes in our review of the published literature on skin substitutes. In addition, a recent PubMed search did not identify any peer-reviewed articles describing the ASTM standard guide and use of the term CTP. CMS still uses the term skin substitutes as noted in their 2018 and 2019 listing of Q codes for individual products. The KIs and external reviewers did not mention this classification system nor indicate it should be used in the report. We have added a paragraph describing the ASTM International classification system. We are not promoting or defining a definition or preferred classification system for skin substitutes. Our task was to review the clinical literature on classification systems and this has been accomplished.

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		LCD for these products, three of them either use the term CTPs in the body and/or title of the coverage policy. For instance, CGS titles its LCD- "Wound Application of Cellular and/or Tissue Based Products (CTPs), Lower Extremities." 5. This term has been adopted by the wound care community and is currently used by physicians when speaking at national wound care conferences and in clinical articles in scientific journals. As such, the Alliance recommends that AHRQ not utilize the term "skin substitute" in its TA and instead use the more clinically accurate term "cellular and/or tissue based products for skin wounds (CTPs)". As a result of this request, the Alliance recommends making the following changes: **1.** Delete the paragraph below in the draft TA describing skin substitutes: *Skin Substitutes Skin substitutes are used as an adjunct to established chronic wound care methods to increase the likelihood of complete healing.20 According to Ferreira et al.,21. "skin substitutes are a heterogeneous group of biological and/or synthetic elements that enable the temporary or permanent occlusion of wounds. Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient's skin." Skin substitutes should have functional and structural characteristics that closely match autologous skin. The ideal skin substitute would be durable, completely autologous, and endothelialized and contain adnexal structures and adult stem cells, but such a construct does not yet exist.20 Commercially manufactured skin substitutes should protect the integument from water loss and infection; provide a stable, biodegradable scaffold to promote the synthesis of new dermal tissue; allow host or other cells to proliferate within the	

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		scaffold that will act as functional dermal cells rather than scar tissue; and resist tearing forces while being easy to handle.22-24Growth factors and other components of the skin substitute may promote cell proliferation, reduce wound degradation caused by matrix metalloproteinases within the wound, and promote wound vascularization. These properties may enhance the wound healing potential of skin substitutes beyond that of wound dressings. **2.** Replace it by using the title "Cellular and/or Tissue Based Products for Skin Wounds and use the definition from the ASTM Standard. The updated definition of CTP should be taken from the ASTM International Standard Guide: F3163-16 Classification of Cellular and/or Tissue-Based Products (CTPs) for Skin Wounds. ASTM International, one of the largest voluntary standards developing organizations in the world, provides a forum for the development and publication of international voluntary consensus standards for materials, products, systems and services. They develop technical documents that are the guidelines for manufacturing, management, procurement, codes and regulations for dozens of industry sectors. The ASTM CTP standard, published by ASTM in January 2016 (from which the CTP definition is taken) is the product of four years of negotiations among a multidisciplinary group of stakeholders, including representatives from the United States Food and Drug Administration (FDA), clinical medicine, scientific research and industry. This standard was voted on and approved by the ASTM Committee F04 on Medical and Surgical Materials and Devices. This process, which reflects the ASTM values of participation, transparency and agreement among members worldwide, ultimately resulted in an international standard that has been designed to accommodate the rapid evolution of innovative wound care technologies. We recommend that it be replaced by this definition from the ASTM standard:	

