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Project Name: Skin Substitutes for Treating Chronic Wounds
Project ID: HCPR0610

Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	AHRQ has included advanced methods of wound treatment in their definition of usual care including growth factor therapy, surgical autologous skin grafts, skin substitutes, and other treatments. These are considered advanced treatments and not part of standard usual care. They, like skin substitutes, are utilized after standard care fails to progress the healing of a chronic wound.	Key Question 2 has been clarified as follows: "For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures…"
1	General	Some of these advanced modalities are not utilized throughout the entire healing process, but have specific functions during the course of healing, and therefore would not be a suitable and appropriate as a comparator for a skin substitute trial to evaluate clinical effectiveness.	We agree with the reviewer's comments.
1	Methods	While randomized controlled trials (RCTs) represent the highest level of evidence regarding individual studies, such studies only provide evidence for efficacy in relatively healthy patients and may exclude vulnerable populations and in particular those with wounds that are more severe in terms of their characteristics.	Patients with comorbidities can be enrolled in RCTs, even though it is often the case that RCTs exclude sicker patients and patients with severe conditions. We have stressed the limitations of the applicability of the evidence to the typical patient with multiple comorbid conditions, medications, and poorer health status than the patients represented in the included studies.
1	Methods	This report examined the use of skin substitutes for the treatment of chronic wound. The evaluation indicated that studies comparing the efficacy of skin substitutes to alternative wound care approaches are limited in number and have a high risk of bias, apply mainly to generally health patients, and examine only a small portion of the skin substitute products available in the U.S.	We have revised our assessment of the risk of bias of individual studies and emphasized issues with applicability of the evidence to typical patients.
1	Methods	This report demonstrates a literature selection biased. In addition to RCTs, other literature such as abstracts, reports, meta-analysis and foreign publications should also be reviewed. Observational studies should be included in this report in addition to the RCTs. Observational studies may provide evidence of efficacy and effectiveness in 'real world' pragmatic setting, in which RC are not conducted. Given the realty that there are limited RCT's available in the field of wound care medicine, we suggest that the authors should also review available observational studies that include risk, benefit, efficacy, effectiveness and cost assessment.	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. We do not disagree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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1	Methods	Also, the category of bias risk level should be more intensely scrutinized. The authors categorized the risk-of-bias for each outcome as, 'low',' medium', or 'high.' Among the list of 10 questions assessing the bias of RCT, question #3 is "was the wound assessor blinded to the patients' treatment group?" This report determines any RCT conducted without an assessment by a blinded assessor as a high bias risk and therefore is relegated to the 'high risk' category. Upon actual review of these RCT's one will find that wound endpoints were actually determined by computerized planimetry of wound tracing (usually done by wound imagine lab as a third party). Therefore, it is this authors opinion that among the 9 clinic endpoints (percentage of wounds completely closed/healed wound, time to wound closure, wound recurrence, wound infection, need for amputation, need for hospitalization, return baseline activities of daily living and function, pain reduction and exudates /odor), at least wound reduction, wound closure, time to wound closure should not be significantly affected without a blinded assessor. In other words, the utilization of a blinded assessor would not significantly alter primary endpoints of these studies. With that said, some clinical endpoints, i.e. return baseline activities of daily living and function, pain reduction and exudates /odor reduction, are more subjective and open to more bias, but to my knowledge this has not been specifically investigated. In short, the lack of a blinded assessor (as seen in Question 3#) should not determine as study to be at high risk of bias.	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing.

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Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	Methods	It appears that the reviewers chose a non-validated approach to assessing bias assessment.	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text describing why these questions are used in a risk of bias assessment has been added to the report.
1	Methods	While some of the elements listed are certainly crucial, definitions of yes, no, or not reported are missing.	Definitions of Yes, No, and Not Reported have been added to the report.
1	Methods	It is also not clear as to the criteria used to judge randomization methods, concealment of treatment group allocation or how they arrived at a consensus. Grading is one of the most notable ways for evidence to be evaluated in terms of the quality of evidence across studies and therefore the omission will affect the value of the overall assessment.	The criteria for judging randomization methods and for concealment of treatment allocation are described under the section Explanation of Quality Assessment Questions. Individual studies are evaluated for these and other aspects of risk of bias on an outcome-by-outcome basis. Grading the strength of evidence is a judgment about all studies for a given population, intervention, comparison and outcome, considering the risk of bias within individual studies, the consistency of findings across studies, the precision and magnitude of the effect, and the directness of the evidence for the question at hand. We have added text to explain this.
2	General	Suggest use of term “masking” rather than “blinding”	“Blinding” is the standard term used in EPC reports for the design feature we are addressing.

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Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
2	General	Suggest use of term "effectiveness" rather than "efficacy" as medical devices are regulated based on effectiveness and it is unclear how to best determine true efficacy for many medical devices	We appreciate the reviewer's comment, but are using the term "efficacy" to reflect studies conducted under (relatively) "ideal" conditions, rather than effectiveness studies, which include a broader range of patients, settings, and treating professionals. We do not mean to imply any regulatory aspect in our use of these terms.
2	General	Suggest re-reading document for grammer/spelling – several typos e.g. misplaced "and" on page 5, "over stating" rather than combined word on page 46.	The final document will be reviewed by a medical copy editor.
2	General	Highly suggest including non-RCTs – given the state of this literature and the fact that the RCTs have high potential for bias, it is reasonable to include observational and non-randomized clinical trials	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. We do not disagree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.
2	Executive Summary-1	3rd paragraph of background: "Skin substitutes are now more important in the treatment of chronic wounds because of the vastly larger number of patients with chronic wounds compared to burn wounds." – this sentence implies that this is the only reason for greater importance in this population. Is that true?	We changed the sentence as follows: "However, skin substitutes are now primarily used in treating chronic wounds rather than for burns, in part because chronic wounds are far more common than burn wounds."
2	Executive Summary-1	4th para – "not likely to be provided by any current skin substitute" – suggest providing rationale for this statement with reference	This sentence and the text that follows has been rewritten and references added to the paragraph: The skin substitutes included in this report contain various combinations of cellular and acellular components intended to stimulate the host to regenerate lost tissue and replace the wound with functional skin. Presumably, successful healing during management with these products would also require maintenance of a moist wound environment and other procedures thought to promote healing. These include removal of exudate and necrotic tissue, infection control, nutritional support, pressure avoidance (e.g., off-loading for diabetic foot ulcers and pressure ulcers), and edema control (e.g., compression for venous leg ulcers).
2	Executive Summary-1	4th para – "however" does not follow logically – may need another sentence?	This paragraph has been rewritten.
2	Executive Summary-2	3rd full para – HDE is required to demonstrate "probable benefit" not effectiveness	This has been corrected.
2	Executive Summary-3	#1 – suggest including links to guidance documents	Links to PMA, 510(k), and PHS 361[21 CFR 1270 & 1271] regulations are contained in the references.

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Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
2	Executive Summary-5	1st para – if determination is made to only include RCT, rationale is needed	We have added an explanation of the reasons for only including RCTs in this report. We do not disagree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.
2	Executive Summary-6	Suggest listing the specific reasons for exclusion and number for each reason within Fig 2 or in the bullets	Tables 19 and 20 contain the explanations for excluding publications that were considered for inclusion.
2	Executive Summary-7/8	Product codes are listed – are these the only devices in those product codes or are these devices only a subset of the products within these codes? (i.e. would someone be able to capture all of the medical device reporting data from the public MAUDE database using the codes provided and would they only get information for the types of devices in this evaluation?)	These are not all of the devices within these codes. To generate our list of skin substitute products we started with the products listed under CMS codes Q4101 to Q4122, located the FDA product codes for these products, and looked for similar products within these FDA codes to generate a list of products. We included only those products indicated for chronic wounds and therefore not all of the products within an FDA product code would have been included in the report.
2	Executive Summary-14	2nd para – "high risk of bias primarily because the studies did not report whether the wound assessor was blinded to patient treatment" – suggest explaining why this is important within the exec summ	This sentence was removed from the Executive Summary. We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. Assessor blinding is still part of the risk of bias assessment tool.
2	Executive Summary-14	3rd para – "Results from one skin substitute cannot be extrapolated to other skin substitutes nor can results from studies of diabetic foot ulcers be extrapolated to venous leg ulcers" – suggest explaining why this is true within the exec sum	Text has been added to the Executive Summary regarding differences in wound pathophysiology.
2	Introduction Background Page 3	Need ref for "Vascular leg ulcers are the result of chronic venous insufficiency (venous leg ulcers, 80% to 95% of vascular ulcers), or arterial insufficiency (arterial leg ulcers, 5% to 10%). Between 10% and 35% of the U.S. population has some type of venous disease, and lower extremity skin ulcers are reported in 1% to 22% of individuals over age 60."	A reference has been added: Sieggreen MY, Kline RA. Recognizing and managing venous leg ulcers. Adv Skin Wound Care 2004 Jul-Aug;17(6):302-11; quiz 312-3. PMID: 15289718
2	Introduction Background Page 5	3rd para – suggest "biomaterial and cellular" so that both terms are singular	This paragraph has been revised and the suggested wording has been added.

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Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
2	Introduction Background Page 6	SOC may not represent the FDA cleared indications. Suggest stating this.	We are unclear as to why this statement is needed or what it refers to. No change has been made.
2	Introduction Background Page 9	Under "Premarket Approval" – what does "most regulated devices" mean?	The sentence was not necessary to the explanation of Class III devices and was removed.
2	Introduction Background Page 10	1st para – "PMAs are typically reviewed by an FDA advisory committee" – suggest 'sometimes' rather than typically or reference statement.	The following reference was used for this statement: PMA approvals. [internet]. Rockville (MD): U.S. Food and Drug Administration; 2009 Jun 18 [accessed 2011 Nov 30]. [3 p]. Available: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm.
2	Introduction Background Page 10	3rd para – "Unlike PMA, which requires demonstration of reasonable safety and effectiveness, 510(k) requires demonstration of substantial equivalence." – Suggest instead … 510(k) confers reasonable assurance of safety and effectiveness via demonstration of substantial equivalence to a legally marketed device that does not require premarket approval. – all medical devices must demonstrate reasonable safety and effectiveness; it is done differently by class.	The sentence was changed according to the suggestion.
2	Introduction Background Page 10	3rd para – "FDA or an order reclassifying the device into class I or an exempt class II device." – suggest including the term "de novo"	We are uncertain as to the reason for this addition. No change has been made.
2	Introduction Background Page 11	"To obtain approval for an HUD, a humanitarian device exemption (HDE) application is submitted to FDA." – statement is incorrect – must have a HUD designation in order to submit an HDE application	These two paragraphs are direct quotes from FDA documents describing HUD and HDE. No change has been made.
2	Introduction Background Page 16	Suggest including Web of Science within search	Thank you for this suggestion. We believe that our searches are complete.
2	Introduction Background Page 16	Suggest including dissertations and theses within search (e.g. through ProQuest Dissertations & Theses)	These items may be picked up in our gray literature searches but we do not routinely seek or include them. If one were brought to our attention by a reviewer, we would evaluate it for inclusion.
2	Introduction Background Page 17	Suggest listing the specific reasons for exclusion and number for each reason within Fig 4 or in the bullets	Tables 19 and 20 contain the explanations for excluding publications.

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Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
2	Introduction Background Page 17	Was quality assessment instrument validated?	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text describing why these questions are used in a risk of bias assessment has been added to the report.
2	Introduction Background Page 17	Was the assessment conducted by multiple people? Did they agree? (Repeatability and kappa measure would be useful in determining if this information was easily noted from the studies by multiple people.)	The assessment was conducted by one analyst and reviewed for accuracy by the lead analyst.
2	Introduction Background Page 18	#2 – concealment from the patient?	Concealment of treatment group allocation refers to the person allocating patients to treatment groups.
2	Introduction Background Page 18	#5 – how was 15% chosen?	We have selected 15% as the threshold when difference in characteristics between treatment groups may indicate a potential for bias. The choice of "15%" was made based on the consensus opinion of systematic review experts.
2	Introduction Background Page 18	#10 – what if partial funding?	Partial funding would have been an indication of potential for bias. However we have removed this question from our quality assessment. Instead, we approached the question of manufacturer funding and bias by looking at selective outcome reporting in manufacturer-sponsored studies.

