Research Review Disposition of Comments Report

June 27, 2019

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

Supplemental Evidence and Data for Systematic Reviews (SEADS)

Research Review Citation: Snyder DL, Sullivan N, Margolis DJ, Schoelles K. Skin substitutes for treating chronic wounds. Systematic Review No. #. *Technology Assessment Program Project ID:039-015-334.* (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. April 2019. Available at: *http://www.ahrq.gov/research/findings/ta/index.html*.

Comments to Research Review

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

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
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	As follow up in support of our March 5, 2019 submission of comments to the AHRQ DRAFT Technology Assessment on Skin Substitutes for Treating Chronic Wounds, Solsys Medical would like to submit Supplemental Evidence and Data for Systematic Reviews (SEADS) to ensure that AHRQ has full access to relevant research, whether or not it is published, containing detailed study-specific information as it relates to TheraSkin. **All studies contained within the study grids, herein, constitute Phase II and above clinical trials and an index outlining the relevant information.** Recall that 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 extra-cellular matrix (ECM) that vascularizes. 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 repair skin 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. We thank you for accepting this supplemental information and hope that AHRQ will find our initial comments and the attached SEADS beneficial in finalizing the 2019 Technology Assessment on Skin Substitutes for Treating Chronic Wounds. Should AHRQ have any questions, additional needs, or wish to discuss the information provided in a live meeting or teleconference, please do not hesitate to reach out to us.	Thank you for your submission including the background information on TheraSkin. We believe we have thoroughly described TheraSkin and other commercially available products relevant to the report. We provide responses to your current submissions below.
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	Completed TheraSkin Studies 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. Design: Retrospective observational study	The Landsman 2011 study did not meet study inclusion criteria due to publication date. We included only studies published since 2012, the publication date of our earlier evidence report Skin

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			Substitutes for Treating Chronic Wounds.
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	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. Design: Prospective randomized clinical trial	The DiDomenico 2011 study was included in the 2012 evidence report *Skin Substitutes for Treating Chronic Wounds*, and did not meet inclusion criteria for this report due to publication date. A summary of the 2012 report will be included in the revised report.
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	Budny AM, Ley A. Cryopreserved allograft as an alternative option for closure of diabetic foot ulcers. Podiatry Management. 2013 Aug:131-136. Design: Case series	The study design of the Budny 2013 study (case series) did not meet study inclusion criteria (see Methods).
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	Sanders, L, Landsman AS, Landsman A, et. al. A prospective, multicenter randomized controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. Ostomy Wound Manage. 2014 Sep;60(9):26-38.	The Sanders 2014 study is included in the report.
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	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. Design: Retrospective medical chart review	The Wilson 2016 study (retrospective medical chart review case series) is not within the scope of our review as described in the Methods section.
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	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):399-406.	Landsman 2016 is not a clinical study so did not meet study inclusion criteria (see Methods).

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Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	Towler, MA, Rush EW, Richardson MK, Williams CL. Randomized, prospective, blinded-enrollment, head-to-head venous leg ulcer trial comparing living, bioengineered skin graft substitute (Apligraf) with living, cryopreserved, human skin allograft (TheraSkin). Clin Podiatr Med Surg. 2018 Jul;35(3)357-365.	The Towler 2018 study is included in the report.
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	Ongoing TheraSkin Studies Large registry study (Wound EMR Registry) of 1,556 DFU patients with matched cohorts comparing TheraSkin (n=778) vs. SOC (n=778) Available on ClinicalTrials.gov? No ClinicalTrials.gov Trial Number: N/A	We are unable to include this registry study as the standard of care was not described. Reporting of similar standard of care used in conjunction with the skin substitute intervention is also an inclusion criteria (see Methods).
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	Large registry study (Wound EMR Registry) of 3,994 patients with wounds below the knee of all etiologies comparing TheraSkin (n=1997) vs. SOC (n=1997) Available on ClinicalTrials.gov? No ClinicalTrials.gov Trial Number: N/A	We are unable to include this registry study as the standard of care was not described. Reporting of similar standard of care used in conjunction with the skin substitute intervention is also an inclusion criteria (see Methods).
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	Registry study (US Wound Registry) of 184 patients in the most difficult to heal VLU comparing TheraSkin (n=87) vs. Apligraf (n=87) Available on ClinicalTrials.gov? No ClinicalTrials.gov Trial Number: N/A	We are unable to include this registry study as the standard of care was not described. Reporting of similar standard of care used in conjunction with the skin substitute intervention is also an inclusion criteria (see Methods).

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Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	RCT in VLU comparing TheraSkin vs. SOC (INOVA) Available on ClinicalTrials.gov? Yes ClinicalTrials.gov Trial Number:NCT03935386	Information on ClinicalTrials.gov trial number NCT03935386 will be added to Guiding Question 5.
Public Reviewer #1 Dr. Arti Masturzo SolSys Medical LLC	Results	RCT in VLU comparing TheraSkin vs. Apligraf Available on ClinicalTrials.gov? Yes ClinicalTrials.gov Trial Number: NCT02047084	Information on ClinicalTrials.gov trial number NCT02047084 is included as the Towler 2018 study.
Public Reviewer #2 Zack Bridges ACELL, INC.	Results	We are grateful for the opportunity to submit to the AHRQ Technical Assessment program additional information about ACell's ongoing phase III clinical trials. ACell is a leading regenerative medicine company that develops and manufactures products designed to facilitate the body's ability to repair and remodel tissue. Our company helps patients in a variety of settings heal differently. ACell's products are gradually incorporated within the patient's body and replaced with site-appropriate tissue. The studies indexed in this letter investigate the clinical efficacy and safety of ACell's proprietary MatriStem UBM (Urinary Bladder Matrix) technology platform which is based on an extracellular matrix, or ECM, derived from porcine urinary bladder. The subjects and products within these studies are relevant to guiding question 5 from the protocol, "What skin substitutes are currently being investigated in ongoing trials." In this letter we have summarized the three ongoing studies that are currently registered and listed on the clinicaltrials.gov website. Two of the three studies listed below (NCT03283787 and NCT03626623) are randomized controlled trials that investigate the use of ACell's UBM technology in chronic wounds, specifically stage II and IV pressure ulcers and diabetic foot ulcers. The third study listed (NCT03632954) is a prospective observational cohort study investigating the use of ACell's UBM technology in multiple wounds including but not limited to chronic wounds. The studies listed below are ongoing and results have not been published.	Thank you for your submission. Information on ClinicalTrials.gov trial number NCT03283787 is included in Guiding Question 5. Information on NCT03626623 will be added to Guiding Question 5. NCT03632954 will not be included. We are excluding observational cohort studies and only including RCTs and non-randomized comparison studies.