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		CTPs are defined primarily by their composition and comprise of cells and/or the extracellular components of tissue. CTPs may contain cells (viable or nonviable), tissues, proteins, and other materials for which there is a rationale for benefit beyond that achievable with conventional wound coverings. CTPs may additionally include synthetic components.[1] Additionally, another way to define a CTP is as a material used to cover wounds and burns where areas of skin are missing. It is a heterogeneous group of products that can be composed of synthetic, xenogeneic, autologous, allogeneic or composite matrices. Such matrices can be cellular, devitalized or acellular. All current CTPs except one serve as temporary grafts, which cover a wound and support the natural wound healing process of the host by providing structural matrix and growth factors to the cells in the wound area required for their cellular activities to facilitate healing. The fate of these grafts is to be resorbed/remodeled overtime. The exception is the autologous skin grafts, which permanently replace lost skin.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	General	*Concerns with Specific Problematic Meta-Analysis, Terminology in TA and Transparency* With respect to The Paggiaro et al. meta-analysis utilized in this TA, the Alliance respectfully requests that this analysis be withdrawn from the TA as it is heavily flawed with significant errors. Numerous system reviewers have pointed out the egregious mistakes in this paper and currently Dr. Marissa Carter is working with the authors and journal to ensure it is corrected.	We reached out to the authors after identifying the reporting error in the publication. We note in Table C-1: "We replicated the meta-analyses, finding the same results for risk ratio/relative risk and mean difference as stated in the paper. Both outcomes are statistically significant and clinically important. In the text, the authors reference the p-values for the tests of heterogeneity, which have no bearing on the statistical significance of the difference between groups. We contacted the authors, who are now submitting an erratum to the journal."
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	General	There are a few areas in which the nature of the topic being discussed in the TA is a bit sensitive and the Alliance would like to request that AHRQ be more respectful to those that have donated tissue. Specifically, – There are a few areas in this document in which AHRQ refers to tissue being "harvested". "Harvested" is an insensitive term that should be removed from all literature which describes any HCT/P as these tissues are graciously consented donated human gifts. In the same vein, in deference to donor and donor	All references to "harvested" and "human cadaver" have been changed.

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		families, we ask that any reference to “human cadaver” dermis or just the term “cadaver” be replaced with the term “donated human dermis” (or a variation thereof). Using the term “cadaver” dehumanizes and disrespects the deceased and their family who have donated this gift of life. As such the Alliance requests that these terms be modified in the final version of the TA.	
Public Reviewer # 10: Marcia Nusgart Alliance of Wound Care Stakeholders	General	Finally, AHRQ states that they consulted with 6 KIs as well as some peer reviewers who provided input into this TA but did not mention the identity of these informants and reviewers. AHRQ merely stated that the names of those individuals would be published only in the final document. The Alliance is disappointed that AHRQ did not identify the names of the people who influenced this report. As the Alliance has often publicly stated, there needs to be more transparency when reports such as these are issued. In fact under the 21st Century Cures Act, it is required. Based on the language in the 21st Century Cures Act the names and affiliations of all key informants and reviewers utilized by AHRQ should have been included not only in AHRQ’s final 2019 Technology Assessment document but also in this Draft given that it is important for stakeholders to better understand which key informers helped shape all aspects of the draft and final reports. [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	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 #11: Manuel Pubillones, MD Noridian Helathcare Services	General	Guiding Questions: Reviewed the complete draft document. Next Steps: None from me. General Comments: Some "potential errors" have been described above.	Thank you for your comments.
Public Reviewer #12: Joseph Rolley Integra LifeSceinces Corporation	General	Background: Integra LifeSciences Corporation (Integra LifeSciences) would like to provide the following comments on the draft technical brief "Skin Substitutes for Treating Chronic Wounds". Integra LifeSciences is a world leader in developing and marketing high quality surgical instruments, as well as innovative devices and products for use in neurosurgery, reconstructive surgery, general surgery, and soft tissue repair. Headquartered in Plainsboro, New Jersey, Integra LifeSciences	Thank you for your review of the report.

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		sells many skin substitute products which are widely used in the physician office, hospital outpatient, and hospital inpatient settings.	
Public Reviewer #14: Kara Gainer American Physical therapy Association	General	General Comments: The American Physical Therapy Association (APTA) represents more than 100,000 member physical therapists, physical therapist assistants, and students of physical therapy. The mission of APTA is to build a community to advance the physical therapy profession to improve the health of society. Physical therapists play a unique role in society in prevention, wellness, fitness, health promotion, and management of disease and disability by serving as a dynamic bridge between health and health services delivery for individuals across the age span. While physical therapists are experts in rehabilitation and habilitation, they also have the expertise and the opportunity to help individuals improve overall health and prevent the need for avoidable health care services. Physical therapists' roles may include education, direct intervention, research, advocacy, and collaborative consultation. These roles are essential to the profession's vision of transforming society by optimizing movement to improve the human experience. APTA is a member of the Alliance of Wound Care Stakeholders (Alliance). We support the Alliance's comments on this Technology Assessment (TA) report and reiterate the Alliance's recommendation that AHRQ change the title and terminology utilized throughout the TA. Within the report, AHRQ refers to the products being assessed as "skin substitutes." The term "skin substitutes" is clinically inaccurate and does not accurately describe the technology. APTA recommends that "skin substitutes" be replaced with a more inclusive descriptor "Cellular and/or Tissue Based Products for Skin wounds (CTPs)." CTPs accurately describes all technologies in this sector, is broad and is inclusive of both current and future technology. APTA believes that the term "skin substitute" is misleading and inaccurate to describe the products that are the subject of this assessment. We also want to take this opportunity to highlight the significant role physical therapists play in the area of wound management and the importance of including physical therapists on a multidisciplinary wound management team. The Academy of Clinical Electrophysiology & Wound Management's Wound Management Special Interest Group developed a white paper, "The Role of Physical Therapists in Wound Management." The	Thank you for your comments. As noted in the report: "For this report, we have not created a definition for a skin substitute product. Instead, we 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."