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Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
2	Introduction Background Page 18	What about severity of answering "no" to a question … e.g. was a 51% response rate for question #8 the same as an 84% response rate?	We use a threshold approach in answering the questions for the sake of consistency, but severity can be considered in the overall judgment about risk of bias.
2	Introduction Background Page 19	High risk – did the "more than 5" include questions #3 and #4	Yes, in the draft report. We revised the categorization in the final report, having decided that the question "Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?" was the most critical.
2	Introduction Background Page 19	Suggest providing rationale for why questions #3 and #4 were determined to be more important than others	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that assessor blinding (question 3 in the draft) was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. We revised the categorization in the final report, having decided that a "No" or "not reported" answer to the question "Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?" was the most critical for considering a study to be at high risk-of-bias.
2	Introduction Background Page 19	1st para – "Appropriate randomization is typically accomplished" – suggest rewording to remove "typically"	"Typically" has been removed.
2	Introduction Background Page 19	6th para – "Proper randomization of enrolled patients should insure that these parameters are evenly distributed across study arms. Assessment Questions 5, 6, and 7 are tests of the randomization process as well as insuring that the potential risks represented in these questions are not present in high-quality studies." – these questions test design and utilization of devices not ongoing conduct of study and outcomes – suggest providing rationale for why outcomes not weighted more heavily in assessment questions when the key questions being studied are based on outcomes	The potential for bias for each outcome is assessed separately with the risk of bias (quality assessment) tool. For this report, complete wound healing was considered the most important outcome. In our final report we have revised our assessment of the risk of bias with a focus on this outcome.
2	Introduction Background Page 19	"Assessment Questions 8 and 9 test whether patient attrition could alter the patient characteristics sufficiently enough to bias study results." – these questions assess loss of randomization – since many of the RCTs did not score "yes" on these questions, this provides rationale for including non-RCT studies in the assessment	We do not disagree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
2	Introduction Background Page 20	"Thus the evidence is assessed for its ability to reflect "real world" situations." – given this statement, it is unclear why observational and non-randomized clinical studies were excluded from the assessment	We agree that additional information on "real world" settings and patients might be found in observational studies; however, the scope of this report was more limited.
2	Results Page 40	Last paragraph - "Eight studies (three for Apligraf and four for Dermagraft)" – 3+4 does not equal 8… suggest re-counting studies	Because of study additions there are now 8 studies (4 for Apligraf and 4 for Dermagraft)
2	Results Page 46	3rd para – "Results from one skin substitute cannot be extrapolated to other skin substitutes" – please provide rationale for this statement	Rationale has been added.
2	Results Page 48	"Publication bias, the failure to publish studies that do not support the efficacy of a new product, may be a possible explanation for the absence of published pressure ulcer studies. Studies may have been conducted but because of poor results compared to usual care, like the Payne et al. study, the study may have been terminated and the results never published." – was any evidence of publication bias noted from gray literature or clinicaltrials.gov?	We found no studies examining the use of skin substitutes to treat pressure ulcers in clinicaltrials.gov. We did not identify unpublished studies of the other chronic wound types, but recognize that they may exist. The limited number of studies of a specific product in a specific wound type meant that any attempt at statistical detection of publication bias would be unreliable.
2	Discussion and Conclusion Page 50	3rd para – "Only generally healthy patients were enrolled in studies" – suggest stating how this differs from the expected patient population	This text has been added: Commonly mentioned reasons for exclusion included the following: infected wounds; use of medications that could impede wound healing; clinically significant medical conditions that could impair wound healing; renal, hepatic, neurologic, or immunologic diseases; significant peripheral vascular disease; malnutrition; and uncontrolled diabetes.
2	Discussion and Conclusion Page 50	4th para – "The results of the available studies cannot be extended to other skin substitute products especially since results from studies of diabetic foot ulcers do not extrapolate to studies of venous leg ulcers. Therefore, no clinical efficacy data are available for the large majority of the skin substitute products identified in this report. The studies that are available are also not generalizable to the broader patient population that is not as healthy as the patients in these studies." - suggest explaining why these extrapolations cannot be made	An explanation has been added: The results of the available studies cannot be extended to other skin substitute products due to differences in active components in the various products. In addition, the results from studies of diabetic foot ulcers do not extrapolate to studies of venous leg ulcers because of differences in pathophysiology and etiology.
2	Appendices Page 65	Which database in the Center for Biologics Evaluation and Research? Suggest including links to each of the regulatory databases.	Our Information Specialist browsed the CBER site (http://www.fda.gov/BiologicsBloodVaccines/default.htm) for information on tissue regulation and lists of registered tissue establishments.

[1] Peer reviewers are not listed in alphabetical order.
[2] If listed, page number, line number, or section refers to the draft report.
[3] If listed, page number, line number, or section refers to the final report.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	General	The Alliance of Wound Care Stakeholders ("Alliance") is submitting the following comments in response to the ECRI draft report entitled, "Skin Substitutes for Treating Chronic Wounds." The Alliance is a 501 (c)(6) multidisciplinary trade association representing 19 physician and clinical organizations whose mission is to promote quality care and patient access to wound care products and services. These comments were written with the advice of Alliance organizations that not only possess expert knowledge in complex acute and chronic wounds, but also in wound care research. A list of our members can be found on www.woundcarestakeholders.org. While we appreciate the opportunity to offer our comments, we are very disappointed in the short amount of time (a little over two weeks) that the AHRQ allowed for a deadline to respond to this very dense document that is so critical to wound care stakeholders. It is our understanding that the Technology Assessment Program provides 2 weeks for public review of its draft reports. However, releasing the report on December 28 and then extending the due date to January 17 includes two holidays (New Years and Martin Luther King's birthday) along with many wound care professionals taking vacations during this time does not constitute a meaningful public comment period. The Alliance has treated writing our comments to this draft very seriously, and has convened many conference calls, conversations and emails to ensure that all stakeholders' input will be included. Since we still do not believe there is enough time to give this important document the careful consideration that it needs, we are submitting these comments, but intend to supplement our filing as we receive more information from our members.	No response needed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	General	This section will be a summary of the issues that we will be addressing later in our comments 1. We would like to commend ECRI for this very detailed analysis since it is very difficult to perform. ECRI has articulated in the report many of the issues the wound care clinical community has been struggled with in attempting to conduct effective and reasonable clinical evaluations for new treatment modalities. RCT studies, as noted by ECRI, do limit the population that can be included in the studies because of required medical exclusion criteria (i.e. uncontrolled diabetes, poor vascularization, immunosuppressive drugs, end stage renal disease, infection) or required restrictions by FDA labeling. These exclusions can destabilize of the patient or would result in poor tissue 'take' and the inappropriate use of a cellular or engineered tissue. Studies are therefore conducted to remove as many of the 'factors' which can artificially impact the outcome and mask the 'effect' of the study tissue, while at the same time have inclusin criteria that encourages wounds that have not responded to standard usual treatment to be evaluated. As ECRI noted, this can result in a more healthy population in the RCT studies. Wound care experts have therefore conducted evidence-based studies to allowed for more diverse groups of patients with longer duration wounds and more complex or larger wounds to understand effectiveness in a more 'real world' application. Unfortunately ECRI has not identified these studies in their review or included them in their analysis. This evidence-based information is valuable data that supports the use of cellular and engineered tissues. We would like to urge ECRI to include other than RCT information in this report and in fact	No response needed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			it should apply the same tool ((risk of bias, consistency, directness and precision) to give a more actual picture of clinical evidence available for cellular and engineered tissue alternatives (previously called skin substitutes as noted below) 2. The Alliance has many serious concerns with this draft – from the products included in the draft to the terminology used to the methodology utilized which led to faulty conclusions. We believe that there was good intent in writing this, but wound care is very complex and different from burns and other diseases. Many of the Alliance physicians and clinicians who are wound care researchers and experts in wound care questioned if those who wrote the draft had a good understanding of wound care since there were many flaws in this draft. That said, the Alliance would be pleased to meet with ECRI, AHRQ as well as CMS staffs to discuss these issues in detail. 3. The Alliance has concerns with the nomenclature "skin substitutes" used throughout this document and in the title of this technology assessment in reference to the products/materials being considered. The term "skin substitutes" is not appropriate for these items and the term "dressing" does not work either since they have different connotations for both FDA and CMS. Therefore, if the terms "skin substitutes" do not really describe these items, and "biologic dressings" have negative connotations for coverage in the eyes of the CMS contractors, then we would propose the term for this document "cellular and engineered tissue alternatives." Alternative meant that these tissues are not substitutes but are different in function and structure. We submit that this terminology would include all the items correctly described in the	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			document.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	ES	The Alliance has concerns with the following issues: **1.Semantics and definitions used in this document to define "dressing" and "skin substitutes" by the FDA may have different meanings and uses by CMS and its contractors. This leads to confusion for all stakeholders. There should be consistent terminology for these items used by all of the regulatory agencies and stakeholders.** The Alliance has concerns with the nomenclature "skin substitutes" used throughout this document and in the title of this technology assessment in reference to the products/materials being considered. The term "skin substitutes" is not appropriate for these items and the term "dressing" does not work either since they have different connotations for both FDA and CMS. For example: • In Tables 2-4, one notes that under FDA's product code—the products for chronic wounds are ALL referred to as "dressing" no matter what the materials are or the process regulated under the FDA. Thus, one might therefore conclude that all the regulatory agencies could adopt this term. • In fact, in the ECRI draft, page ES-1 in the fourth paragraph under "Background" states that "However, for chronic wounds a skin substitute should be able to provide a temporary biologic dressing that stimulates the host to regenerate lost tissue and replace the wound with functional skin." One could conclude that these materials could then be called "biologic dressings". • However, if one looks at the CMS contractors, the A/B MACs', local coverage determinations for these products, one will not find coverage in many circumstances for those products which are "biological dressings."	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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. The term "biological dressing" was removed from the report.

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			• Moreover, there is additional confusion with the term "dressing" used in the Medicare Part B area by the DMEMAC coverage policies which include such products as hydrogels and hydrocolloids and name them as "surgical dressings" designated as "A codes". • The term "skin substitute" may not be a correct term to use anymore. It is not used by the FDA in its classification as demonstrated by the tables 2-4. CMS' division that addresses HCPCS coding for these products also abandoned this term effective 2010 when a manufacturer requested that CMS delete this term since it was an incorrect descriptor. The manufacturer stated at the 2010 CMS HCPCS Public Meeting that that this language was wrong since allografts are mislabeled as "skin substitutes." Allografts differ in structure, tissue origin, and in some cases differ from cellular and engineered tissue in terms of how they are approved by the FDA (human skin for transplantation not devices). CMS thus changed the descriptors and eliminated the term "skin substitutes" from all of its Q codes for these items. • If one uses a medical dictionary to also look at the definitions for skin substitutes—one would see that it states it as a wound covering—which does not fare well to obtain coding and coverage under CMS; likewise, the biologic dressing has it being used for burns rather than chronic wounds. o Farlex's online medical dictionary confirms the differences of using products to treat a wound versus to protect a wound (as a wound cover dressings). o Skin Substitute: "a material used to cover wounds and burns where extensive areas of skin are missing, *to promote healing.*	

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			o Biologic Dressing: "one used in treatment of a burn or other large denuded area of skin to *prevent infection and fluid loss.* See http://medicaldictionary.thefreedictionary.com/skin+substitute (Accessed November 17, 2011) uses Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition. © 2003 by Saunders, an imprint of Elsevier, Inc.) **Therefore, if the terms "skin substitutes" do not really describe these items, and "biologic dressings" have negative connotations for coverage in the eyes of the CMS contractors, then we would propose the term for this document "cellular and engineered tissue alternatives." Alternative meant that these tissues are not substitutes but are different in function and structure. We believe that this terminology would include all the items correctly described in the document.**	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	General	**2. Grouping of "cellular and engineered tissue alternatives"** This draft attempts to create a common grouping for these wound care products. Unfortunately, as is true for many devices, using FDA classifications do not always help. The groupings are not "like" based on mode of action of the products, material components, or how they are clinically used. If ECRI's goal is to create a generalizable assessment of the products then the authors must understand wound care better by knowing how these products are used and not how the FDA chooses to categorize them. Many of the products in the listing would not be used for all wounds and several are very rarely used. Finally, based on FDA practices many of these products did not need to provide evidence of comparative efficacy to gain approval. Thus, they do not have this level of evidence.	We created groupings specific for this report only to address the goals of this report. The primary purpose of this report was to examine the regulatory pathways required for a broad range of wound care products that are commonly referred to as "skin substitutes." The second reason for writing this report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds.

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods: Key Question 1	**3. Evidence for Skin Substitutes** Question #1 of this paper is devoted to how the FDA regulates cellular and tissue engineer alternatives. The Alliance has the following concerns about this section: • Why was this question chosen? • One of the statements in the "Background" is not correct: o "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process." The regulatory process is risk-based, not product origin-based. For example, PMA devices are products that the FDA deemed as a Class III device (devices that "support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.")Therefore, these devices are deemed Class III because they "present a potential, unreasonable risk of illness or injury." • In the Methods of the Review section, ECRI states that as part of the review, it developed Key Questions to answer, which included "What are the U.S. Food and Drug Administration (FDA) regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361[21CFR 1270 & 1271]?" However, it is unclear why this question is important for the evaluation of device *efficacy*, as FDA classifications also don't indicate whether a	CMS requested a description of regulatory information provided in FDA documents relevant to treatment of chronic wounds. Changes to the text suggested by the FDA reviewer have addressed the issues raised regarding the description of the regulatory processes.