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		NCT03283787 (https://www.clinicaltrials.gov/ct2/show/NCT03283787?term=acell&draw=1&rank=5) Title: Comparing Concomitant Use of ACell MicroMatrix® and ACell Cytal™ to Standard of Care in Stage 3 or 4 Pressure Injuries Study Design: A three arm, parallel-design, randomized study comparing 2 experimental arms to a single control arm. The primary comparison will be Group 1 (MicroMatrix® and ACell Cytal™ Wound Matrix 2-Layer vs. Group 3 (NPWT) to determine if Group 1 is superior to Group 3. NPWT is the standard of care (SOC) for patients with Stage 3 or 4 pressure ulcers and is the active control arm for the study. Primary Objective: Incidence of complete epithelization Principle Investigator: Carol Bowen-Wells, MD Location: St. Vincent's Medical Center Jacksonville NCT03626623 (https://www.clinicaltrials.gov/ct2/show/NCT03626623?term=acell&draw=1&rank=9) Title: Diabetic Foot Ulcer Study Comparing Cytal Wound Matrix 1-Layer to Standard of Care Study Design: This is a prospective, two-armed, multi-center randomized controlled trial (RCT) comparing Cytal Wound Matrix 1-Layer intervention to standard of care (SOC) intervention in patients presenting with diabetic foot ulcers (DFU). Up to one hundred and fifty patients recruited from US based medical centers and randomized (using a 2(active):1(control) randomization scheme) to receive either Cytal Wound Matrix 1-Layer intervention or standard of care intervention. Primary Objective: Incidence of complete wound closure Principle Investigator: Multiple Locations: Multiple NCT03632954 (https://www.clinicaltrials.gov/ct2/show/NCT03632954?term=acell&draw=1&rank=3) Title: Cytal® Wound Matrix and MicroMatrix® All Wound Study Study Design: A single-site, prospective, observational clinical study of Cytal® Wound Matrix alone or in combination with MicroMatrix® for the	

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		management of wounds. Up to 100 patients with multiple wound types including but not limited to, venous ulcers, diabetic foot ulcers, trauma wounds, and external surgical wounds will be treated either with Cytal® Wound Matrix alone or with Cytal® Wound Matrix and MicroMatrix® for wounds exceeding 3mm in depth. Primary Objectives: Incidence of completely healed wounds; number and percentage of completely healed wounds; Wound size Principle Investigator: Scott Gorenstein, DO Location: NYU Winthrop Hospital The index lists all ongoing Phase II and above clinical trials sponsored by ACell that are relevant to the Skin Substitutes for Treating Chronic Wounds Protocol. Please do not hesitate to contact our organization with any additional questions.	
Public Reviewer #3 Dr. Jadranka Dobra PolyMedics Innovations GmbH	Results	Supplemental Evidence and Data for the Skin Substitutes for Treating Chronic Wounds Protocol submitted by Polymedics Innovations GmbH on Suprathel® Clinical Trial to Investigate the Application of the Resorbable Wound Covering Suprathel® at the Local Treatment of Ulcus Cruris Status: completed ClinicalTrial.gov number: n.a. (not registered) Phase: n.a. (trial of device) Summary file: Clinical Trial Summary & Comments	Thank you for your submission. SUPRATHEL® is out of scope of the report since the product is marketed as “a synthetic one-time application wound and burn dressing for the treatment of dermal wounds.” Only products that were mainly indicated for chronic wounds were included. In addition, we only included peer-reviewed publications in the report (see Methods).
Public Reviewer #3 Dr. Jadranka Dobra	Results	Suprathel CW in Ulcer cruris venosum, arteriosum and mixum and diabetic foot ulcer Status: ongoing ClinicalTrial.gov number: n.a. (not registered)	SUPRATHEL® is out of scope of the report since the product is marketed as “a synthetic one-time

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PolyMedics Innovations GmbH		Phase: n.a. (trial of device) Summary file: Summary Overview Observational study Protocol	application wound and burn dressing for the treatment of dermal wounds." Only products that were mainly indicated for chronic wounds were included. In addition, we only included peer-reviewed publications in the report (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Enclosed in this submission are the five additional clinical trials that are either completed or are on-going through today's date associated with DermACELL. The specifics of each trial has been downloaded from the Clinical Trials.gov website are also included as attachments.	We will add information on the ClinicalTrials.gov trial number NCT03589586 to Guiding Question 5. Information on ongoing clinical trials NCT03285698, and NCT03476876 are already included in the report. NCT03667560 will not be included in the report since breast reconstruction is out of scope for the report. NCT03044132 is a single-arm study and will not be included in the report. We are excluding observational cohort studies and only including RCTs and non-randomized comparison studies.
Public Reviewer #4	Results	1. Clinical Effectiveness of DermACELL AWM in Subjects with Chronic Venous Leg Ulcers	We will add information on ClinicalTrials.gov

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Bud Brame LifeNet Health		• 50 patients enrolled to date, still recruiting other patients • Phase IV clinical trial, post market launch surveillance	trial number NCT03589586 to Guiding Question 5.
Public Reviewer #4 Bud Brame LifeNet Health	Results	2. Comparing the Clinical Outcomes of DermACELL® With Integra® Bilayer Wound Matrix • Also 50 patients enrolled, in analysis with Georgetown now. • Phase IV clinical trial, post market launch surveillance	Information on NCT03285698 is already included in the report.
Public Reviewer #4 Bud Brame LifeNet Health	Results	3. DermACELL AWM® in Chronic Wagner 3/4 Diabetic Foot Ulcers • Study is complete and the manuscript has been accepted for publication with Advances in Wound Management • Phase IV clinical trial, post market launch surveillance	NCT03044132 is a single-arm study and will not be included in the report. We are excluding observational cohort studies and only including RCTs and non-randomized comparison studies.
Public Reviewer #4 Bud Brame LifeNet Health	Results	4. Dermacell ADM without Basement Membrane • DermACELL utilized in Breast reconstruction • 4 patients have been enrolled, still recruiting other patients • Phase II clinical trial, non-basement membrane DermACELL is not clinically available	Information on NCT03667560 will not be included in the report since breast reconstruction is out of scope for the report (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	5. Comparative Effectiveness of Two Acellular Matrices (Dermacell vs. Integra) for Management of Deep Diabetic Foot Ulcers • 18 patients enrolled, still recruiting other patients • Phase IV clinical trial, post market launch surveillance	Information on NCT03476876 is already included in the report.
Public Reviewer #4 Bud Brame LifeNet Health	Results	I have also included additional pilot studies (Drs. Yonehiro, Mulder, Buchbaum, Cole, Bertassi, Roussalis, and Walters), and a compendium of DermACELL studies when utilized in Breast Reconstruction so the entire body of work can be reviewed. If you like to see the hard copies of these studies, please let me know and I will forward them immediately.	The study designs of Yonehiro 2013 (case series), Mulder 2012 (case report), Cole 2016 (case series), Bertassi [Shitrit] 2014 (case report), and Roussalis 2014 (case report) do not meet study inclusion criteria (see Methods).