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		white paper explores the specific interventions physical therapists use for wounds associated with pressure injuries, diabetes, and venous and arterial vascular insufficiencies. It also discusses the education of physical therapists. Physical therapists' entry-level education "uniquely prepares physical therapists to begin very early practice in a more specialized area of patient care – wound management. In fact, the physical therapist's in-depth knowledge and skill in movement science, body system screening, anatomy, and pathophysiology provide the perfect foundation for practitioner involvement in the early detection, direct wound management, and prevention of integumentary system compromise. Principles of range of motion, stretching and strengthening, gait training, positioning, and soft tissue mobilization common in all entry-level programs are vital interventions in a comprehensive plan of care focused on wound closure and return to function. Additionally, appropriate use of active biophysical agents unique to physical therapist training and education can be equally important. Modern technologies allow for easy and effective application of pulsed lavage, sound, electrical, and mechanical energies for wound cleansing, debridement, edema reduction and control, and tissue stimulation." Many physical therapists also achieve board certified specialization in the area of wound management as a mechanism of documenting their high level of training. (See: https://acewm.org/wp-content/uploads/2017/01/The-Role-of-Physical-Therapists-in-Wound-Management.pdf). Should you have any questions or would like to learn more about the role of physical therapists in wound management, please do not hesitate to contact APTA and/or APTA's Academy of Clinical Electrophysiology and Wound Management (https://acewm.org/). We thank you for the opportunity to submit comments and look forward to working with AHRQ as the agency finalizes the TA report.	
Public Reviewer #17: Arti Balar Masturzo, MD Practicing physician in Ohio	General	General Comments: I submitted my comments as the Chief Medical Officer of Solsys Medical, but am now submitting a private comment with my corporate hat "off". Chronic wound care is an unrealized epidemic and I worry about the future of the field because so much of it is led by manufacturer science; some of it is propaganda and some of it is valuable and innovative. When I think of CTPs, I realize that EVERY product on the market is one of three things: cells, growth factors/cytokines, or an ECM. There is variability on what age of human the cells came from (placental,	We agree with your comments. Future evidence reports may need to include real-world data. Cost was not a consideration in this report.

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		neonatal, adult), concentration and types of growth factors/cytokines, and the type of ECM (human minimally manipulated, radiated human, porcine, fish, horse, bovine, ovine, etc... the list goes on and on). In an RCT where the SOC is a hydrogel, each and every one of these products, whether they have one or two of these components will see some benefit!! The three components described above are the three major components in regular human skin. Real world evidence would be hugely beneficial to understand how they work in REAL patients; not in RCTs where the wounds are small, have no deep structures, have perfectly controlled DMII and normal arterial flow. I would urge AHRQ to consider well designed real-world studies. Also, the cost of care (frequency of applications) is an important element that gets missed analysis. I can tell you that ALL of these products will work to a certain extent but how many applications does it take? The skin substitute manufacturers find the AHRQ report threatening to some extent because they fear it will have consequences on reimbursement; I'm concerned we will never really get to the definition of a skin substitute this way. Most plastic surgeons would say that a skin substitute should vascularize and incorporate into the host; everything else is a covering; this doesn't mean that coverings don't WORK... it's just that their mechanism of action is different. Again, I hope that AHRQ will consider RWE to help elucidate when and where these technologies are most appropriately used.	
Public Reviewer #18: William H. Tettelbach, MD, FACP, FIDSA, FUHM, CWS MiMedx Group, Inc.	General	We appreciate the opportunity to review and comment on the AHRQ Technology Assessment Brief: Skin Substitutes for Treating Chronic Wounds. MiMedx is the leading biopharmaceutical company in the development and marketing of regenerative and therapeutic biologics, and in the utilization of human placental tissue allografts. We are in overall support of this technology assessment brief, and appreciate the time, dedication and expertise of the reviewers: • Our strongest and primary concern is pertaining to a perceived error in the data collection (please see our comments under “Methods”). • We have additional comments that we hope are helpful regarding the guiding questions of study design. Thank you in turn for your consideration of our input.	Thank you for your review of the report.