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			device is an *effective* treatment modality. The executive summary only comments on the 3-letter classifications that are used to designate the different categories of products and specific terminology that is used in the FDA indication statement. • Moreover, we have concerns about the emphasis that ECRI places on this specific terminology that is used in the FDA indication statements ("treatment" or "management") since the way that they are used by the FDA to delineate the products may be totally different than how they would be used in its sister agency, CMS. Both agencies have their separate and distinct regulatory processes and their own definitions and terminology. To further illustrate this point, when determining whether a product is a biological the FDA follows its own guidance – as ECRI has described earlier. CMS follows the Social Security Act (SSA) definition of drugs and biologicals which is: *t)(1) The term "drugs" and the term "biologicals", except for purposes of subsection (m)(5) and paragraph (2), include only such drugs (including contrast agents) and biologicals, respectively, as are included (or approved for inclusion) in the United States Pharmacopoeia, the National Formulary, or the United States Homeopathic Pharmacopoeia, or in New Drugs or Accepted Dental Remedies (except for any drugs and biologicals unfavorably evaluated therein), or as are approved by the pharmacy and drug therapeutics committee (or equivalent committee) of the medical staff of the hospital furnishing such drugs and biologicals for use in such hospital.* Since CMS commissioned this study there may be a linkage of the two agencies on this issue, which	

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			would be inappropriate. For instance, CMS' goals as stated in this report are: o To determine the extent of available clinical evidence in support of the efficacy of the various cellular and engineered tissue alternatives products regulated by the FDA and to determine the strength of this evidence base. (page 50) o To facilitate CMS's evaluation of HCPCS coding for skin substitutes and information obtained by CMS will be used for consideration of coding changes. (page 12) We would not want CMS to misinterpret the intent of FDA's classification and terminology of "management" and "treatment" when these same cellular and tissue engineered products obtain Medicare coverage, coding and payment.	

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Results: Key Question 1	**4. <u>ECRI should only list of "cellular and engineered tissue alternatives" in this draft document</u>** The list of cellular and engineered tissue alternative products included in the report are not all marketed or indicated for use in chronic wounds, as noted by the researchers, and would not have clinical data in the literature for chronic wounds. In addition, some are used for burns and, as stated in this report, are not supposed to be in it. Some are also "surgical dressings" and should be removed. Therefore, the following should be removed from this draft report and we would recommend that in ECRI's final report that only those are cellular and engineered tissue alternatives be included. • AlloDerm Regenerative Tissue Matrix, Allopatch HD, Flex HD, Matrix HD, Puros Dermis [dental implant tissue], Repliform • Epicel, Transcyte • E-Z Derm, InteXen, Permacol, Strattice , Tissuemend • BioBrane -biosynthetic dressing constructed of a silicone film with a nylon fabric w/ trifilament thread to which collagen is chemically bound used for burns • Hyalomatrix - non-woven pad dressing made a benzyl ester of hyaluronic acid, and a semi permeable silicone membrane • Laserskin & Jaloskin -transparent film dressing composed of a benzyl ester of hyaluronic acid]: benzyl esters of hyaluronic acid • LyoFoam Extra "C"- polyurethane foam dressing • Suprathel- absorbable, synthetic wound dressing of polyalactic acid for donor sites and burns	All products not indicated for chronic wounds have been removed.

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Background: Skin Substitutes	**5. Specific comments on Background** 1- "This report specifically examined the use of skin substitutes for the treatment of the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (includes venous ulcers and arterial ulcers). Treatment of burn wounds with skin substitutes is outside the scope of this report." *This statement is incorrect since Epicel and Transcyte have been cited. We believe it should be restricted to chronic wounds as stated above.* 2- "Skin substitutes were developed as an alternative to skin grafts especially for burn patients." *Good statement, we now know these skin substitutes are "just" biological dressing. Therefore they should not be called skin substitutes.* 3- "The ideal skin substitute should adhere to the wound bed and provide the physiological and mechanical function of normal skin while not being rejected by the host. This ideal situation is not likely to be provided by any current skin substitute." *This is not completely true, Steven Boyce has worked on a skin replacement for burns with autologous cells and biomateriaux. See for example: Boyce ST, Hansbrough JF. Biologic attachment, growth, and differentiation of cultured human epidermal keratinocytes on a graftable collagen and chondroitin-6-sulfate substrate. Surgery 1988;103:421-31. Boyce ST, Kagan RJ, Greenhalgh DG, et al. Cultured skin substitutes reduce requirements for harvesting of skin autograft for closure of excised, full-thickness burns. J Trauma 2006;60:821-9.*	All products not indicated for chronic wounds have been removed. The paragraph mentioning an "ideal" skin substitute has been rewritten.
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods: Key Question 2	**6. Definition of usual wound care** In its second question, ECRI asks "For patients with chronic wounds (pressure ulcers, diabetic foot ulcers or arterial ulcers) are skin substitutes more effective than	Key Question 2 has been changed to compare skin substitutes to any type of wound care as a comparison rather than trying to define a usual care for comparison. Key Question 2 has been changed to:

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			usual care (synthetic dressings, growth factors, skin grafts or other treatments used as a control) in promoting wound healing for the following outcome measures…." The Alliance disagrees with the definition of usual wound care utilized by the researchers to compare to cellular and engineered tissue alternatives treatment for chronic wounds. The usual care group that was stated is not a standard care arm but an advanced care arm and should be properly identified as such. Usual care for chronic wounds was addressed in the 2005 MedCAC meeting which the Alliance and its members had an active role. CMS had stated that usual care was defined as: debridement, cleansing, dressing, compression, antibiotics and off-loading. In *FDA's Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment,* usual care for chronic cutaneous ulcers include the following: • Removal of necrotic or infected tissue • Off-loading • Compression therapy for venous stasis ulcers • Establishment of adequate blood circulation • Maintenance of a moist wound environment • Management of wound infection • Wound cleansing • Nutritional support, including blood glucose control for subjects with diabetic ulcers • Bowel and bladder care for subjects with pressure ulcers at risk for contamination Others have stated that usual standard wound care is the removal of necrotic or nonviable tissue from the wound [debridement], management of the local wound environment [exudate control, maintenance of moist healing environment, cleaning of debris], protection from bacterial invasion, treatment of infection or gross contamination, protection of viable tissues from	For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures

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			pressure, friction and shear through offloading or pressure reduction and reduction of edema and improved venous return with sustained, graduated compression for leg ulcers. These approaches will vary throughout the course of a particular wound's cycle of healing and are not consistent from wound to wound. Hence, in the study of chronic wounds, reference to 'usual wound care' would include the use of various types of wound dressing over the course of a study as the local wound environment changes, different intervals and numbers of debridement procedures as required for a particular wound, inclusion of antibiotic therapy as needed, varying intervals for the application of compression therapy, offloading techniques, pressure reduction all the 'usual wound care approached. As indicated in your review, if a wound fails to respond within 30 days to usual 'standard' care, the clinician will then evaluate the most appropriate 'advanced approach' to facilitate wound healing. As stated above, ECRI has included advanced methods of wound treatment in their definition of usual care including growth factor therapy, surgical autologous skin grafts, skin substitutes, and other treatments. These are considered advanced treatments and *not* part of standard usual care. They, like cellular and engineered tissue, are utilized after standard care fails to progress the healing of a chronic wound. Some of these advanced modalities are not utilized throughout the entire healing process, but have specific functions during the course of healing, and therefore would not be a suitable and appropriate as a comparator for a cellular and engineered tissue trial to evaluate clinical effectiveness.	

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	ES: Table 3 and Table 5	**7. Inclusion of Studies** In ***Table 3***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. In ***Table 5***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.	The first 510(k) clearance document referring to chronic wounds for Oasis is the 2006 date. We could not locate any earlier approval date for chronic wounds. The 2000 date probably refers to the Oasis Burn Matrix but we could not locate a publicly available clearance or approval document for this device on the FDA Web site. Landsman et al., 2008 has been added to the report.
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	ES	**8. Concerns about Methodology** The executive summary addresses in its evidence and conclusion issues which we have concerns with such as the methodology—please see the Methods part of our comments to obtain this information.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Introduction/ Background:	In the ***Complementary or Competing Products*** portion of this section, the focus does not seem to be on products; instead the focus seems to be more upon factors that need to be controlled in any treatment algorithm for all wounds. In the ***Usual Care for Chronic Wounds*** portion of this section, the authors state: " 'Standard of care' (SOC) was commonly used in the studies included in this report when referring to the control group wound care or base wound care to which a skin substitute was added…Standard of care is also frequently used in presentations on manufacturer Web sites. However, as described above, usual care or standard of care is not a consistent term that describes an agreed upon set of procedures to be used when treating chronic wounds." Standard of care (SOC) is an industry vernacular that is used to describe the prescribed treatment that is most *currently* accepted to be effective, which means that this is the treatment that is most currently used. In the ***U.S. Food and Drug Administration Regulations Governing Skin Substitute Products*** portion of this section, the authors provide an expanded	The Complementary or Competing Products section heading has been removed. The paragraph was incorporated into the Usual Care section. If standard of care is *currently* accepted to be effective therapy then it should be described fully in any publication since the definition of 'standard of care' changes over time.

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			explanation of the regulatory categories; however, as above, there is no explanation as to how this relates to this review. In this discussion, statements such as, "Therefore, wound care products regulated under the PMA process will require evidence that they promote wound healing before they are approved for marketing." and "Therefore, wound care products regulated under the 510(k) process will typically require less evidence that they promote wound healing compared to products regulated under the PMA process." These statements are untrue as these FDA categories are ***risk-based*** categories, which mean that higher risk classifications (Class III devices approved through PMA) may mean that less is known about whether the product is safe. As such, there are devices that may have been cleared by the FDA without clinical data (e.g. Specturm 5000Q Electroconvulsive Therapy Device by Mecta Corporation) Additionally, the discussion of these categories is inconsistent with the Executive Summary statement: "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process." The Alliance has addressed the problems with this statement in the Executive Summary.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods	***General Comments*** This section states that the review will facilitate CMS' evaluation of HCPCS coding for skin substitutes by providing CMS with relevant studies and information for	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. The second reason

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			consideration of coding changes. We have concerns about this and would request a meeting with CMS staff to discuss this. **Methodology of the Systematic Review** The Alliance believes that the methodological approach of this review has several major flaws including: (1) selection of studies; (2) outcomes; (3) bias assessment; and (4) reporting. ***Selection of studies*** 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.[1,2] The percentage of "real world" patients excluded in such studies in wound care can be high.[2] RCTs are appropriate for establishing an effect under controlled conditions but are problematic when solely used to translate outcomes to "real-world" patients with chronic wounds because many patients do not fit the populations used in RCTs.[3] A good example of why some promising wound care products do not work well in all wound care 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"[4] or as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.[5] In other words, the	for writing this report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited. The two studies mentioned by the reviewer have been added to the report.

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			approach does not only look at 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."[6] Because the authors of this systematic review chose only to examine RCTs published in the peer-reviewed literature, much of the evidence on cellular and engineered tissue alternatives is missing, and thus the conclusions in terms of coverage of these products are therefore skewed. Furthermore, we question why the authors apparently searched the gray literature but did not report on it. Typically, Cochrane reviews look for abstracts, unpublished material, ongoing clinical trials, and so forth, so as to minimize publication bias, particularly when conducting meta-analysis, which was not done in this review. Granted, it can be very difficult to analyze such studies published as abstracts or research letters, but their inclusion is important, even if detailed analysis is not possible. Furthermore, we submit that the authors should have searched for evidence published in the peer-reviewed literature even if that evidence is not published in English. Given the extensive effort that was put into searching, we believe that the authors could have found studies that would have had English abstracts, and then decided upon their relevance and had them translated. Not doing so is another form of selection bias. We also believe that many studies should have been included in this section. The O'Donnell systematic review (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.) should have been included as should any other	

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			systematic review that the authors have dismissed merely for the fact that it is a review. As 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. Two other studies should also be included since they are "head to head" studies of two "skin substitute" products: • Dr. Adam Landsman has a study of Oasis versus Dermagraft. 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. • 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	

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods	***Outcomes*** The authors of this report chose to ignore many valuable outcomes that are linked to partial wound healing, in part because they chose to ignore observational trials, although sometimes this information is reported in RCTs. This is important because healing chronic wounds often requires many repeated, sequential, or overlapping treatments to completely heal a wound,[1,7] and this approach cannot be easily accomplished in an RCT.[8] For example, a venous leg ulcer would have to receive adequate compression, and might be treated with silver-impregnated dressings to reduce infection before receiving a cellular and tissue engineered alternative to ensure that the wound is not clinically infected . There is an increasing body of evidence that partial wound-healing outcomes, such as time to reach 50% reduction wound area, are valid and clinical useful endpoints that can be used in real world wound care patients to determine whether the wound is clinically responding to a given treatment regimen.[9-16] In ignoring these types of outcomes and focusing only on RCTs, the reviewers seem to have entirely dismissed evidence-based practice altogether.	The most important patient-oriented outcome is complete wound healing and is therefore the focus of the final report.
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods	***Bias assessment*** The Alliance is concerned of AHRQ's condemnation of the comparative efficacy studies with respect to bias. The authors should note that many of these studies were designed with respect to the FDA requirements and thus can be very difficult to conduct these studies in a blinded fashion. Additionally, we note that the reviewers chose a non-validated approach to assessing bias assessment, which does not seem to have been reported in the literature. While some of the elements listed are certainly crucial, definitions of yes, no, or not reported are missing. For example, by what criteria did the reviewers judge that a study used appropriate	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare

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			randomization methods or concealment of treatment group allocation? Second, the authors seem to have singled out wound size/duration as and number of comorbidities the only important baseline parameters, suggesting 15% as the split point. The Alliance questions how did they arrive at these specific criteria? 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. 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. Finally, there was no GRADING reported. GRADE is becoming one of the most important techniques by which the synthesis of the evidence is evaluated in terms of the quality of evidence across studies for each important outcome; which outcomes are critical to a decision; the overall evidence across these critical outcomes; the balance between benefits and harms; and the strength of recommendations.[17] Instead, the reviewers used the EPC approach, which is conceptually similar to the GRADE system of evidence rating; it requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate include dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias. Strength of evidence receives a single grade: high, moderate, low, or insufficient.[18] This would have been a reasonable approach had it been followed in a thorough fashion. Instead there are only one or two sentences in the entire 121-page report devoted to directness and consistency, and precision was entirely ignored at the expense of	Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text has been added to define "Yes," "No," and "Not Reported" in the risk of bias assessment. We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. Individual studies are evaluated for risk of bias on an outcome-by-outcome basis. Grading the strength of evidence is a judgment about all studies for a given population, intervention, comparison and outcome, taking into account the risk of bias within individual studies, the consistency of findings across studies, the precision and magnitude of the effect, and the directness of the evidence for the question at hand. We have added text to explain this. Unfortunately, there were few instances in which more than one study used the same products in comparable populations and measured the outcome of complete wound healing. We have added tables to the report to add clarity to the presentation of results and strength of evidence.