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			Buchbaum does not meet study inclusion criteria due to study design (case report) and not being peer-reviewed. Chen 2012 (focused on burns) and studies using DermACELL in breast reconstruction are outside the scope of the report. Lastly, data from Walters 2016 (NCT01970163) is already included in the report (Cazzell 2017).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Mulder G. Tissue augmentation and replacement of a heel fat pad with a decellularized sterile human dermal matrix. Wounds. 2012 Jul;24(7):185-9.	The Mulder 2012 study (case report) did not meet study inclusion criteria (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Cole W. Human Acellular Dermal Matrix Paired With Silver-zinc Coupled Electroceutical Dressing Results in Rapid Healing of Complicated Diabetic Wounds of Mixed Etiology: A Novel Case Series. Wounds. 2016 Jul;28(7):241-7.	The Cole 2016 study (case series) did not meet study inclusion criteria (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Yonehiro L, Burleson G, Sauer V. Use of a new acellular dermal matrix for treatment of nonhealing wounds in the lower extremities of patients with diabetes. Wounds. 2013 Dec;25(12):340-4.	The Yonehiro 2013 study (case series) did not meet study inclusion criteria (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers. Eplasty. 2016;16:e10	Data from Walters 2016 (NCT01970163) is already included in the report (Cazzell 2017).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Roussalis JL. Novel use of an acellular dermal matrix allograft to treat a chronic scalp wound with bone exposure: a case study. Int J Burns Trauma. 2014;4(2):49-52.	The Roussalis 2014 study (case report) did not meet study

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			inclusion criteria (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Chen SG, Tzeng YS, Wang CH. Treatment of severe burn with DermACELL(®), an acellular dermal matrix. Int J Burns Trauma. 2012;2(2):105-9.	Burns are outside the scope of the report (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Clinical Reports using DermACELL in Breast Reconstruction	Breast reconstruction is outside the scope of the report (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Treatment of Plantar Diabetic Ulcer with Human Acellular Dermal Matrix (ADM): Buchbaum Case Study [internal document]	Buchbaum is an unpublished case report which did not meet study inclusion criteria (see Methods).
Public Reviewer #4 Bud Brame LifeNet Health	Results	Shitrit SB, Ramon Y, Bertasi G. Use of a novel acellular dermal matrix allograft to treat complex trauma wound: a case study. Int J Burns Trauma. 2014;4(2):62-5.	The Shitrit 2014 study (case report) did not meet study inclusion criteria (see Methods).
Public Reviewer #5 Dr. William Tettelbach MiMedx	Results	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. MiMedx appreciates the opportunity, provided by the AHRQ Evidence-based Practice Center (EPC), to submit additional evidence under the call for Supplemental Evidence and Data for Systematic Reviews (SEADS). We are confident that providing this avenue for input from wound care industry and providers will result in a more complete (and therefore more durable) Technology Assessment (TA) that will function as a long term resource to those evaluating the clinical and scientific evidence related to skin substitutes. Please note our original comments to the draft TA, which were submitted online 03/07/19. We are attaching a copy for your convenience. Although we submitted some suggestions we believe would strengthen the TA, we also expressed support for the overall value, comprehensiveness and even-handed evaluation (including areas for improvement) of the existing clinical and scientific data.	The two Tettelbach 2019 studies (RCTs referenced) are included in the report. Data from the intent-to-treat analysis from the Bianchi 2019 will be added to the report. Case series are outside the scope of the report (see Methods). The ongoing trial "NCT03529578" will not be included in the report since this is a case series.

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		Within our original comments, we noted two Randomized Controlled Trials (RCTs) that were not included. The first was a multicenter EpiFix RCT;[1] because it met the date cutoff and other search parameters, we believe this represented a potential oversight in the search methodology. However, there was also an EpiCord RCT[2] that did not meet date cutoff but--published shortly thereafter--we believe the inclusion of which would bolster the TA. It should be noted that both studies are unique in that there is statistical analysis of the role of adequate debridement in healing; including them aligns with recommendation of the TA to diversify wound care research. In addition to the two RCTs outlined in our original comments, we believe the SEADS represents an opportunity to include a third publication, which is the Intent-to-Treat (ITT) analysis of the landmark Bianchi Venous Leg Ulcer RCT[3] referenced in the draft TA. The ITT data was released in March 2019, and so was not included in either the draft or the original MiMedx response. Lastly, in the spirit of inclusivity we are listing a newly published case series highlighting the efficacy of dHACM (EpiFix) in the treatment of pressure ulcers (PU).[4] We are aware that case series represent lower-level clinical evidence relative to RCTs. However, we believe it is important to include this article because of 1) the very recent publication date (May 2019) means that the EPC would not otherwise have seen it, as well as 2) its investigation of a chronic ulcer type less explored by current studies. Reference to this study was also made in the original draft TA report in Appendix E, as an ongoing study. This aligns with draft TA recommendation that research diversifies beyond Diabetic Foot Ulcers and Venous Leg Ulcers. Below, please see the information requested under the SEADS (study number, study period, design, methodology, etc.) concerning these three RCTs and one case series. We are delighted that the EPC has opened this TA for further collection of clinical and scientific research. Again, we appreciate the opportunity to strengthen the Technology Assessment as a resource for wound care practitioners and researchers. NOTATION OF PREVIOUS CLINICAL RESEARCH	Lastly, the following studies are already included in the report: Bianchi 2018, Zelen 2013, Serena 2014, and Zelen 2016.

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		MiMedx is confident that aside from the four studies listed in this submission (two RCTs, one ITT analysis and one case series), the draft TA report accurately captured previously published (wound care) RCTs related to MiMedx products. However, we will provide a full list of our studies and clinicaltrials.gov registration numbers as an appendix to these comments. NOTATION OF RECENT CLINICAL RESEARCH The draft TA combined with the four studies outlined in this submission, represents the totality of results from completed RCTs related to skin substitutes for treating chronic wounds. It *does not* represent the totality of RCTs for MiMedx products in other usages (for example: plantar fasciitis and osteoarthritis), nor does it represent the totality of ongoing lower-level research (retrospectives and case studies) related to wound care (for example: MiMedx is currently performing a retrospective analysis of hard-to-treat Mohs cases). In addition, the RCTs listed in the draft TA or in the MiMedx SEADS submission do not capture the full body of lower-level clinical and scientific evidence related to dehydrated human amnion/chorion or umbilical cord products.	
Public Reviewer #5 Dr. William Tettelbach MiMedx	Results	STUDY 1 FOR INCLUSION: DEHYDRATED HUMAN AMNION/CHORION MEMBRANE (DHACM) FOR THE TREATMENT OF DFU (RCT) Publication: 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. STUDY 2 FOR INCLUSION: DEHYDRATED HUMAN UMBILICAL CORD (DHUC – EPICORD) FOR THE TREATMENT OF DFU (RCT) Publication: 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.	Both Tettelbach 2019 studies are included in the report.

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Public Reviewer #5 Dr. William Tettelbach MiMedx	Results	STUDY 3 FOR INCLUSION: DEHYDRATED HUMAN AMNION/CHORION MEMBRANE (DHACM) FOR THE TREATMENT OF VLU (ITT STATISTICAL ANALYSIS OF BIANCHI RCT) Publication: Bianchi C, Tettelbach W, Istwan N, Hubbs B, Kot K, Harris S, Fetterolf D. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. Int Wound J. 2019 Mar 12. doi: 10.1111/iwj.13094.	Data from the intent-to-treat analysis of Bianchi 2019 will be added to the report.
Public Reviewer #5 Dr. William Tettelbach MiMedx	Results	STUDY 4 FOR REVIEW: DHACM ALLOGRAFT FOR PRESSURE ULCER TREATMENT (CASE SERIES) Publication: Berhane CC, Brantley K, Williams S, Sutton E, Kappy C. An evaluation of dehydrated human amnion/chorion membrane allografts for pressure ulcer treatment: a case series. J Wound Care. 2019 May 1;28(Sup5):S4-S10. doi: 10.12968/jowc.2019.28.Sup5.S4.	Case series are outside the scope of the report (see Methods). The ongoing trial NCT03529578 will not be included since it is a case series. We are only including RCTs and non-randomized comparison studies.
Public Reviewer #5 Dr. William Tettelbach MiMedx	Results	RCTS FOR INCLUSION IN FINAL TECHNOLOGY ASSESSMENT RCTs Appropriately Included in Draft TA Below represent RCTs appropriately included in the original TA draft, *Skin Substitutes for Treating Chronic Wounds.* For convenience, as well as to support their continued inclusion within the final document, please see the full citation as well as clinicaltrials.gov registration number: Bianchi C, Cazzell S, Vayser D, et al. 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):114-22. Epub 2017 Oct 11. Also available: http://dx.doi.org/10.1111/iwj.12843. PMID: 29024419. Zelen CM, Serena TE, Denoziere G, et al. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J. 2013 Oct;10(5):502-7. Also available: http://dx.doi.org/10.1111/iwj.12097. PMID: 23742102.	As noted, Bianchi 2018, Zelen 2013, Serena 2014, and Zelen 2016 are already included in the report.