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		Thank you again for the opportunity for public review and comment. We truly appreciate the expertise and efforts of the reviewers, and the resultant draft. Our hope is that you find our comments to be thoughtful and to provide insight that will assist in the finalization of this valuable Tech Assessment. William H Tettelbach, MD, FACP, FIDSA, FUHM, CWS Associate Chief Medical Officer--MiMedx Group, Inc. Medical Director of Wound Care & Infection Prevention--Landmark Hospital, Salt Lake City, UT Adjunct Assistant Professor, Duke University School of Medicine btettelbach@mimedx.com whtettelbach@landmarkhospitals.com 1-470-392-5115	
Public Reviewer #19: American Podiatric Medical Association	General	General Comments: On behalf of the members of the American Podiatric Medical Association (APMA), the national organization representing the vast majority of the estimated 15,000 podiatrists in the country, we appreciate the opportunity to review "Skin Substitutes for Treating Chronic Wounds."	Thank you for reviewing the report.
Public Reviewer #20: Sergio Finkielsztein Marine Polymer Technologies, Inc.	General	To Whom It May Concern: Marine Polymer Technologies, Inc. ("Marine Polymer") hereby submits the following comment in response to the Agency for Healthcare Research and Quality's ("AH.RQ") draft Technology Assessment entitled, "Skin Substitutes for Treating Chronic Wounds" (Project ID: 039-015-334). We respectfully request that AHRQ incorporate two studies into their Final Technology Assessment that were excluded from the Draft Teclmology Assessment, as they relate to Talymed®, a U.S. Food and Drug Administration ("FDA") approved novel poly-N- acetyl glucosmine (pGlcNAc) scaffold wound matrix. These studies include: (1) Hankin et al., "Clinical and Cost Efficacy of Advanced Wound Care Matrices for Venous Ulcers" (2012); and (2) Kelechi ef' al., "A randomized, investigator-blinded, controlled pilot study to evaluate the	Thank you for your summary of the two studies of Talymed™. The Hankin 2012 review was “not a study of interest” since the review had no data to extract (e.g., no meta-analysis). Hankin was thus excluded and is listed in Appendix B. The Kelechi 2011 study was included in the 2012 report and did not meet publication date inclusion criteria for the current report (see Methods).

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		safety and efficacy of a poly-N-acetyl glucosamine-derived membrane material in patients with venous leg ulcers"(2011). We strongly support AHRQ's goal to evaluate the available studies and evidence regarding skin substitutes for treating chronir wounds. However, upon review of the Draft Technology Assessment, we are concerned that the agency's draft report is not comprehensive because it fails to consider two key studies. To support this effort, we provide below a brief summary of two (2) key studies that were not included in AHRQ's Draft Technology Assessment, but provide vital clinical evidence for key treatment of chronic wounds. I. Background on TALYMED™ TALYMED™ is a sterile wound matrix comprised of shortened fibers of poly-N-acetyl glucosamine, isolated from microalgae. FDA cleared TALYMED™ for marketing as a medical device under the 510(k) process in July 2010. The FDA determined that TALYMED™ is indicated for the management of wounds, including the following: • Diabetic ulcers • Venous ulcers • Pressure wounds • Ulcers caused by mixed vascular etiologies • Full thickness and partial thickness wounds • Second degree burns • Surgical wounds-donor sites/grafts, post-Mohs surgery, post laser surgery, and other bleeding surface wounds • Abrasions and lacerations	