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			pages on risk of bias. We would submit that according that according to AHRQ's own procedures and criteria that this systematic review was poorly done. Consequently, its conclusions must be regarded as uncertain.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods	***Reporting*** The gold standard for reporting systematic reviews are the PRISMA guidelines. In this review, several items were missing (e.g., method of data extraction, and summary measures presented as differences in means and risk ratios). Moreover, no rationale was given for not conducting meta-analysis, as this is usually a key part of any systematic review. **References** 1. Serena T, Bates-Jensen B, Carter MJ, et al. Consensus principles for wound care research Obtained using a Delphi process. Wound Repair Regen 2011;in press. 2. 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. 3. 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. 4. Gray JA. Evidence-based Health Care: How to Make Health Policy and Management Decisions. London: Churchill Livingstone, 1997. 5. Institute of Medicine (2001). Crossing the Quality Chasm: A New Health System for the 21st Century, Washington, DC: National Academy Press. 6. Tunis SR. A clinical research strategy to support shared decision making. Health Aff (Millwood)	The PRISMA checklist is a useful tool but is not a standard component of the Technology Assessment reports for CMS program. The original scope of the report did not include quantitative analysis. Risk differences, relative risks and odds ratios are presented in the final report. The studies included in this report are extremely diverse in terms of populations, wound types, interventions and comparators. The original scope of the report did not include meta-analysis, but we have added details about studies that illustrate the reasons we did not combine many of them in a meta-analysis and have added the two meta-analyses that were performed.

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			2005;24:180-4. 7. Sussman C, Bates-Jensen B. Wound care. A collaborative practice manual for health professionals. 3rd ed. Philadelphia, Pa: Lippincott, Williams & Wilkins, 2007:500. 8. Carter MJ, Warriner RA 3rd. Evidence-based medicine in wound care: time for a new paradigm.Adv Skin Wound Care 2009;22:12-6. 9. Bolton L, McNees P, van Rijswicijk L, et al. Wound healing outcomes using standardized assessment and care in clinical practice. J Wound Ostomy Continence Nurs 2004;31:65-71. 10. Parnell LK, Ciufi B, Gokoo CF. Preliminary use of a hydrogel containing enzymes in the treatment of stage II and stage III pressure ulcers. Ostomy Wound Manage 2005;51:50-60. 11. Snyder RJ, Cardinal M, Dauphine´e DM, et al. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage 2010;56:44-50. 12. Coerpe S, Beckert S, Ku¨ per MA, et al. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single-center cohort of 704 diabetic patients. J Diabetes Complications 2009;23:49-53. 13. Sheehan P, Jones P, Caselli A, et al. 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;26:1879-82. 14. Phillips TJ, Machado F, Trout R, et al. Prognostic indicators in venous ulcers. J Am Acad Dermatol 2000;43:627-30. 15. van Rijwijk L. Full-thickness leg ulcers: patient demographics and predictors of healing.Multi-Center Leg Ulcer Study Group. J Fam Pract 1993;36:625-32.	

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			16. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatol 2000;142:960-4. 17. Carter MJ. Evidence-based medicine: an overview of key concepts. Ostomy Wound Manage 2010;56:68-85. 18. Owens DK, Lohr KN, Atkins D, et al. ECRIseries paper 5: grading the strength of a body of evidence when comparing medical interventions—agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol 2010;63:513-23.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods: Study Risk-of-Bias Assessment	***Specific Comments--List of Quality Assessment Questions and Concerns:*** **#3. Was the wound assessor blinded to the patient's treatment group?** While we appreciate the issue mention regarding blinding of the investigator as a potential source of bias, we need to point out to the research group, that when studies are conducted comparing a cellular and engineered tissue alternative or device versus standard care (moist dressings and other supporting treatments) that it is virtually impossible to blind the investigator. Unlike comparative trials of one wound dressing versus another or one device versus another, where the dressing or device is removed before the investigator evaluates the wound, a cellular and engineered tissue alternative is not 'removed'. It is incorporating into the wound bed. As soon as an investigator evaluates a wound treated with a cellular and engineered tissue alternative he/she immediately knows the wound is in the cellular and engineered tissue alternative arm of the study and therefore blinding is not relevant. Additionally, the reapplication of a cellular and engineered tissue alternative, if required, is a physician procedure and therefore the investigator would be involved and	After reviewing several comments and giving further thought to this issue, we recognized that assessor blinding is not critical for determining the outcome of complete wound healing. While we consider assessor blinding a method for reducing potential for bias, we decided that it should not be given so much weight in this assessment given our focus on complete wound healing. For the sake of consistency, we have selected 15% as the threshold when difference in characteristics between treatment groups may indicate a potential for bias. This figure is based on a consensus opinion of systematic review experts, but certainly other thresholds could be used. Assessment of risk of bias involves many judgments; by specifying a threshold, we are attempting to make them transparent. We have removed the question regarding funding from our quality assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.

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			recognize this wound is in the cellular and engineered tissue alternative arm. We are also in agreement with the authors that it is far more important to have the patient be blinded than the wound assessor. **#5 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' situation 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. As stated earlier in our comments, this factor can be adjusted for in analysis. **#6 Were the mean wound durations 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. Longer duration of a chronic wound has 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. **#9 Was there a ≤15% difference in completion rates in the study arms?** This criteria does not seem to be based on any known standard and is irrelevant. Drop out rates of >20% are important and large differentials between groups are important, too, but we don't know the critical number. **# 10. Was the study funded by an organization**	

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			other than the skin substitute manufacturer? 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. 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 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 trial 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 manufacturers that have to fund these studies in order to obtain the clinical evidence that is needed to obtain approval/clearance to market the devices. 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.	

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Results	The Alliance recognizes that by submitting our answers to AHRQ by section rather than in a full paper online, different reviewers may be reading different areas—however, since we believe we have not been given enough time to thoroughly respond in full to all of the questions, we would ask that the reviewers of this section to please read our comments in the Executive Summary since they pertain to this section also. We do have some specific comments as noted below. ***Specific Comments*** • In answering Key Question 1, the authors list several products, such as AlloDerm Regenerative Tissue Matrix, Flex HD, Puros Dermis, Repliform, InteXen, and Permacol, which are not used/ cleared for the treatment of chronic wounds. • In ***Table 8*****,** the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. • In answering Key Question 2, the authors state that their searches identified 14 RCTs that met the inclusion criteria. However, one notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers. • In ***Table 10*****,** Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.	Products not indicated for chronic wounds have been removed. Our product descriptions are taken from company Web sites or the description provided in FDA regulatory documents. We appreciate your clarifications. The first 510(k) clearance document referring to chronic wounds for Oasis is the 2006 date. We could not locate any earlier date for chronic wounds. The 2000 date probably refers to the Oasis Burn Matrix but we could not locate a clearance or approval document for this device on the FDA web site. Landsman et al., 2008 has been added to the report.

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Results: Key Question 2, Risk of Bias in the Evidence Base	***Quality of the Evidence Base*** In the ***Quality of the Evidence Base*** portion of this section, the authors state: "All four studies of Oasis were considered at high risk of bias because wound assessor blinding was not reported. Reporting of comorbidities was absent in three of the studies." It is not always possible to blind the wound assessor to wound care treatments, as the treatments often result in differences in wound appearance during the course of treatment. As such, there are objective wound evaluation techniques, such as wound dimensions and depth that are incorporated into the assessment of wounds. Additionally, there are publication limits (i.e. space constraints of the manuscript), which means that many of the unreported data fields are eliminated because they are insignificant in relation to outcome.	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. We decided that the most critical of the questions for assessing risk of bias in these studies was "Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?"
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Results: Key Question 2, Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics	***Page 44- Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics.*** *"Several important areas of study design and patient information of interest to this report were poorly reported. Prior wound treatments were not reported in any of the studies and reporting of comorbidities was sparse*. " • Chronic wounds may have been present for months up to over a year before entrance into a clinical study. Patients may have been seen by several clinicians over that time. It is virtually impossible to list all prior treatments for each subject in a wound healing study. This will vary widely across the patient population and has minimal value in determining the effect of the current treatment. Therefore it is not tracked and evaluated in chronic wound studies. • A majority of clinical studies define exclusion criteria that ensure the use of another advanced treatment, prior to enrollment in the current study, must not have occurred within a certain timeframe	Information on comorbidities, health status and prior treatments for chronic wounds would assist reviewers in assessing the comparability of populations within and across studies.

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			before entering the study. This helps eliminates the cross-over effect of other treatment(s). • Patients with chronic wounds typically have multiple medical conditions which contribute to the development of their wound. Co-morbidities are not specifically identified in chronic wound studies as a data point for analysis since only a few are directly linked to non-healing. However, medical conditions that may impede the healing process to such an extent that the patient would highly likely not respond to the study treatment are usually identified in the exclusion criteria (i.e. end stage renal disease, autoimmune compromised patient, uncontrolled diabetes, severe vascular insufficiency, etc.). The studies include these exclusion criteria to ensure patients' major health conditions are in relative control, to eliminate patient with reduced ability to respond to either the study treatment or the control.	

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Results: Key Question 2, Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics	Page 44- "*Wound duration and wound severity prior to enrolling in a study were also poorly reported. Patients were generally excluded from studies if their health was suboptimal, they were taking medication that would interfere with wound healing or their wounds were infected."* • Removing the patients on medication which interferes with wound healing is appropriate in wound healing trials, since those patients would adversely affect the outcomes for any arm of the study. Unless all patients are taking the medication, it is not appropriate to include them in the study as this will impact the data results negatively. • Removing patients with infected wounds from skin substitute clinical trials is medically appropriate since healing does not occur in the presence of infection. Many of the listed biological materials are required by the FDA labeling, to be applied only to a non-infected wound. It would be medically negligent to apply an active biological material to an infected wound knowing the tissue graft would fail.	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies.
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Results: Key Question 2, Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics	*Page 44- "Several studies also indicated they excluded patients who responded to usual care during screening periods (see studies of Apligraf, Dermagraft, and Oasis described below for details)."* Most studies in chronic wounds include a 2-3 week screening period with standard care to identify wounds that will progress to healing adequately with standard care. This is to ensure the wounds evaluated in skin substitute or other advanced treatment trials are truly non-responding 'chronic wounds'. This is essential to eliminate these patient's from the study that will heal without the need for an advanced treatment and that would not be a candidate in the 'real world' for advanced treatment.	We agree with the reviewer's comments. We added the following sentence: "This procedure insures that only patients with hard-to-heal chronic wounds are enrolled in the study."

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Discussion/ Conclusion	The Alliance recognizes that in submitting our comments to AHRQ online in the various sections rather than in one total paper, different reviewers may be reading different areas—however, since we believe we have not been given enough time to thoroughly respond in full to all of the questions, we would ask that the reviewers of this section to please read our comments in the Executive Summary since they pertain to this section also. However, we are copying below some of our responses in the Methods section since they are so relevant to the discussion and conclusions. We will first give you some our specific comments and then the information from the Methods section. While we appreciate the issue mention regarding blinding of the investigator as a potential source of bias, we need to point out to the research group, that when studies are conducted comparing a skin substitute or a device versus standard care (moist dressings and other supporting treatments) that it is virtually impossible to blind the investigator. Unlike comparative trials of one wound dressing versus another or one device versus another, where the dressing or device is removed before the investigator evaluates the wound, cellular and engineered tissue alternative in not 'removed'. It is incorporating into the wound bed. As soon as investigators evaluate a wound treated with cellular and engineered tissue alternative, they immediately know the wound is in the cellular and engineered tissue alternative arm of the study and therefore blinding is not relevant. Additionally, the reapplication of cellular and engineered tissue alternative, if required, is a physician procedure and therefore the investigator would be involved and recognize this wound is in the cellular and engineered tissue alternative arm. ***Only five of 31 products listed in the report were examined in RCTs:***	We have removed any products not indicated for chronic wounds. To generate our list of skin substitute products we started with the products listed under CMS codes Q4101 to Q4122, located the FDA product codes for these products, and looked for similar products within these FDA codes to generate a list of products. We included only those products indicated for chronic wounds and therefore not all of the products within an FDA product code would have been included in the report. Pressure ulcers are an important chronic wound and were considered for this report before the literature search was performed. The Landsman et al., 2008 study has been included.