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		Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. 2014 Nov-Dec;22(6):688-93. Also available: http://dx.doi.org/10.1111/wrr.12227. PMID: 25224019 Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. 2016 Apr;13(2):272-82. Also available: http://dx.doi.org/10.1111/iwj.12566. PMID: 26695998.	
Public Reviewer #5 Dr. William Tettelbach MiMedx	Results	Additional Completed RCTs for Inclusion in Final TA Below represents two completed RCTs that were omitted from the draft TA, as well as the separately published ITT analysis performed on Bianchi et al. MiMedx recommends these for inclusion in the final TA, for the reasons outlined in our original submitted comments (03/07/19) as well as this SEADS submission. 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. 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 Bianchi C, Tettelbach W, Istwan N, Hubbs B, Kot K, Harris S, Fetterolf D. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. Int Wound J. 2019 Mar 12. doi: 10.1111/iwj.13094. [Epub ahead of print]	The two Tettelbach 2019 studies (RCTs referenced) are included in the report. Data from the intent-to-treat analysis of Bianchi 2019 will be added to the report.

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		FOOTNOTES 1. 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. 2. 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 3. Bianchi C, Tettelbach W, Istwan N, Hubbs B, Kot K, Harris S, Fetterolf D. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. Int Wound J. 2019 Mar 12. doi: 10.1111/iwj.13094. [Epub ahead of print] 4. Berhane CC, Brantley K, Williams S, Sutton E, Kappy C. An evaluation of dehydrated human amnion/chorion membrane allografts for pressure ulcer treatment: a case series. J Wound Care. 2019 May 1;28(Sup5):S4-S10. doi: 10.12968/jowc.2019.28.Sup5.S4.	
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	Organogenesis appreciates the opportunity to respond to the Supplemental Evidence and Data for Systematic Review (SEADS) request related to the review of evidence for Skin Substitutes for Treating Chronic Wounds. Organogenesis is a leading regenerative medicine company. Our main products are Apligraf®, which is approved by the Food and Drug Administration (FDA) for the treatment of diabetic foot ulcers and venous leg ulcers; Dermgraft®, which is FDA approved for the treatment of diabetic foot ulcers; PuraPly and PuraPly Antimicrobial which are FDA cleared for use with a variety of wounds; and Affinity and NuShield which are amniotic membrane allografts for use in wound repair and healing.	Thank you for your submission. We provide responses below regarding the eleven submissions by Organogenesis including five published comparative effectiveness research studies, three manuscripts, and three ongoing clinical trials.

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		In this document Organogenesis Inc. provides a list of eight clinical studies that have been published or accepted for publication which our organization has sponsored to evaluate skin substitute treatment of Venous Leg Ulcers (VLUs), Diabetic Foot Ulcers (DFUs), and Pressure Ulcers and which were not captured in the draft technology review. These studies include both Comparative Effectiveness Research (CER) studies and Randomized Controlled Trials (RCTs). These supplemental data are intended to address specific questions raised by AHRQ regarding skin substitute use for chronic wounds and to provide more comprehensive evidence for the Agency's final report. Organogenesis agrees that access to pertinent scientific information will enhance the report and that the report may have significant effects on wound treatment algorithms and clinical practice. We request that the Organogenesis' publications, particularly the CER studies that look at the real-world clinical outcomes of treatment, be added to the 2019 report to provide a more comprehensive and complete presentation of clinical effectiveness data for skin substitutes. Currently published RCTs are the only type of study that AHRQ has taken under consideration. However, RCTs have several limitations that CERs do not. RCTs show what a treatment **can do** in narrowly defined patient populations under rigorously controlled treatment regimens. CER studies demonstrate what a treatment **does** do in real-world clinical practice. In CER studies, safety and effectiveness is evaluated in patients outside of expert clinical research centers. CERs answer the question of whether RCT-derived data can be translated to routine practice settings. CER studies are performed on much larger patient populations at many more centers. Large samples sizes, regional diversity in clinical facilities, and long follow-up times post-treatment are all significant strengths of CERs compared to RCTs. Data presented on the Organogenesis products Apligraf (bilayered living cellular construct (BLCC)) and Dermagraft (human fibroblast-derived dermal substitute (HFDS)) in CER publications contribute valuable information that is not typically available through RCT trials required for product registration by the Food and Drug Administration (FDA). These studies utilize the WoundExpert EMR database which is used in 90% of wound care clinics across the United States. The number of patients in the skin substitute databases used for the CER analyses are between	Lastly, please note that while our original searches were initially limited to RCTs, systematic reviews, and meta-analyses published since 2012 (the publication date of the evidence report *Skin Substitutes for Treating Chronic Wounds*), literature searches were expanded to include additional study designs (e.g., prospective nonrandomized comparative studies) after preliminary searches did not identify sufficient evidence for pressure ulcers and arterial leg ulcers.

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		100 to 1,000 times greater than the samples sizes of wound care RCTs and include between 10 to 100 times more treatment centers. The number of wounds and centers providing information for the analysis make it less likely that a uniform bias was present and affected study results. None of the CER studies are included on clinicaltrials.gov, but all of the completed studies have been published or accepted for publication in peer-reviewed journals. Specifically, in response to the SEAD request, we are providing summaries and enclosing full copies of the following items: o Five published articles from 2014 through the present that describe CER studies of the use of Apligraf or Dermagraft o Two manuscripts of CER studies on Dermagraft that have been accepted for publication o One RCT on Affinity that has been accepted for publication. AHRQ also requested, "A list of ongoing studies that your organization has sponsored for this indication (treatment of chronic wounds with skin substitutes)". We also provide summaries of ongoing wound care clinical trials sponsored by Organogenesis. The Organogenesis wound care products under study are: 1) PuraPly AM, cleared for marketing as a 510(k), and 2) NuShield dehydrated human amniotic membrane, classified as an HCT/P (human cell tissue product). "Phase" of studies does not strictly apply to these trials. The two products are currently being sold and marketed in the US in compliance with all FDA regulations and federal law. The trials described below are comparable to Phase II and above clinical trials. These studies do not represent all Organogenesis wound trials listed on the ClinicalTrials.gov but constitute a complete listing of "Phase II and above" type studies. We strongly recommend that AHRQ incorporate the eight publications describing the completed studies into its evidence review on the use of skin substitutes for treating chronic wounds. We anticipate publishing data from the ongoing trials following study completion and urge AHRQ to consider those data in any future updates of the technology review.	
Public Reviewer #6 Antonio S. Montecalvo	Results	Attachments: Published Comparative Effectiveness Research Studies 1. Marston WA, Sabolinski ML, Parsons NB, Kirsner RS. Comparative effectiveness of a bilayered living cellular construct and a porcine	The Marston 2014 study does not meet our study inclusion criteria due to the