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		• Traumatic wounds healing by secondary intention • Chronic vascular ulcers • Dehisced surgical wounds TALYMED™ is packaged in a convenient blister pack that can be stored at room temperature for up to 3 years. It is available in three sizes (3 X 3 cm, 5 X 5 cm and 10 X 10 cm), and provides easy-to-use, convenient wound care, as there are no pre-mixing or reagents required, no special storage conditions, and fewer dressing changes compared to conventional wound care dressings. TALYMED™ is non-immunogenic and there are no known contraindications to treatment with the prod uct. II. AHRQ's Draft Technology Assessment AHRQ's Draft Technology Assessment entitled, '4Skin Substitutes for Treating Chronic Wounds" describes skin substitute products commercially available in the United States used to treat chronic wounds, examines systems used to classify skin substitutes, identifies and assesses randomized controlled trials ("RCTs"), and suggests best practices for future studi es. As part of AHRQ's review, the agency identified 17 RCTs and 3 systematic reviews analyzing commercially available skin substitutes to treat chronic wounds. However, AHRQ's assessment failed to review two (2) relevant studies that meet the criteria set forth in the draft assessment, including a 2012 review of published articles entitled, "Clinical and Cost Efficacy of Advanced Wound Care Matrices for Venous Ulcers"; and a 2011 RCT study entitled, "A randomized, investigator-blinded, controlled pilot study to evaluate the safety and efficacy of a poly-N-acety l glucosamine-derived membrane material in patients with venous leg ulcers." First, AHRQ failed to consider a 2012 review of published articles that identified RCTs evaluating complete wound closure rates for up to 24 weeks in patients with venous leg ulcers ("VLUs") treated with targeted advanced wound care matrices ("AW CMs") (Apligraf, Oasis, or Talymed) plus compression therapy compared with compression therapy alone.1 According to	

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		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 two key studies that were excluded from the initial draft report. For the reasons set forth above, we respectfully request that AHRQ review and evaluate these two studies as part of its Final	

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		Technology Assessment for "Skin Substitutes for Treating Chronic Wounds." Thank you for your consideration of this comment. Attachments: 1 See Hankin, C, et al. Clinical and Cost Efficacy of Advanced Wound Care Matrices for Venous Ulcers. J. Man. Care Pharmacy, 375-384, Vol. 18, No. 5, June 20 12. 2 Kelechi TJ, Mueller M, Hankin CS, et al. A randomized, investigator-blinded, controlled pi lot study to evaluate the safety and efficacy of a poly-N-acctyl glucosamine-derived membrane material in patients with venous leg ulcers. J Am Acad Dermatol., e209-e2 I 5, May 20 I l (PMID:216205 15).	
Public Reviewer #20: Sergio Finkielsztein Marine Polymer Technologies, Inc.	General	Second, AHRQ specifically excluded a June 2012 study by Kelechi et al. entitled, "A randomized, investigator-blinded , controlled pilot study to evaluate the safety and efficacy of a poly-N-acetyl glucosamine-derived membrane material in patients with venous leg ulcers."2 AHRQ excluded this study because it was included in the agency's 2013 Technology Assessment on Skin Substitutes for Treating Chroni9 Wounds (published December 18, 2012). The Kelechi study is a randomized, investigator-blinded, parallel-group, controlled study, where eligible patients with venous leg ulcers were randomized to treatment with standard care (i.e., compression therapy) plus TALYMED™ (applied only once, every other week, or every 3 weeks) or to standard care alone. At 20 weeks, the proportion of patients with completely healed venous leg ulcers was 45.0% for groups receiving standard care plus TALYMED™ only once, 86.4% for groups receiving standard care plus TALYMED™ every other week, and 65.0% for groups receiving standard care plus TALYMEDTM every 3 weeks, versus only 45.0% for those receiving standard care alone. The study results concluded that TALYMED™ is well-tolerated, safe and effective for the treatment of ve:nous leg ulcers.3 In the 2013 Final Technology Assessment Report for "Skin Substitutes for Treating Chronic Wound s," AHRQ consistently references this Kelechi study. Indeed, the Final Report explains that in the study by Kelechi, "Talymed plus standard of care was	The Kelechi 2011 study was included in the 2012 report and did not meet publication date inclusion criteria for the current report (see Methods). The 2019 report does not invalidate any assessments published in the 2012 report. The 2012 report “Skin Substitutes for Treating Chronic Wounds” is currently available in PubMed (PubMed PMID:25356454).

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		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 Although AHRQ previously assessed this study in the 20 13 Final Technology Assessment, it is still relevant and important for purposes of the 2019 Draft Technology Report for skin substitutes for treating chronic wound s. Ultimately, these Technology Assessments are utilized by the Centers for Medicare and Medicaid Services ("CMS") to inform its national coverage decisions for the Medicare program, as well as provide information to Medicare carriers. To therefore exclude from review and analysis an important study because it was previously reviewed by AHRQ means that CMS has an incomplete view of the relevant studies. Furthermore, this was the only study excluded in the 2019 Draft Technology Assessment because it was previously included in the 2013 Final Technology Assessment. We therefore respectfully request that AHRQ incorporate this study and correspond ing analysis into the Final Technology Assessment.	