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			• 19 products listed in the report are not indicated or labeled for clinical treatment of chronic wounds and would therefore not have been identified in chronic wound studies. 6 of the 19 are wound dressings used to cover and protect the wound and are not biological skin substitutes. These products should not be included in the analysis. ***No studies of pressure ulcers met our inclusion criteria.*** • Very few if any cellular and engineered tissue alternatives are indicated for the treatment of pressure ulcers so perhaps pressure ulcers should have not been considered in this report. ***Only one of the 14 studies compared two skin substitute products (OASIS vs. Hyaloskin):*** • This assumption is incorrect. OASIS is a bovine collagen matrix (biological skin substitute) which is surgically applied for tissue re-growth. Hyaloskin is a manufactured dressing with fibers of collage blended in the dressing center and is a cover dressing that is meant to be removed at selected time during wound management. This reference needs to be corrected. • One notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Discussion	***Only generally healthy patients were enrolled in studies.*** *The researchers noted patients with infected wounds, who used medications that could impede wound healing, had clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes were excluded.* • The exclusion criteria for wound studies for diabetic patients and those for vascular/ arterial ulcers must be consistent with the (FDA) labeling and be compliant with medical appropriateness and	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies. We have added to the text with regard to PMA regulated products included in this report: "The indications for use of these products is also more specific compared to products regulated under the 510(k) process. The wounds must be non-infected, greater than one month in duration, and not responded to conventional treatment." We have removed the question regarding funding from our

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			coverage policy criteria. All of the skin substitutes are not indicated for use on an infected wound or a wound with inadequate vascular supply to support tissue growth. Malnutrition and uncontrolled diabetes will affect healing and therefore must be corrected before a skin substitute would be medically appropriate. In almost all Medicare and private coverage policies, they include criteria for coverage which are medically appropriate. Some examples are: • Applied to wounds reasonably expected to heal and not applied to wounds demonstrating such hostile host environment that destruction of the substitute is highly likely. • Applied to wounds that are clean and free of infection. • Applied only to wound with adequate circulation/oxygenation to support tissue growth/wound healing as evidenced by physical examination with presence of acceptable peripheral pulses and/or Doppler toe signals and/or ankle–brachial index (ABI) of no less than 0.65. **Concerns regarding studies sponsored by the manufacturers are biased** • 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. One must also question – where will the studies come from if they are 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.	quality assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.

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			• Similarly, as the federal and state governments are limited in the funds that they can provide to conduct randomized controlled trial 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 manufacturers that have to fund these studies in order to obtain the clinical evidence that is needed to obtain approval/clearance to market the devices. 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.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods	**Methodology of the Systematic Review** The Alliance believes that the methodological approach of this review has several major flaws including: (1) selection of studies; (2) outcomes; (3) bias assessment; and (4) reporting. ***Selection of studies*** 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.[1,2] The percentage of "real world" patients excluded in such studies in wound care can be high.[2] RCTs are appropriate for establishing an effect under controlled conditions but are problematic when solely used to translate outcomes to "real-world" patients with chronic wounds because many patients do not fit the populations used in RCTs.[3] A good example of why some promising wound care products do not work well in all wound care 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	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. We do not disagree that additional information may be gleaned from observational studies; however, the scope of this report was more limited. The two studies mentioned by the reviewer have been added to the report.

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			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"[4] or as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.[5] In other words, the approach does not only look at 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."[6] Because the authors of this systematic review chose only to examine RCTs published in the per-reviewed literature, much of the evidence on cellular and engineered tissue alternatives is missing, and thus the conclusions in terms of coverage of these products are therefore skewed. Furthermore, we question why the authors apparently searched the gray literature but did not report on it. Typically, Cochrane reviews look for abstracts, unpublished material, ongoing clinical trials, and so forth, so as to minimize publication bias, particularly when conducting meta-analysis, which was not done in this review. Granted, it can be very difficult to analyze such studies published as abstracts or research letters, but their inclusion is important, even if detailed analysis is not possible. Furthermore, we submit that the authors should have searched for evidence published in the peer-reviewed literature even if that evidence is not published in English. Given the extensive effort that was put into searching, we believe that the authors could have found studies that would have had English abstracts, and then decided upon their	

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			relevance and had them translated. Not doing so is another form of selection bias. We also believe that many studies should have been included in this section. The O'Donnell systematic review (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.) 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 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. Two other studies should also be included since they are "head to head" studies of two "skin substitute" products: • Dr. Adam Landsman has a study of Oasis versus Dermagraft 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 • 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	

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Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods	***Outcomes*** The authors of this report chose to ignore many valuable outcomes that are linked to partial wound healing, in part because they chose to ignore observational trials, although sometimes this information is reported in RCTs. This is important because healing chronic wounds often requires many repeated, sequential, or overlapping treatments to completely heal a wound,[1,7] and this approach cannot be easily accomplished in an RCT.[8] For example, a venous leg ulcer would have to receive adequate compression, and might be treated with silver-impregnated dressings to reduce infection before receiving a cellular and tissue engineered alternative to ensure that the wound is not clinically infected . There is an increasing body of evidence that partial wound-healing outcomes, such as time to reach 50% reduction wound area, are valid and clinical useful endpoints that can be used in real world wound care patients to determine whether the wound is clinically responding to a given treatment regimen.[9-16] In ignoring these types of outcomes and focusing only on RCTs, the reviewers seem to have entirely dismissed evidence-based practice altogether.	The most important patient-oriented outcome is complete wound healing and is the focus of this report.
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	Methods	***Bias assessment*** The Alliance is concerned of AHRQ's condemnation of the comparative efficacy studies with respect to bias. The authors should note that many of these studies were designed with respect to the FDA requirements and thus can be very difficult to conduct these studies in a blinded fashion. Additionally, we note that the reviewers chose a non-validated approach to assessing bias assessment, which does not seem to have been reported in the literature. While some of the elements listed are certainly crucial, definitions of yes, no, or not reported are missing. For example, by what criteria did the	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare

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			reviewers judge that a study used appropriate randomization methods or concealment of treatment group allocation? Second, the authors seem to have singled out wound size/duration as and number of comorbidities the only important baseline parameters, suggesting 15% as the split point. The Alliance questions how did they arrive at these specific criteria? 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. 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. Finally, there was no GRADING reported. GRADE is becoming one of the most important techniques by which the synthesis of the evidence is evaluated in terms of the quality of evidence across studies for each important outcome; which outcomes are critical to a decision; the overall evidence across these critical outcomes; the balance between benefits and harms; and the strength of recommendations.[17] Instead, the reviewers used the EPC approach, which is conceptually similar to the GRADE system of evidence rating; it requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate include dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias. Strength of evidence receives a single grade: high, moderate, low, or insufficient.[18] This would have been a reasonable approach had it been followed in a thorough fashion. Instead there are only one or two sentences in the entire	Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text has been added to define "Yes," "No," and "Not Reported" in the risk of bias assessment. We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. Individual studies are evaluated for risk of bias on an outcome-by-outcome basis. Grading the strength of evidence is a judgment about all studies for a given population, intervention, comparison and outcome, taking into account the risk of bias within individual studies, the consistency of findings across studies, the precision and magnitude of the effect, and the directness of the evidence for the question at hand. We have added text to explain this. Unfortunately, there were few instances in which more than one study used the same products in comparable populations and measured the outcome of complete wound healing. We have added tables to the report to add clarity to the presentation of results and strength of evidence.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			121-page report devoted to directness and consistency, and precision was entirely ignored at the expense of pages on risk of bias. We would submit that according to AHRQ's own procedures and criteria that this systematic review was poorly done. Consequently, its conclusions must be regarded as uncertain.	
Anonymous Reviewer 1		Methods	***Reporting*** The gold standard for reporting systematic reviews are the PRISMA guidelines. In this review, several items were missing (e.g., method of data extraction, and summary measures presented as differences in means and risk ratios). Moreover, no rationale was given for not conducting meta-analysis, as this is usually a key part of any systematic review. References 1. Serena T, Bates-Jensen B, Carter MJ, et al. Consensus principles for wound care research Obtained using a Delphi process. Wound Repair Regen 2011;in press. 2. 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. 3. 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. 4. Gray JA. Evidence-based Health Care: How to Make Health Policy and Management Decisions. London: Churchill Livingstone, 1997. 5. Institute of Medicine (2001). Crossing the Quality Chasm: A New Health System for the 21st	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Century, Washington, DC: National Academy Press. 6. Tunis SR. A clinical research strategy to support shared decision making. Health Aff (Millwood) 2005;24:180-4. 7. Sussman C, Bates-Jensen B. Wound care. A collaborative practice manual for health professionals. 3rd ed. Philadelphia, Pa: Lippincott, Williams & Wilkins, 2007:500. 8. Carter MJ, Warriner RA 3rd. Evidence-based medicine in wound care: time for a new paradigm.Adv Skin Wound Care 2009;22:12-6. 9. Bolton L, McNees P, van Rijswicijk L, et al. Wound healing outcomes using standardized assessment and care in clinical practice. J Wound Ostomy Continence Nurs 2004;31:65-71. 10. Parnell LK, Ciufi B, Gokoo CF. Preliminary use of a hydrogel containing enzymes in the treatment of stage II and stage III pressure ulcers. Ostomy Wound Manage 2005;51:50-60. 11. Snyder RJ, Cardinal M, Dauphine´e DM, et al. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage 2010;56:44-50. 12. Coerpe S, Beckert S, Ku¨ per MA, et al. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single-center cohort of 704 diabetic patients. J Diabetes Complications 2009;23:49-53. 13. Sheehan P, Jones P, Caselli A, et al. 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;26:1879-82. 14. Phillips TJ, Machado F, Trout R, et al. Prognostic indicators in venous ulcers. J Am Acad Dermatol	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			2000;43:627-30. 15. van Rijwijk L. Full-thickness leg ulcers: patient demographics and predictors of healing.Multi-Center Leg Ulcer Study Group. J Fam Pract 1993;36:625-32. 16. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatol 2000;142:960-4. 17. Carter MJ. Evidence-based medicine: an overview of key concepts. Ostomy Wound Manage 2010;56:68-85. 18. Owens DK, Lohr KN, Atkins D, et al. ECRIseries paper 5: grading the strength of a body of evidence when comparing medical interventions—agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol 2010;63:513-23.	
Anonymous Reviewer 1	Alliance of Wound Care Stakeholders	ES: Tables	• In ***Table 3***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. • In ***Table 5***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted. • In ***Table 8***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. • In ***Table 10***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted. • Theraskin should be listed in the keywords section of Table 15 or in the search statement in Table 16.	The first 510(k) clearance document referring to chronic wounds for Oasis is the 2006 date. We could not locate any earlier date for chronic wounds. The 2000 date probably refers to the Oasis Burn Matrix but we could not locate a clearance or approval document for this device on the FDA web site. Landsman et al., 2008 has been added to the report.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 2	American College of Surgeons	General	On behalf of the more than 78,000 members of the American College of Surgeons (ACS), we appreciate the opportunity to submit comments on the AHRQ Draft Technology Assessment: Skin Substitutes for Treating Chronic Wounds, which was published through the Technology Assessment Program (TAP). This report sought to analyze the use of skin substitutes for the treatment of the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (including venous ulcers and arterial ulcers). The ACS is a scientific and educational association of surgeons, founded in 1913, to improve the quality of care for the surgical patient by setting high standards for surgical education and practice. The ACS appreciates the AHRQ's efforts with this draft technology assessment and would like to offer general comments regarding the assessment. Chronic wound management is an area of great interest as it is a key issue that lies within the purview of many surgeons. As the AHRQ continues to refine its process for studying skin substitutes, the ACS would like the AHRQ to consider future participation by ACS members in helping to design guidelines along with clinical trials and criteria for determining "outcome," early in the process.	No response needed