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Organogenesis		collagen wound dressing in the treatment of venous leg ulcers. *Wound Repair Regen*. 2014;22(3). doi:10.1111/wrr.12156	retrospective study design. Reporting of similar standard of care used in conjunction with the skin substitute intervention is also an inclusion criteria (see Methods).
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	2. 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	The Kirsner 2015 study does not meet our study inclusion criteria due to the retrospective study design. Reporting of similar standard of care is also an inclusion criteria (see Methods).
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	3. 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.	The Kraus 2017 study does not meet our study inclusion criteria due to the retrospective study design. Reporting of similar standard of care is also an inclusion criteria (see Methods).
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	4. 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	The Treadwell 2017 study does not meet our study inclusion criteria due to the retrospective study design. Reporting of similar standard of care is also an inclusion criteria (see Methods).
Public Reviewer #6	Results	5. Sabolinski ML, Gibbons G. Comparative effectiveness of a bilayered living cellular construct and an acellular fetal bovine collagen dressing	The Sabolinski 2018 study does not meet our study inclusion

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Antonio S. Montecalvo Organogenesis		in the treatment of venous leg ulcers. J Comp Eff Res. 2018;7(8):cer-2018-0031. doi:10.2217/cer-2018-0031	criteria due to the retrospective study design. Reporting of similar standard of care is also an inclusion criteria (see Methods).
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	Comparative Effectiveness Research Study Manuscripts (accepted for publication): 6. Fitzgerald RH, Sabolinski ML, Skornicki M. Parsons NB. Comparative effectiveness of a human fibroblast-derived dermal substitute versus a fetal bovine collagen dressing for the treatment of diabetic foot ulcers in a real-world setting. *Ostomy Wound Management*. 2019;(accepted for publication, minor revisions; scheduled for July 2019, *OWM* Innovations Issue)	The Fitzgerald manuscript did not meet our study inclusion criteria since we only included peer-reviewed publications (see Methods).
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	7. Sabolinski ML. Comparative Effectiveness Research Study of a Human Dermal Substitute and a Placental Membrane Allograft for the Treatment of Diabetic Foot Ulcers. J Comp Eff Res. 2019; (accepted for publication, minor revisions)	The Sabolinski manuscript did not meet our study inclusion criteria since we only included peer-reviewed publications (see Methods).
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	Randomized Controlled Study (RCT) Manuscript (accepted for publication): 8. Serena T, Yaakov R, Moore S, Cole W, Coe S, Snyder R, Patel K, Doner B, Kasper M, Hamil R, Sabolinski ML. A Prospective Multicenter Randomized Controlled Clinical Trial of a Hypothermically Stored Amniotic Membrane for the Management of Diabetic Foot Ulcers. Advances in Wound Care. 2019; (accepted for publication, minor revisions)	The Serena 2019 study will be included in the report.
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	Ongoing Randomized Controlled Trials (RCTs): 9. PuraPly® AM Plus the Standard of Care to Standard of Care Alone for the Management of Stage II-IV Pressure Ulcers.	Information on ClinicalTrials.gov trial number NCT03502824 is included in Guiding Question 5.
Public Reviewer #6 Antonio S. Montecalvo	Results	10. The RESPOND Registry (RESPOND) – PuraPly® AM	We are unable to include this registry study as the standard of care was not

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Organogenesis			described. Reporting of similar standard of care used in conjunction with the skin substitute intervention is also an inclusion criteria (see Methods).
Public Reviewer #6 Antonio S. Montecalvo Organogenesis	Results	11. Randomized Clinical Study Assessing NuShield Versus Standard of Care in Diabetic Foot Ulcers a(DFUs)	Information on ClinicalTrials.gov trial number NCT03855514 will be added to Guiding Question 5.
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	On behalf of Smith & Nephew, Inc. (SNI) a global medical technology business dedicated to helping healthcare professionals improve patient's lives, I would like offer additional clinical evidence that was not included in the Draft Technical Brief for Skin Substitutes for Treating Chronic Wounds published on January 28, 2019. We are submitting these studies as it appears that not all studies (including studies identified in the 2012 Skin Substitute Technical Assessment) have been included in the 2019 draft. I would like encourage you to consider several key points in your decision making process pertaining to OASIS Matrix before issuing a final report. As AHRQ and CMS evaluates Skin Substitutes, we believe it is imperative to include both Randomized Control Trials (RCTs) and other types of evidence that support clinical efficacy and wound closure. Although the title of the technical brief is "Skin Substitutes for Treating Chronic Wounds" and lists 74 commercially available skin substitutes relevant to this report, it does not address the clinical efficacy of skin substitutes such as OASIS Wound Matrix. In order to assist you in this process, I have attached a clinical evidence summary table and copies of several studies specific to OASIS Matrix for you to consider including in the final AHRQ Skin Substitute Technical Assessment.	Thank you for your submission. We provided a detailed response to each submission below.
Public Reviewer #7	Results	Mostow EN, Haraway GD, Dalsing M, Hodde JP, King D. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of	The Mostow 2005 study was included in the 2012 technology

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LuAnn Russo, RN Smith & Nephew		chronic leg ulcers: A randomized clinical trial. *J Vasc Surg* 2005; 41:856-862.	assessment and did not meet publication date inclusion criteria for the current report (see Methods). The 2012 evidence report *Skin Substitutes for Treating Chronic Wounds* is currently available in PubMed (PubMed PMID:25356454). A summary of the 2012 report will be included in the revised report.
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Niezgoda JA, Van Gils CA, Frykberg RG, Hodde JP. Randomized clinical trial comparing Oasis Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care* 2005; 18:258-266.	The Niezgoda 2005 study was included in the 2012 technology assessment and did not meet publication date inclusion criteria for the current report (see Methods). A summary of the 2012 report will be included in the revised report.
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Romanelli M, Dini V, Bertone M, Barbanera S, Brilli C. OASIS Wound Matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. *Int Wound J* 2007; 4:3-7.	The Romanelli 2007 study was included in the 2012 technology assessment and did not meet publication date inclusion criteria for the current report (see Methods). A summary of the 2012 report will be included in the revised report.
Public Reviewer #7	Results	Romanelli M, Dini V, Bertone MS. Randomized Comparison of OASIS Wound Matrix versus Moist Wound Dressing in the Treatment of Difficult-	The Romanelli 2010 study was included in

Commentator & Affiliation	Section	Comment	Response
LuAnn Russo, RN Smith & Nephew		to-Heal Wounds of Mixed Arterial/Venous Etiology. *Adv Skin Wound Care* 2010; 23:34-38.	the 2012 technology assessment and did not meet publication date inclusion criteria for the current report (see Methods). A summary of the 2012 report will be included in the revised report.
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Landsman A, Roukis TS, DeFronzo DJ, Agnew P, Petranto RD, Surprenant M. Living cells or collagen matrix: Which is more beneficial in the treatment of diabetic foot ulcers? *Wounds*.2008;20:111-116.	The Landsman 2008 study was included in the 2012 technology assessment and did not meet publication date inclusion criteria for the current report (see Methods). A summary of the 2012 report will be included in the revised report.
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Cazzell SM, Lange DL, Dickerson JE, Slade HB. The Management of Diabetic Foot Ulcers with Porcine Small Intestine Submucosa Tri-Layer Matrix: A Randomized Controlled Trial. *Adv Wound Care*. 2015 [epub].	The Cazzell 2015 was excluded from the 2019 report since the standard of care provided to patients was dissimilar (see Methods). The control group received standard of care selected by the investigator resulting in 6 different treatments including wet-to-dry which is not acceptable treatment for chronic wounds.