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 2	American College of Surgeons	General	Additionally, the ACS would like to recommend AHRQ to re-evaluate its goals as well as its target questions in order to include a wider scope of studies and provide more sound evidence. One of the goals of this report was to determine the extent of available clinical evidence in support of the efficacy of the various skin substitute products regulated by the Food and Drug Administration (FDA) and to determine the strength of this evidence base*. However, only fourteen randomized controlled trials, which in turn dealt with only five of the products, met the inclusion criteria. Of these studies, only one had moderate bias and the rest had a high level of bias. As a result, there was very limited actual clinical evidence for the efficacy of using skin substitutes. Consequently, the target questions were poorly addressed.	This report and questions were requested by CMS. The scope of the report was limited, and evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.
Anonymous Reviewer 2	American College of Surgeons	General	While the ACS appreciates the research put forth by the AHRQ, we also believe that it is imperative that AHRQ seek involvement from a diverse range of experts in order to enhance their research and further develop their analysis. Until this process is improved, there is very little added value to the research. The American College of Surgeons appreciates the ability to provide input on Using Skin Substitutes for Chronic Wounds. We look forward to a continued partnership with AHRQ on improving the quality of care for surgical patients.	No response needed.
Anonymous Reviewer 3	Anika Therapeutics	General	Anika Therapeutics, as the developer and manufacturer of three products included in this AHRQ Skin Substitute Technology Assessment (Hyalomatrix, Laserskin and Jaloskin), has reviewed the above Technology Assessment and submits the following comments.	We have renamed this grouping Biosynthetic.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 3	Anika Therapeutics	Results: Key Question 1	The classification of Hyalomatrix, Laserskin and Jaloskin in the report as Synthetic products is incorrect. These products are composed of HYAFF which is a benzyl ester of hyaluronic acid, a natural polysaccharide which is a major component of the extra-cellular matrix of the skin. Therefore, these products should be designated as Biologically-derived as evidenced by the 510(k) Summary for Hyalomatrix (K073251, Technological Characteristics Section).	
Anonymous Reviewer 3	Anika Therapeutics	General	In the Tables and the body of the document, Hyalomatrix, Laserskin and Jaloskin, should be placed in a separate category defined as ?Biologically-derived materials regulated under 510(k) process. Alternatively, the denomination of the group of products in which Hyalomatrix. Laserskin and Jaloskin are currently included could be changed from the current Synthetic products regulated under the 510(k) process to Biologically-derived and synthetic products regulated under the 510(k) process.	We have renamed this grouping Biosynthetic instead of Synthetic.
Anonymous Reviewer 3	Anika Therapeutics	General	Anika Therapeutics Inc. (Bedford, MA, U.S.A.) acquired Fidia Advanced Biopolymers S.r.l. (current Anika Therapeutics S.r.l.) in December 2009.	This change was made to the text.
Anonymous Reviewer 3	Anika Therapeutics	ES	On pages ES-1 and ES-2, we propose to include HYAFF in the natural sources as follows: Natural sources include human cadaver skin processed to remove the cellular components and retain the structural proteins of the dermis, collagen obtained from bovine and porcine sources and the biologically-derived material, HYAFF (a benzyl ester of hyaluronic acid).	We have renamed this grouping Biosynthetic.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 3	Anika Therapeutics	Results: Key Question 1	In the Tables and the body of the document, Hyalomatrix, Laserskin and Jaloskin, should be placed in a separate category defined as Biologically-derived materials regulated under 510(k) process. Alternatively, the denomination of the group of products in which Hyalomatrix. Laserskin and Jaloskin are currently included could be changed from the current Synthetic products regulated under the 510(k) process? to Biologically-derived and synthetic products regulated under the 510(k) process.	We have renamed this grouping Biosynthetic.
Anonymous Reviewer 3	Anika Therapeutics	ES	Page ES-8 line 8 Hyalomatrix PA should be replaced with Hyalomatrix, as it is current trade name of the product.	This change was made to the text.
Anonymous Reviewer 3	Anika Therapeutics	Introduction/ Background	A paragraph on Hyaluronic Acid-based dressings should be included in the Wound Dressings Section following the paragraph on Collagen.-based dressings. Hyaluronic acid is a major component of the extra-cellular matrix in skin and is supportive to the wound healing process. This group of hyaluronic acid-based dressings would comprise Anika?s dressings based on HYAFF (a benzyl ester of hyaluronic acid) such as HYALOFILL.	No changes were made in the introduction. Sufficient description was provided in the results section.
Anonymous Reviewer 3	Anika Therapeutics	Results: Key Questin 1	Page 22 line 17. Hyalomatrix PA should be replaced with Hyalomatrix, as it is current trade name of the product.	Changes were made to the document referring to Hyalomatrix PA as Hyalomatrix.
Anonymous Reviewer 3	Anika Therapeutics	Results: Key Question 1	Page 30. The section Hyalomatrix, Laserskin, and Jaloskin (Anika Therapeutics) needs to be fully revised because much information is not correct. It should be noted, for instance, that the product Hyalomatrix CO was described in this paragraph for reason that was not clear. Hyalomatrix CO, in fact, is not intended for wound management. Therefore description of this product should be cancelled and reference n. 100 should be removed from References as well. **The revised paragraph is reported hereinafter.**	We have made changes we thought appropriate and provide a link to the manufacturer's website for readers interested in additional details.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Hyalomatrix, Laserskin, and Jaloskin (Anika Therapeutics S.r.l., Italy). Hyalomatrix (Anika Therapeutics S.r.l., former Fidia Advanced Biopolymers S.r.l., Italy) was cleared for marketing under the 510(k) process in December 2007 (K073251). In the 510(k) documents Hyalomatrix is described as a bilayer dressing composed of a non-woven pad made of a benzyl ester of hyaluronic acid (HYAFF 11) and a semi-permeable silicone membrane. The non-woven pad contacts the wound and according to the Anika Therapeutics Inc. Web site provides a three dimensional matrix for cellular invasion and capillary growth. The silicone membrane controls water vapor loss, provides a flexible covering for the wound surface, and adds increased tear strength to the device. The HYAFF 11 matrix is biodegradable. The company believes that ?when the integration of the HYAFF based material in the newly formed dermal matrix has progressed, a well-vascularized granulation tissue forms. This provides for wound closure via spontaneous re-epithelialization or acts as a suitable dermal layer for skin grafting.99 Hyalomatrix is indicated for the management of wounds including: partial and full-thickness wounds; second-degree burns; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery , post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds. The device is intended for one-time use. Hyalomatrix is included in FDA product code FRO (dressing, wound, drug). In the FDA 510(k) database number K073251 refers to Hyalomatrix PA as the device. However in the 510(k) summary for K073251, the trade name is Hyalomatrix. 102 The predicate devices included ?Hyalomatrix KC (Laserskin) Wound	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Dressing.?102 Laserskin (Hyalomatrix KC Wound Dressing) (Anika Therapeutics S.r.l., former Fidia Advanced Biopolymers S.r.l., Italy) was cleared for marketing under the 510(k) process in July 2001 (K001508) for the management of wounds in the granulation phase such as pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, wounds and burns treated with meshed grafts. It is intended for use as a temporary coverage for wounds and burns to aid in the natural healing process. Laserskin is included in FDA product code MGP (dressing, wound and burn, occlusive). In the FDA 510(k) database number K001508 refers to Laserskin Dressing as the device. However in the 510(k) summary for K001508, the proprietary name is Hyalomatrix KC Wound Dressing and the name Laserskin is not mentioned.101 Jaloskin (Anika Therapeutics S.r.l., former Fidia Advanced Biopolymers S.r.l., Italy) was cleared for marketing under the 510(k) process in January 2010 (K092257) for the management of superficial moderately exuding wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, skin tears) and first and second degree bums. Jaloskin is a semi-permeable, transparent film dressing, composed of HYAFF 11 only. The hyaluronic acid is derived from bacterial fermentation. Jaloskin is included in FDA product code FRO (dressing, wound, drug).103	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 3	Anika Therapeutics	Results	Anika Therapeutics Inc. (Bedford, MA, U.S.A.) acquired Fidia Advanced Biopolymers S.r.l. (current Anika Therapeutics S.r.l.) in December 2009. The Anika Therapeutics Inc. Web site advertises Hyalomatrix and Jaloskin.	This change was made in the document
Anonymous Reviewer 3	Anika Therapeutics	Results	Page 44. In the HYAFF paragraph, please delete the sentence In addition no information on comorbidities was reported as information on comorbidities is actually reported.	This change was made in the document.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 3	Anika Therapeutics	Results	Page 46. The paragraph starting with Hyalograft 3D impregnated with autologous fibroblasts followed by Laserskin impregnated with autologous keratinocytes should be revised as follows: Hyalograft 3D with autologous fibroblasts followed by Laserskin with autologous keratinocytes was examined in two studies of diabetic foot ulcers (ref 19 + new ref for Uccioli et al) and compared to non-adherent paraffin gauze. In Caravaggi multicenter study (ref 19) 82 patients were screened and randomized, after 15 days of run-in all patients with an area less than 1 cm2 were excluded, thus 79 patients were enrolled from six outpatient centers in Italy. Over 85% of the patient population was Type II diabetics. The two groups were similar in clinical and wound characteristics with no significant differences. Mean TcPO2 was similar in the 2 groups and > 30mmHg. In Uccioli study (new ref needed) 180 patients were screened and randomized from seven Italian centers; after a 2-week run-in period with nonadherent paraffin gauze only, patients with an ulcer area ?1 cm2 received their randomized treatment at baseline visits. A total of 160 patients were enrolled and analyzed; over 88% of the patient population was Type II diabetics. The 2 study groups were similar with the exception of ulcer area, which was significantly larger in the treatment group (8.8 ? 9.4 vs 6.7 ? 7.7). Mean TcPO2 was similar in the 2 groups, with 25 patients in the treatment group and 29 in the control group with TcPO2 less than or equal to 30 mm Hg, at high risk of amputation.	We retained the most of the original text but clarified it as we thought appropriate.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 3	Anika Therapeutics	Results	Page 47. The paragraph staring with in the study by Caravaggi et al. 2003 Hyalograft 3D ?..? should be revised as follows: In the study by Caravaggi et al. 2003 Hyalograft 3D with autologous fibroblasts followed by Laserskin with autologous keratinocytes were grafted to diabetic foot ulcers. The control treatment was non-adherent paraffin gauze. Hyalograft 3D and Laserksin are hyaluronic acid-derived matrix. Laserskin is described in the Background section of this report. After 11 weeks, more wounds (dorsal and plantar) were healed in the Hyalograft/Laserskin group than in the control group but the difference was not statistically significant (65% vs. 50%). Dorsal ulcer healing was significantly better in the Hyalograft/Laserskin group (67% vs. 31%).(see Table 47).	We retained the most of the original text but clarified it as we thought appropriate

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 3	Anika Therapeutics	Results	In the study by Uccioli et al.2011 complete ulcer healing at 12 weeks was achieved in 19 (24%) patients in the treatment group versus 17 (21%) in the control group (P = .850, ns). A 50% reduction in ulcer area was achieved significantly faster in the treatment group compared with the control group (mean 40 vs 50 days; P = .018). At 20 weeks in the dorsal ulcer subgroup, after adjusting for ulcer area and duration, treatment was found to have a statistically significant effect on the probability of wound healing (P = .047). The estimated hazard ratio indicated that an average ulcer treated with Hyalograft-3D /Laserskin had a 2.17-fold better chance for closure per unit time than an ulcer treated with standard care. In the subgroup of nonhealing dorsal ulcers, treatment with the Hyalograft/Laserskin had a statistically significant beneficial effect on the probability of wound healing (P = .035). The estimated hazard ratio indicated that an average ulcer in this particular subpopulation treated with Hyalograft-3D/Laserskin had a 3.65-fold better chance for closure per unit time than that in a control patient.(see Table 47)	We retained the most of the original text but clarified it as we thought appropriate
Anonymous Reviewer 3	Anika Therapeutics	Results	Page 47 line 28: reported text Hyaloskin containing the extracellular matrix protein hyaluronan,.... There are two mistakes to be corrected: 1) Jaloskin should substitutes for Hyaloskin; 2) hyaluronan is a glycosaminoglycan, not a protein. Therefore the whole text should be changed to Jaloskin containing the extracellular matrix component hyaluronan	The tables and text were changed and reference to a protein was removed.
Anonymous Reviewer 3	Anika Therapeutics	Results	Page 47, line 31. Hyaloskin should be changed to Jaloskin	This section contains the product names and descriptions as presented in FDA documents so we have retained these names and provided the trade name information provided by the manufacturer

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 3	Anika Therapeutics	Tables	In Table 4 and Table 9, the information provided for Hyalomatrix, Laserskin and Jaloskin in the columns Product and Manufacturer and Description is not correct. Here is the revised information. oPRODUCT AND MANUFACTURER - Laserskin (Hyalomatrix KC Wound Dressing) - Anika Therapeutics S.r.l. DESCRIPTION: Laserskin (Hyalomatrix KC Wound Dressing) is a semi-permeable, perforated transparent film dressing, composed of HYAFF 11 (a benzyl ester of hyaluronic acid) only	This section contains the product names and descriptions as presented in FDA documents so we have retained these names and provided the trade name information provided by the manufacturer
Anonymous Reviewer 3	Anika Therapeutics	Tables	PRODUCT AND MANUFACTURER - Hyalomatrix - Anika Therapeutics S.r.l. DESCRIPTION: Hyalomatrix is a bilayered advanced wound dressing composed of a non-woven pad made of HYAFF 11 (a benzyl ester of hyaluronic acid) and a semi-permeable silicone membrane.	This section contains the product names and descriptions as presented in FDA documents so we have retained these names and provided the trade name information provided by the manufacturer
Anonymous Reviewer 3	Anika Therapeutics	Tables	PRODUCT AND MANUFACTURER - Jaloskin -Anika Therapeutics S.r.l. DESCRIPTION: Jaloskin is a semi-permeable, transparent film dressing, composed of HYAFF 11 (a benzyl ester of hyaluronic acid) only.	This section contains the product names and descriptions as presented in FDA documents so we have retained these names and provided the trade name information provided by the manufacturer
Anonymous Reviewer 3	Anika Therapeutics	Tables	Table 22, For Question 7 please revise NR designation to Y according to Table 32 and 42 where comorbidities are reported	This change has been made in the document.
Anonymous Reviewer 3	Anika Therapeutics	Tables	Table 27 : For Length of study, please revise NR to 11 weeks.	This change has been made in the document.
Anonymous Reviewer 3	Anika Therapeutics	Tables	Tables 5, 10,11, 12,22,27,32,37,42,47,52 should be revised with the introduction of Uccioli et al. 2011 publication	These changes have been made in the document.
Anonymous Reviewer 3	Anika Therapeutics	References	The following reference should be added: Uccioli L. et al. Two step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: Results of a multicenter, randomized controlled clinical trial with long-term follow-up. The International Journal Lower Extremity Wounds 2011;10(2):80-5.	This change has been made in the document.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	General	On behalf of the Coalition of Wound Care Manufacturers ("CWCM"), I am submitting the following comments in response to the AHRQ Technology Assessment on Skin Substitutes For Treating Chronic Wounds. I serve as the Executive Director of the CWCM. The CWCM represents leading manufacturers of skin substitutes, of negative pressure wound therapy and other medical devices and supplies used by Medicare beneficiaries for the treatment of wounds. While we appreciate the opportunity to offer our comments, we are very disappointed in the short amount of time (a little over two weeks) that the AHRQ allowed for a deadline to respond to this very dense document that is so critical to wound care stakeholders. It is our understanding that the Technology Assessment Program provides 2 weeks for public review of its draft reports. However, releasing the report on December 28 and then extending the due date to January 17 includes two holidays (New Years and Martin Luther King's birthday) along with many taking vacations during this time does not constitute a meaningful public comment period. The Coalition has treated writing our comments to this draft very seriously, and has convened many conference calls, conversations and emails to ensure that all stakeholders' input will be included. Since we still do not believe there is enough time to give this important document the careful consideration that it needs, we are submitting these comments, but intend to supplement our filing as we receive more information from our members. This section will be a summary of the issues that we will be addressing later in our comments 4. The Coalition has many serious concerns with this draft – from the products included in the draft to the terminology used to the methodology utilized which	No response needed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			led to faulty conclusions. We believe that there was good intent in writing this, but wound care is very complex and different from burns and other diseases. The Coalition would be pleased to meet with ECRI, AHRQ as well as CMS staffs to discuss these issues in detail. 5. The Coalition has concerns with the nomenclature "skin substitutes" used throughout this document and in the title of this technology assessment in reference to the products/materials being considered. The term "skin substitutes" is not appropriate for these items and the term "dressing" does not work either since they have different connotations for both FDA and CMS. Therefore, if the terms "skin substitutes" do not really describe these items, and "biologic dressings" have negative connotations for coverage in the eyes of the CMS contractors, then we would propose the term for this document "cellular and engineered tissue alternatives." Alternative meant that these tissues are not substitutes but are different in function and structure. We submit that this terminology would include all the items correctly described in the document. 6. The Coalition has many issues with regards to the discussion of bias in this technology assessment. One of our concerns is that ECRI believes that if a manufacturer funds a study then there is automatically bias. First of all – as manufacturers – we question where the studies will come from if they are not funded by manufacturers. The types of studies that CMS and the FDA require either now or in the future in order for our products to come into the market place are not the subject of those studies currently funded by NIH, PCORI or AHRQ. Secondly – the source of investment for a clinical	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			study is not an automatic cause of bias or concern for the integrity of data generated. The Coalition 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. Yet ECRI does not mention this in its assessment. 7. As stated in the Methods part of our remarks, we would have appreciated ECRI including more non-RCT studies which would more likely demonstrate the "effectiveness" of the cellular and engineered tissue alternatives than the "efficacy of the RCTs. By using these studies, there would have been more real-world patients.	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	ES	The Coalition has concerns with the following issues: **1.Semantics and definitions used in this document to define "dressing" and "skin substitutes" by the FDA may have different meanings and uses by CMS and its contractors. This leads to confusion for all stakeholders. There needs to be consistent terminology for these items in all of the regulatory agencies.** The Coalition has concerns with the nomenclature "skin substitutes" used throughout this document and in the title of this technology assessment in reference to the products/materials being considered. The term "skin substitutes" is not appropriate for these items and the term "dressing" does not work either since they have different connotations for both FDA and CMS. For example: In Tables 2-4, one notes that under FDA's product code—the products for chronic wounds are ALL referred to as "dressing" no matter what the materials are or the process regulated under the FDA. Thus, one might therefore conclude that all the regulatory agencies could adopt this term.	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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. The second reason for writing this report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited. This report specifically examines the use of skin

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			In fact, in the ECRI draft, page ES-1 in the fourth paragraph under "Background" states that "However, for chronic wounds a skin substitute should be able to provide a temporary biologic dressing that stimulates the host to regenerate lost tissue and replace the wound with functional skin." One could conclude that these materials could then be called "biologic dressings". However, if one looks at the CMS contractors, the A/B MACs', local coverage determinations for these products, one will not find coverage in many circumstances for those products which are "biological dressings." Moreover, there is additional confusion with the term "dressing" used in the Medicare Part B area by the DMEMAC coverage policies which include such products as hydrogels and hydrocolloids and name them as "surgical dressings" designated as "A codes". The term "skin substitute" may not be a correct term to use anymore. It is not used by the FDA in its classification as demonstrated by the tables 2-4. CMS' division that addresses HCPCS coding for these products also abandoned this term effective in 2010 when a manufacturer requested that CMS delete this term since it was an incorrect descriptor. The manufacturer stated at the 2010 CMS HCPCS Public Meeting that that this language was wrong since allografts are mislabeled as "skin substitutes." Allografts differ in structure, tissue origin, and in some cases differ from cellular and engineered tissue in terms of how they are approved by the FDA (human skin for transplantation not devices). CMS thus changed the descriptors and eliminated the term "skin substitutes" from all of its Q codes for these items. If one uses a medical dictionary to also look at the definitions for skin substitutes—one would see that it states it as a wound covering—which does not fare well	substitutes for treating the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (including venous ulcers and arterial ulcers). Treatment of burn wounds with skin substitutes is outside the scope of this report." The term "biological dressing" was removed from the report.

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			to obtain coding and coverage under CMS; likewise, the biologic dressing has it being used for burns rather than chronic wounds. Farlex's online medical dictionary confirms the differences of using products to treat a wound versus to protect a wound (as a wound cover dressings). Skin Substitute: "a material used to cover wounds and burns where extensive areas of skin are missing, *to promote healing.* Biologic Dressing: "one used in treatment of a burn or other large denuded area of skin to *prevent infection and fluid loss.* See http://medicaldictionary.thefreedictionary.com/skin+substitute (Accessed November 17, 2011) uses Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition. © 2003 by Saunders, an imprint of Elsevier, Inc.) Therefore, if the terms "skin substitutes" do not really describe these items, and "biologic dressings" have negative connotations for coverage in the eyes of the CMS contractors, then we would propose the term for this document "cellular and engineered tissue alternatives." Alternative meant that these tissues are not substitutes but are different in function and structure. We submit that this terminology would include all the items correctly described in the document.	

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	General	**2. Grouping of "cellular and engineered tissue alternatives"** This draft attempts to create a common grouping for these wound care products. Unfortunately, as is true for many devices, using FDA classifications do not always help. The groupings are not "like" based on mode of action of the products, material components, or how they are clinically used. If ECRI's goal is to create a generalizable assessment of the products then the authors must understand wound care better by knowing how these products are used and not how the FDA chooses to categorize them. Many of the products in the listing would not be used for all wounds and several are very rarely used. Finally, based on FDA practices many of these products did not need to provide evidence of comparative efficacy to gain approval. Thus, they do not have this level of evidence.	We created groupings specific for this report only to address the goals of this report. The primary purpose of this report was to examine the regulatory pathways required for a broad range of wound care products that are commonly referred to as "skin substitutes." The second reason for writing this report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds.
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods: Key Question 1	**3. Evidence for Skin Substitutes** Question #1 of this paper is devoted to how the FDA regulates cellular and tissue engineer alternatives. The Alliance has the following concerns about this section: • Why was this question chosen? • One of the statements in the "Background" is not correct: "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process." The regulatory process is risk-based, not product origin-based. For example, PMA devices are products that the FDA deemed as a Class III device (devices that "support or sustain human life, are of	CMS requested a description of regulatory information provided in FDA documents relevant to treatment of chronic wounds. Changes to the text suggested by the FDA reviewer have addressed the issues raised regarding the description of the regulatory processes.

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			substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.")Therefore, these devices are deemed Class III because they "present a potential, unreasonable risk of illness or injury." In the Methods of the Review section, ECRI states that as part of the review, it developed Key Questions to answer, which included "What are the U.S. Food and Drug Administration (FDA) regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361[21CFR 1270 & 1271]?" However, it is unclear why this question is important for the evaluation of device *efficacy*, as FDA classifications also don't indicate whether a device is an *effective* treatment modality. The executive summary only comments on the 3-letter classifications that are used to designate the different categories of products and specific terminology that is used in the FDA indication statement. Moreover, we have concerns about the emphasis that ECRI places on this specific terminology that is used in the FDA indication statements ("treatment" or "management") since the way that they are used by the FDA to delineate the products may be totally different than how they would be used in its sister agency, CMS. Both agencies have their separate and distinct regulatory processes and their own definitions and terminology. To further illustrate this point, when determining whether a product is a biological the FDA follows its own guidance – as ECRI has described earlier. CMS follows the Social Security Act (SSA) definition of drugs and biologicals which is:*t)(1) The term "drugs" and the term "biologicals", except for purposes of subsection (m)(5) and paragraph (2), include only such drugs (including contrast agents) and biologicals, respectively, as are included (or approved for inclusion) in the United States*	

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			Pharmacopoeia, the National Formulary, or the United States Homeopathic Pharmacopoeia, or in New Drugs or Accepted Dental Remedies (except for any drugs and biologicals unfavorably evaluated therein), or as are approved by the pharmacy and drug therapeutics committee (or equivalent committee) of the medical staff of the hospital furnishing such drugs and biologicals for use in such hospital. Since CMS commissioned this study there may be a linkage of the two agencies on this issue, which would be inappropriate. For instance, CMS' goals as stated in this report are: To determine the extent of available clinical evidence in support of the efficacy of the various cellular and engineered tissue alternatives products regulated by the FDA and to determine the strength of this evidence base. (page 50) To facilitate CMS's evaluation of HCPCS coding for skin substitutes and information obtained by CMS will be used for consideration of coding changes. (page 12) We would not want CMS to misinterpret the intent of FDA's classification and terminology of "management" and "treatment" when these same cellular and tissue engineered products obtain Medicare coverage, coding and payment.	

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Results: Key Question 1	**4. <u>ECRI should only list of "cellular and engineered tissue alternatives" in this draft document</u>** The list of products included in the report are not all marketed or indicated for use in chronic wounds, as noted by the researchers, and would not have clinical data in the literature for chronic wounds. In addition, some are used for burns and, as stated in this report, are not supposed to be included. Some are also "surgical dressings" and should be removed. Therefore, the Coalition recommends the following products should be removed from this assessment. We would also recommend that in ECRI's final report that only those which are cellular and engineered tissue alternatives be included. • AlloDerm Regenerative Tissue Matrix, Allopatch HD, Flex HD, Matrix HD, Puros Dermis [dental implant tissue], Repliform • Epicel, Transcyte • E-Z Derm, InteXen, Permacol, Strattice , Tissuemend • BioBrane -biosynthetic dressing constructed of a silicone film with a nylon fabric w/ trifilament thread to which collagen is chemically bound used for burns • Hyalomatrix - non-woven pad dressing made a benzyl ester of hyaluronic acid, and a semi permeable silicone membrane • Laserskin & Jaloskin -transparent film dressing composed of a benzyl ester of hyaluronic acid]: benzyl esters of hyaluronic acid • LyoFoam Extra "C"- polyurethane foam dressing • Suprathel- absorbable, synthetic wound dressing of polyalactic acid for donor sites and burns	All products not indicated for chronic wounds have been removed.

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Background: Skin Substitutes	**5. Specific comments on Background** 1- "This report specifically examined the use of skin substitutes for the treatment of the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (includes venous ulcers and arterial ulcers). Treatment of burn wounds with skin substitutes is outside the scope of this report." *This statement is incorrect since Epicel and Transcyte have been cited. We believe it should be restricted to chronic wounds as stated above.* 2- "Skin substitutes were developed as an alternative to skin grafts especially for burn patients." *Good statement, we now know these skin substitutes are "just" biological dressing. Therefore they should not be called skin substitutes* 3- "The ideal skin substitute should adhere to the wound bed and provide the physiological and mechanical function of normal skin while not being rejected by the host. This ideal situation is not likely to be provided by any current skin substitute." *This is not completely true, Steven Boyce has worked on a skin replacement for burns with autologous cells and biomateriaux. See for example: Boyce ST, Hansbrough JF. Biologic attachment, growth, and differentiation of cultured human epidermal keratinocytes on a graftable collagen and chondroitin-6-sulfate substrate. Surgery 1988;103:421-31. Boyce ST, Kagan RJ, Greenhalgh DG, et al. Cultured skin substitutes reduce requirements for harvesting of skin autograft for closure of excised, full-thickness burns. J Trauma 2006;60:821-9.*	All products not indicated for chronic wounds have been removed. The paragraph mentioning an "ideal" skin substitute has been rewritten.
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods: Key Question 2	**6. Definition of usual wound care** In its second question, ECRI asks "For patients with chronic wounds (pressure ulcers, diabetic foot ulcers or arterial ulcers) are skin substitutes more effective than usual care (synthetic dressings, growth factors, skin	Key Question 2 has been changed to compare skin substitutes to any type of wound care as a comparison rather than trying to define a usual care for comparison. Key Question 2 has been changed to: For patients with chronic wounds (pressure ulcers,