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Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Brown-Etris M, Milne CT, Hodde JP. An extracellular matrix graft (Oasis® Wound Matrix) for treating full-thickness pressure ulcers: A randomized clinical trial. *J Tissue Viability*.2019;28:21-26.	The Brown-Etris 2019 study is included in the report.
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	O'Donnell TF Jr, Lau J. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. *J Vasc Surg* 2006; 44:1118-1125.	The O'Donnell 2006 study was excluded from the 2012 technology assessment (due to study design) and did not meet publication date inclusion criteria for the current report (see Methods).
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Carter MJ, Waycaster C, Schaum K, Gilligan AM. Cost-Effectiveness of Three Adjunct Cellular/Tissue-Derived Products Used in the Management of Chronic Venous Leg Ulcers. *Value Health*. 2014;17:801-813.	We are not including publications centered on cost data in the current report (see Methods).
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Gilligan AM, Waycaster CR, Landsman AL. Wound closure in patients with DFU: a cost-effectiveness analysis of two cellular/tissue-derived products. *J Wound Care*. 2015;24:149-156.	We are not including publications centered on cost data in the current report (see Methods).
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Romanelli M, Gilligan AM, Waycaster CR, Dini V. Difficult-to-heal wounds of mixed arterial/venous etiology: a cost-effectiveness analysis of extracellular matrix. *Clinicoecon Outcomes Res*. 2016;8:153-161.	We are not including publications centered on cost data in the current report (see Methods).
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Guest JF, Weidlich D, Singh H, et al. Cost-effectiveness of using adjunctive porcine small intestine submucosa tri-layer matrix compared to standard care in managing diabetic foot ulcers in the US. *J Wound Care*. 2017;26:S12-S24.	We are not including publications centered on cost data in the current report (see Methods).
Public Reviewer #7	Results	Guest JF, Rana K, Singh H, Vowden P. Cost-effectiveness of using a collagen-containing dressing plus compression therapy in non-healing venous leg ulcers. *J Wound Care*. 2018;27:68-78.	We are not including publications centered on cost data in the

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LuAnn Russo, RN Smith & Nephew			current report (see Methods).
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Barendse-Hofman MG, van Doorn LP, Oskam J, Steenvoorde P. Extracellular matrix prevents split-skin grafting in selected cases. *J Wound Care* 2007; 16:455-458.	The Barendse-Hofman 2007 study did not meet publication date inclusion criteria for the current report (see Methods) and did not examine chronic wounds.
Public Reviewer #7 LuAnn Russo, RN Smith & Nephew	Results	Martinson M, Martinson N. A comparative analysis of skin substitutes used in the management of diabetic foot ulcers. *J Wound Care*. 2016;25:S8-S17.	The Martinson 2016 study did not meet our study inclusion criteria due to the retrospective study design. Reporting of similar standard of care is also an inclusion criteria (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Please accept this supplemental clinical evidence for Osiris CTP products (Grafix and Stravix) as requested for the 2019 AHRQ technology assessment on skin substitutes. We are submitting this comprehensive information on our CTP products, Grafix and Stravix. We trust that information and comments previously submitted in February 2019 were received and will be included in the final report. Osiris supports the general position outlined in the first AHRQ draft that clinical evaluation of CTP/Skin Substitute products should be primarily based on the results of randomized-controlled clinical studies (RCTs). We also believe there is value in evaluating additional clinical evidence from non-RCT trials, but only as supplemental evidence, not as a replacement or alternative to RCTs. Real-world clinical evidence, non-randomized prospective studies, retrospective analysis and even cases studies provide clinically relevant insights, especially for special populations and patients ineligible for admittance into RCTs. However, we do not believe these types of studies should be used to determine the	Thank you for your submission. We believe that we have thoroughly addressed all requested Grafix- and GrafixPrime-related concerns in the report. An additional public comment period is not scheduled, however the final report will be reviewed by several key personnel from AHRQ and Centers for Medicare & Medicaid Services.

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		health benefit of products in the absence of well-designed and appropriately powered RCTs. Best wishes on completing your reviews and publishing the final AHRQ Technology Assessment. Because we found serious errors in the first draft, we hope there will be an additional public comment period on the next draft prior to final publication.	
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Summary of Studies: List of Completed Studies, Outcomes for All Completed Studies, and Detailed Study Design and Results A. Chronic Diabetic Foot Ulcers, Arterial Ulcers and Pressure Ulcers *Randomized Clinical trials:* Diabetic Foot Ulcers Ananian CE, Dhillon YS, Gils CCV, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. *Wound Rep Reg,* 2018 - PMID: 30098272, Clinicaltrials.gov ID: NCT02675855	Ananian 2018 is included in the report.
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J*., 2014 Clinicaltrials.gov ID: NCT01596920 • Lavery LA, Fulmer J, Shebetka KA, et al. Open-label Extension Phase of a Chronic Diabetic Foot Ulcer Multicenter, Controlled, Randomized Clinical Trial Using Cryopreserved Placental Membrane. *Wounds*, 2018 - PMID: 25048468 • Nuccio EJ, Lavery LA, Min SJ. Innovative Treatment of Chronic Diabetic Foot Ulcer in a Controlled Randomized Clinical Trial Produces Fewer Adverse Events, Faster Wound Closure, and Lower Costs. *J Clin Diabetes Pract*., 2016 - PMID: 30256747	The Lavery 2014 study is included in the report. The Lavery 2018 study did not meet our study inclusion criteria since it is a single-arm open-label extension phase of an RCT (see Methods). The Nuccio 2016 study was out of scope for the report since we are not including publications center on cost data (see Methods).

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Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Comparative Studies:* Diabetic Foot Ulcers Ananian CE, Dhillon YS, Gils CCV, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. *Wound Rep Reg* 2018 - PMID: 30098272, Clinicaltrials.gov ID: NCT02675855	The Ananian 2018 study is included in the report.
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Comparative Studies:* Diabetic, Vascular, and Pressure ulcers Johnson E, Marshall J and Michael GM A comparative outcomes analysis evaluating clinical effectiveness in two different human placental membrane products for wound management. *Wound Repair Regen*. 2017; 25(1):145-149. - PMID: 27997744	The Johnson 2017 study does not meet inclusion criteria based on retrospective design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Non-randomized Studies – prospective:* Complex Diabetic Foot Ulcers with exposed tendon or bone 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,* 2018 - PMID: 29683538 Frykberg RG, Gibbons GW, Walters JL et al, A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane, *Int Wound J.* 2017 - PMID: 27489115, Clinicaltrials.gov ID: NCT02260609	The Raspovic 2018 and Frykberg 2017 studies did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Non-randomized Studies – prospective:* Diabetic and Venous Foot Ulcers D'Costa WF and, Phelan DHK. Surgical application of viable cryopreserved placental membrane for the treatment of chronic wounds in 12 high-risk patients. *Wounds* 2018. - PMID: 30418161	The D'Costa 2018 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant	Results	*Non-randomized Studies – prospective:* Diabetic, Venous and Pressure ulcers	The Reyzelman 2019 and Regulski 2013 studies did not meet our study inclusion

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Osiris Therapeutics, Inc.		Reyzelman AM, Vartivarian M, Danilkovitch A, et al. A prospective, single-center, open-label case series evaluating the clinical outcomes of lyopreserved placental membrane containing viable cells in the treatment of chronic wounds. *Wounds.* 2019 - PMID: 30924793 Regulski M, Jacobstein DA, Petranto RD, et al. A retrospective analysis of a human cellular repair matrix for the treatment of chronic wounds. *Ostomy Wound Manage*. 2013 - PMID: 24334364	criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Non-randomized Studies – prospective:* Venous Ulcers Farivar BS, Toursavadkohi S, Monahan TS et al. Prospective study of cryopreserved placental tissue wound matrix in the management of chronic venous leg ulcers, *Journal of Vascular Surgery: Venous and Lymphatic Disorders,* 2018 - PMID: 30621916	The Farivar 2018 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Non-randomized Studies – prospective:* Mixed Vascular Ulcers Smedley J, Michael GM, Tamire YG. Wound Closure in Smoking Peripheral Arterial Disease Patients with Treatment-Refractory Ulcerations: A12-Month Follow-up Case Series. *Int J Low Extrem Wounds*., 2016 - PMID: 27852883	The Smedley 2016 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Non-randomized Studies – prospective:* Arterial and Pressure Ulcers Anselmo DS, McGuire JB, Love E, Vlahovic T. Application of Viable Cryopreserved Human Placental Membrane Grafts in the Treatment of Wounds of Diverse Etiologies: A Case Series. *Wounds*., 2018 - PMID: 29584601	The Anselmo 2018 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	*Non-randomized Studies – prospective:* Pressure Ulcers Golla D and Phelan DHK. Stage IV perineal pressure ulcers in immobile patients treated with surgical flap closure augmented with cryopreserved placental membrane containing viable cells: A report of four cases, *Wounds*. 2019. - PMID: 30620708 Gibbons GW. Grafix®, a Cryopreserved Placental membrane, for the Treatment of Chronic/Stalled Wounds. *Advances in Wound Care*, 2015 - PMID: 26339532	Case reports were not a study design of interest (see Methods).
Public Reviewer #8	Results	*Non-randomized Studies – prospective:* Pressure Ulcers with exposed tendon or bone	The Suzuki 2016 study does not meet criteria

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Lou Savant Osiris Therapeutics, Inc.		Suzuki K, Michael G, Tamire Y. Viable intact cryopreserved human placental membrane for a non-surgical approach to closure in complex wounds. *Journal of wound care*, 2016 - PMID: 27681807	for inclusion based on its single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	B. Surgical Wounds and Surgical Procedures: Laparoscopic hysterectomy Karon M and Hesp ZC. Augmentation of vaginal cuff closure during laparoscopic hysterectomy using viable cryopreserved umbilical tissue. *Journal of Gynecologic Surgery* 2018.	Surgical wounds are out of scope for the report (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Surgical Wounds and Surgical Procedures: Split thickness skin graft Lavor MA, Michael GM, Tamire YG, et al. Meshed split-thickness autograft with a viable cryopreserved placental membrane overlay for lower-extremity recipient sites with increased risk of graft failure. *Eplasty*. 2018 - PMID: 30023038	Surgical wounds are out of scope for the report (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Surgical Wounds and Surgical Procedures: Dupuytrens' disease Dress CM and Tassis EK. A case of Dupuytren's disease managed with viable cryopreserved placental membrane adjunct to open palmar fasciectomy. *J Surg Case Rep.* 2018 - PMID: 29644033	Surgical wounds are out of scope for the report (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Surgical Wounds and Surgical Procedures: Keloid Gupta RJ, Connelly ST, Silva RG and Gwilliam NR. Use of viable cryopreserved placental membrane as an adjunct to facial keloid resection. *Plast Reconstr Surg Glob Open*. 2018 - PMID: 29464167	Surgical wounds are out of scope for the report (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Surgical Wounds and Surgical Procedures: Surgical wounds Johnson E, Marshall J and Michael GM A comparative outcomes analysis evaluating clinical effectiveness in two different human placental membrane products for wound management. *Wound Repair Regen*. 2017 - PMID: 27997744	The Johnson 2017 study does not meet study inclusion criteria based on retrospective study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Surgical Wounds and Surgical Procedures: Dehiscence Suzuki K, Michael G and Tamire Y. Viable intact cryopreserved human placental membrane for a non-surgical approach to closure in complex wounds. *J Wound Care.* 2016 - PMID: 27681807	This Suzuki 2016 study does not meet criteria for inclusion based on its single-arm study design (see Methods).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	C. Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Radiation necrosis Regulski MJ, Danilkovitch A, Saunders MC, Management of a chronic radiation necrosis wound with lyopreserved placental membrane containing viable cells, *Clinical Case Reports*, 2019 - PMID: 30899471	Radiation necrosis wounds are out of scope for the report (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Necrotizing fasciitis/ Gangrene D'Costa WF and Phelan DHK. Surgical application of viable cryopreserved placental membrane for the treatment of chronic wounds in 12 high-risk patients. *Wounds* 2018 - PMID: 30418161	The D'Costa 2018 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Gas gangrene McGinness K and Kertz-Phelan D. Use of a viable cryopreserved umbilical tissue for soft tissue defects in patients with gas gangrene: a case series. *Wounds*. 2018 - PMID: 29718818	The McGinness 2018 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Necrotic nasal tip Johnson EL and Danilkovitch A, Nonsurgical management of a large necrotic nasal tip wound using a viable cryopreserved placental membrane, *Clin Case Rep*. 2018. - PMID: 30455913	This is a case report of a single patient and thus would not meet criteria for inclusion (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Pyoderma gangrenosum Anselmo DS, McGuire JB, Love E, Vlahovic T. Application of viable cryopreserved human placental membrane grafts in the treatment of wounds of diverse etiologies: a case series. Wounds. 2018 - PMID: 29584601	The Anselmo 2018 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Burns with exposed deep structures Johnson EL, Tassis EK, Michael GM and Whittinghill SG. Viable placental allograft as a biological dressing in the clinical management of full-thickness thermal occupational burns: Two case reports. Medicine (Baltimore). 2017 - PMID: 29245303	Case reports were not a study design of interest (see Methods).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Chronic wounds with exposed tendon or bone Suzuki K, Michael G, Tamire Y. Viable intact cryopreserved human placental membrane for a non-surgical approach to closure in complex wounds. Journal of wound care, 2016 - PMID: 27681807	The Suzuki 2016 study does not meet criteria for inclusion based on its single-arm study design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Trauma / Pyoderma gangrenosum, Poly neuropathic, Dog bite, Vasculitis, Burns Johnson E, Marshall J and Michael GM A comparative outcomes analysis evaluating clinical effectiveness in two different human placental membrane products for wound management. Wound Repair Regen. 2017; 25(1):145-149. - PMID: 27997744	Johnson et al. 2017 does not meet inclusion criteria due to retrospective design (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Complex excoriation disorder Bain MA and Vincent J, Management of a complex excoriation disorder-induced wound with a viable cryopreserved placental membrane. *Plast Reconstr Surg Glob Open*. 2016 - PMID: 28293501	Complex excoriation disorder-induced wounds are out of scope for the report.
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Other Wound Types (complex wounds with exposed structures, necrotic wounds, infected wounds): Refractory shrapnel wound Gibbons GW. Grafix®, a cryopreserved placental membrane, for the treatment of chronic/stalled wounds. Advances in Wound Care, 2015 - PMID: 26339532	Case reports were not a study design of interest (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	D. Sinus Tracts and Fistulas: Rectovaginal Fistula Taylor JP and Gearhart S, The use of viable cryopreserved placental tissue in the management of a chronic rectovaginal fistula, Ann R Coll Surg Engl. 2017 - PMID: 29046080	Chronic rectovaginal fistulas are out of scope for the report.
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Sinus Tracts and Fistulas: Enterocutaneous Fistula Nichols F and Overly A. Novel approach for enterocutaneous fistula treatment with the use of viable cryopreserved placental membrane, Case Rep Surg. 2016 - PMID: 27847669	Enterocutaneous fistulas are out of scope for the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Sinus Tracts and Fistulas: Refractory cutaneous sinus tract Johnson EL, Michael GM, Tamire YG. Placental membranes for management of refractory cutaneous sinus tracts of surgical origin: a pilot study, J Am Coll Clin Wound Spec. 2017 - PMID: 30276122	Surgical wounds are out of scope for the report.
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Summary of Studies: List of Ongoing Studies, and Detailed Study Design Venous Ulcers Study to Evaluate Safety and Efficacy of GrafixPL for the Treatment of Venous Leg Ulcers: ClinicalTrials.gov ID: NCT03629236	Information on ClinicalTrials.gov trial number NCT03629236 will be added to Guiding Question 5.
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Chronic wounds of diff. etiologies (DFUs, VLUs, Pus, AUs, surgical wounds, gangrenous wounds, hematomas) Study to Evaluate Clinical Equivalency between Lyopreserved and Cryopreserved Placental Membranes Containing Viable Cells – ClinicalTrials.gov ID: N/A	We are unable to include this study as the standard of care was not described. Reporting of similar standard of care used in conjunction with the skin substitute intervention is also an inclusion criteria (see Methods).
Public Reviewer #8 Lou Savant Osiris Therapeutics, Inc.	Results	Complex wound Study To Evaluate Viable Cryopreserved Umbilical Tissue (Stravix) for Complex Wounds, Failed Previous Flaps, or Autografts - ClinicalTrials.gov ID: N/A	We are unable to include information on this clinical trial since Stravix is intended for surgical procedures and was not included in our list of skin substitute products. Stravix is similar to Grafix which is intended for chronic wounds.
Public Reviewer #8 Lou Savant	Results	Urinary fistulas Efficacy of Amniotic Membranes in Complex Genitourinary Reconstruction - ClinicalTrials.gov ID: NCT03685955	Urinary fistulas are out of scope for this report (see Methods).

Commentator & Affiliation	Section	Comment	Response
Osiris Therapeutics, Inc.			
Public Reviewer #9 Gunnar Johannsson Kerecis Limited	Results	Kerecis LLC is a medical device company that provides a medical device from intact fish skin. Recent research, some sponsored by the company and other indipendent investigator initiated, have shown that the intact fish skin graft improves tissue regeneration and healing rates for full thickness wounds, including venous and diabetic foot ulcers. With the announcement of the extended deadline of the AHRQ review and search for real world data we have reached out to our research partners and users for papers that they have in publication or under review. Attached are three manuscripts that are in review for publication that focus on the treatment of diabetic foot ulcers, cost benefit analysis of fish skin versus standard of care and comparative trial of slow-healing donor wounds in cancer patients versus standard of care. Furthermore there are attached previously published studies in peer reviewed journals on the use of the fish skin graft in real world setting. We hope that the evidence provided helps your technological review of cell and tissue based products and that intact fish skin will be included in further analysis.	Thank you for your submission. We provide responses below regarding the seven submissions including three manuscripts, a cost-benefit analysis and a comparative trial on slow-healing donor wounds.
Public Reviewer #9 Gunnar Johannsson Kerecis Limited	Results	The Cost Effectiveness Of Intact Fish Skin Treatment Of Diabetic Foot Ulcers Compared To SOC	We are not including publications centered on cost data in the current report, and the study needs to be peer-reviewed to meet our study inclusion criteria (see Methods).
Public Reviewer #9 Gunnar Johannsson Kerecis Limited	Results	Preliminary study: interest of the acellular fish skin matrix on thin-skin graft donor sites in patients treated for head and neck cancer with reconstructive surgery by radial forearm free flap.	The study needs to be peer-reviewed and a chronic wound of interest to meet our study inclusion criteria (see Methods).
Public Reviewer #9	Results	Alam K, Jeffery SLA. Acellular Fish Skin Grafts for Management of Split Thickness Donor Sites and Partial Thickness Burns: A Case Series. Mil	Burns are not a wound of interest for the report (see Methods).

Commentator & Affiliation	Section	Comment	Response
Gunnar Johannsson Kerecis Limited		Med. 2019 Mar 1;184(Suppl 1):16-20. Also available: http://dx.doi.org/10.1093/milmed/usy280.	
Public Reviewer #9 Gunnar Johannsson Kerecis Limited	Results	Dorweiler B, Trinh T, Dünschede F, Vahl CF, Debus ES, Storck M, Diener H. Marine Omega-3 Wound for the Treatment of Complicated Wounds: A Multi-Center Report. Gefässchirurgie, 2017 Dec 1;22(8):558–67.	The Dorweiler study did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #9 Gunnar Johannsson Kerecis Limited	Results	Acellular Fish Skin Graft for Diabetic Lower Extremity Wound Healing- A Retrospective Study of 58 Ulcerations and A Literature Review	Studies need to be peer-reviewed and prospective study designs to meet our study inclusion criteria (see Methods).
Public Reviewer #9 Gunnar Johannsson Kerecis Limited	Results	Fagerdahl AM. Wound Treatment with Cod Skin – An Exciting Development for the Future. Sårmagasinet, 2017 Jun;(3):34-36.	Fagerdahl 2017 did not meet our study inclusion criteria due to the single-arm study design (see Methods).
Public Reviewer #9 Gunnar Johannsson Kerecis Limited	Results	Yang CK, Polanco TO, Lantis JC. A Prospective, Postmarket, Compassionate Clinical Evaluation of a Novel Acellular Fish-skin Graft Which Contains Omega-3 Fatty Acids for the Closure of Hard-to-heal Lower Extremity Chronic Ulcers. Wounds. 2016 Apr;28(4):112-8.	The Yang 2016 study did not meet our study inclusion criteria due to the single-arm study design (see Methods).