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			grafts or other treatments used as a control) in promoting wound healing for the following outcome measures…." The Coalition disagrees with the definition of usual wound care utilized by the researchers to compare to cellular and engineered tissue alternatives treatment for chronic wounds. The usual care group that was stated is not a standard care arm but an advanced care arm and should be properly identified as such. Usual care for chronic wounds was addressed in the 2005 MedCAC meeting – and the Coalition agreed with its conclusion. CMS had stated that usual care was defined as: debridement, cleansing, dressing, compression, antibiotics and off-loading. In FDA's Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment, usual care for chronic cutaneous ulcers include the following: • Removal of necrotic or infected tissue • Off-loading • Compression therapy for venous stasis ulcers • Establishment of adequate blood circulation • Maintenance of a moist wound environment • Management of wound infection • Wound cleansing • Nutritional support, including blood glucose control for subjects with diabetic ulcers • Bowel and bladder care for subjects with pressure ulcers at risk for contamination Others have stated that usual standard wound care is the removal of necrotic or nonviable tissue from the wound [debridement], management of the local wound environment [exudate control, maintenance of moist healing environment, cleaning of debris], protection from bacterial invasion, treatment of infection or gross contamination, protection of viable tissues from pressure, friction and shear through offloading or	diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures

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			pressure reduction and reduction of edema and improved venous return with sustained, graduated compression for leg ulcers. These approaches will vary throughout the course of a particular wound's cycle of healing and are not consistent from wound to wound. Hence, in the study of chronic wounds, reference to 'usual wound care' would include the use of various types of wound dressing over the course of a study as the local wound environment changes, different intervals and numbers of debridement procedures as required for a particular wound, inclusion of antibiotic therapy as needed, varying intervals for the application of compression therapy, offloading techniques, pressure reduction all the 'usual wound care approached. As indicated in your review, if a wound fails to respond within 30 days to usual 'standard' care, the clinician will then evaluate the most appropriate 'advanced approach' to facilitate wound healing. As stated above, ECRI has included <u>advanced methods</u> of wound treatment in their definition of usual care including growth factor therapy, surgical autologous skin grafts, skin substitutes, and other treatments. These are considered advanced treatments and *not* part of standard usual care. They, like cellular and engineered tissue, are utilized after standard care fails to progress the healing of a chronic wound. Some of these advanced modalities are not utilized throughout the entire healing process, but have specific functions during the course of healing, and therefore would not be a suitable and appropriate as a comparator for a cellular and engineered tissue trial to evaluate clinical effectiveness.	

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	ES: Table 3 and Table 5	**7. Inclusion of Studies** In ***Table 3*****,** the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. In ***Table 5***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.	The first 510(k) clearance document referring to chronic wounds for Oasis is the 2006 date. We could not locate any earlier date for chronic wounds. The 2000 date probably refers to the Oasis Burn Matrix but we could not locate a clearance or approval document for this device on the FDA Web site. Landsman et al., 2008 has been added to the report.
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	ES	**8. Concerns about Methodology** The executive summary addresses in its evidence and conclusion issues which we have concerns with such as the methodology—please see the Methods part of our comments to obtain this information.	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Introduction/ Background	In the ***Complementary or Competing Products*** portion of this section, the focus does not seem to be on products; instead the focus seems to be more upon factors that need to be controlled in any treatment algorithm for all wounds. In the ***Usual Care for Chronic Wounds*** portion of this section, the authors state: " 'Standard of care' (SOC) was commonly used in the studies included in this report when referring to the control group wound care or base wound care to which a skin substitute was added…Standard of care is also frequently used in presentations on manufacturer Web sites. However, as described above, usual care or standard of care is not a consistent term that describes an agreed upon set of procedures to be used when treating chronic wounds." Standard of care (SOC) is an industry vernacular that is used to describe the prescribed treatment that is most *currently* accepted to be effective, which means that this is the treatment that is most currently used. In the ***U.S. Food and Drug Administration Regulations Governing Skin Substitute Products*** portion of this section, the authors provide an expanded explanation of the regulatory categories; however, as above, there is no explanation as to how this relates to	The Complementary or Competing Products section heading has been removed. The paragraph was incorporated into the Usual Care section. If standard of care is *currently* accepted to be effective therapy then it should be described fully in any publication since the definition of 'standard of care' changes over time. The FDA has reviewed the draft report and provided input for editing the regulatory section of the report.

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			this review. In this discussion, statements such as, "Therefore, wound care products regulated under the PMA process will require evidence that they promote wound healing before they are approved for marketing." and "Therefore, wound care products regulated under the 510(k) process will typically require less evidence that they promote wound healing compared to products regulated under the PMA process." These statements are untrue as these FDA categories are ***risk-based*** categories, which mean that higher risk classifications (Class III devices approved through PMA) may mean that less is known about whether the product is safe. As such, there are devices that may have been cleared by the FDA without clinical data (e.g. Specturm 5000Q Electroconvulsive Therapy Device by Mecta Corporation) Additionally, the discussion of these categories is inconsistent with the Executive Summary statement: "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process." This issue has also been addressed in our comments in the Executive Summary.	

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	***General Comments*** This section states that the review will facilitate CMS' evaluation of HCPCS coding for skin substitutes by providing CMS with relevant studies and information for consideration of coding changes. We have concerns about this and would request a meeting with CMS staff to discuss this. **Methodology of the Systematic Review** The methodological approach of this review has several major flaws: (1) selection of studies; (2) outcomes; (3) bias assessment; and (4) reporting. *Selection of studies* 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.[1,2] The percentage of "real world" patients excluded in such studies in wound care can be high.[2] RCTs are appropriate for establishing an effect under controlled conditions but are problematic when solely used to translate outcomes to "real-world" patients with chronic wounds because many patients do not fit the populations used in RCTs.[3] A good example of why some promising wound care products do not work well in all wound care 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"[4] or	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. The second reason for this report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited. The Landsman and DiDimenico studies have been included in the final report.

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			as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.[5] In other words, the approach does not only look at 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."[6] Because the authors of this systematic review chose only to examine RCTs published in the per-reviewed literature, much of the evidence on cellular and engineered tissue is missing, and thus the conclusions in terms of coverage of these products are therefore skewed. Furthermore, it is a puzzling why the authors apparently searched the gray literature but did not report on it. Why do this in the first place? Typically, Cochrane reviews look for abstracts, unpublished material, ongoing clinical trials, and so forth, so as to minimize publication bias, particularly when conducting meta-analysis, which was not done in this review. Granted, it can be very difficult to analyze such studies published as abstracts or research letters, but their inclusion is important, even if detailed analysis is not possible. Furthermore, there is no excuse not to search for evidence published in the peer-reviewed literature if that evidence is not published in English. Given the extensive effort that was put into searching, the authors could have found studies that would have had English abstracts, and then decided upon their relevance and had them translated. Not doing so is another form of selection bias. We also believe that many studies should have been included in this section. For example - The O'Donnell systematic review of randomized controlled trials of wound dressings for chronic venous ulcers (. J Vasc	

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			Surg 2006;44:1118-25.) 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 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. Two other studies should also be included since they are "head to head" studies of two "skin substitute" products: • 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 • 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	

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	*Outcomes* The authors of this report chose to ignore many valuable outcomes that are linked to partial wound healing, in part because they chose to ignore observational trials, although sometimes this information is reported in RCTs. This is important because healing chronic wounds often requires many repeated, sequential, or overlapping treatments to completely heal a wound,[1,7] and this approach cannot be easily accomplished in an RCT.[8] For example, a venous leg ulcer would have to receive adequate compression, and might be treated with silver-impregnated dressings to reduce infection before receiving Apligraf to ensure that the wound is not clinically infected . There is an increasing body of evidence that partial wound-healing outcomes, such as time to reach 50% reduction wound area, are valid and clinical useful endpoints that can be used in real world wound care patients to determine whether the wound is clinically responding to a given treatment regimen.[9-16] In ignoring these types of outcomes and focusing only on RCTs, the reviewers seem to have entirely dismissed evidence-based practice altogether.	The most important patient-oriented outcome is complete wound healing and is therefore the focus of the final report.
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	*Bias assessment* The Coalition is concerned of ECRI's condemnation of the comparative efficacy studies with respect to bias. The authors should note that many of these studies were designed with respect to the FDA requirements and thus can be very difficult to conduct these studies in a blinded fashion. We note that the reviewers chose a non-validated approach to assessing bias assessment, which does not seem to have been reported in the literature. While some of the elements listed are certainly crucial, definitions of yes, no, or not reported are missing. For example, by what criteria did the reviewers judge that a	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare

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			study used appropriate randomization methods or concealment of treatment group allocation? Second, the authors seem to have singled out wound size/duration as and number of comorbidities the only important baseline parameters, suggesting 15% as the split point. How did they arrive at these specific criteria? 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. 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. Finally, there was no GRADING reported. GRADE is becoming one of the most important techniques by which the synthesis of the evidence is evaluated in terms of the quality of evidence across studies for each important outcome; which outcomes are critical to a decision; the overall evidence across these critical outcomes; the balance between benefits and harms; and the strength of recommendations.[17] Instead, the reviewers used the EPC approach, which is conceptually similar to the GRADE system of evidence rating; it requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate include dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias. Strength of evidence receives a single grade: high, moderate, low, or insufficient.[18] This would have been a reasonable approach had it been followed in a thorough fashion. Instead there are only one or two sentences in the entire 121-page report devoted to directness and consistency,	Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text has been added to define “Yes,” “No,” and “Not Reported” in the risk of bias assessment. We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing intermediate outcomes for wounds, but we have focused the review on the outcome of complete wound healing. Individual studies are evaluated for risk of bias on an outcome-by-outcome basis. Grading the strength of evidence is a judgment about all studies for a given population, intervention, comparison and outcome, taking into account the risk of bias within individual studies, the consistency of findings across studies, the precision and magnitude of the effect, and the directness of the evidence for the question at hand. We have added text to explain this. Unfortunately, there were few instances in which more than one study used the same products in comparable populations and measured the outcome of complete wound healing. We have added tables to the report to add clarity to the presentation of results and strength of evidence.

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			and precision was entirely ignored at the expense of pages on risk of bias. We would submit that according to ECRI's own procedures and criteria that this systematic review was poorly done. Consequently, its conclusions must be regarded as uncertain.	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	*Reporting* The gold standard for reporting systematic reviews are the PRISMA guidelines. In this review, several items were missing (e.g., method of data extraction, and summary measures presented as differences in means and risk ratios). Moreover, no rationale was given for not conducting meta-analysis, as this is usually a key part of any systematic review. **References** 1. Serena T, Bates-Jensen B, Carter MJ, et al. Consensus principles for wound care research Obtained using a Delphi process. Wound Repair Regen 2011;in press. 2. 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. 3. 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. 4. Gray JA. Evidence-based Health Care: How to Make Health Policy and Management Decisions. London: Churchill Livingstone, 1997. 5. Institute of Medicine (2001). Crossing the Quality Chasm: A New Health System for the 21st Century, Washington, DC: National Academy Press.	The PRISMA checklist is a useful tool but is not a standard component of the Technology Assessment reports for CMS program. The original scope of the report did not include quantitative analysis. Risk differences, relative risks and odds ratios are presented in the final report. The studies included in this report are extremely diverse in terms of populations, wound types, interventions and comparators. The original scope of the report did not include meta-analysis, but we have added details about studies that illustrate the reasons we did not combine many of them in a meta-analysis and have added the two meta-analyses that were performed.

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			6. Tunis SR. A clinical research strategy to support shared decision making. Health Aff (Millwood) 2005;24:180-4. 7. Sussman C, Bates-Jensen B. Wound care. A collaborative practice manual for health professionals. 3rd ed. Philadelphia, Pa: Lippincott, Williams & Wilkins, 2007:500. 8. Carter MJ, Warriner RA 3rd. Evidence-based medicine in wound care: time for a new paradigm.Adv Skin Wound Care 2009;22:12-6. 9. Bolton L, McNees P, van Rijswicijk L, et al. Wound healing outcomes using standardized assessment and care in clinical practice. J Wound Ostomy Continence Nurs 2004;31:65-71. 10. Parnell LK, Ciufi B, Gokoo CF. Preliminary use of a hydrogel containing enzymes in the treatment of stage II and stage III pressure ulcers. Ostomy Wound Manage 2005;51:50-60. 11. Snyder RJ, Cardinal M, Dauphine´e DM, et al. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage 2010;56:44-50. 12. Coerpe S, Beckert S, Ku¨ per MA, et al. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single-center cohort of 704 diabetic patients. J Diabetes Complications 2009;23:49-53. 13. Sheehan P, Jones P, Caselli A, et al. 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;26:1879-82. 14. Phillips TJ, Machado F, Trout R, et al. Prognostic indicators in venous ulcers. J Am Acad Dermatol 2000;43:627-30. 15. van Rijwijk L. Full-thickness leg ulcers: patient	

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			demographics and predictors of healing.Multi-Center Leg Ulcer Study Group. J Fam Pract 1993;36:625-32. 16. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatol 2000;142:960-4. 17. Carter MJ. Evidence-based medicine: an overview of key concepts. Ostomy Wound Manage 2010;56:68-85. 18. Owens DK, Lohr KN, Atkins D, et al. ECRIseries paper 5: grading the strength of a body of evidence when comparing medical interventions—agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol 2010;63:513-23.	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods: Study Risk-of-Bias Assessment	***Specific Comments--List of Quality Assessment Questions and Concerns:*** **#3. Was the wound assessor blinded to the patient's treatment group?** We disagree with ECRI that there is high risk for bias when the investigating clinician (unblinded) evaluates the wound parameters. These measurements (wound size/ depth measurements, percent of granulation or epitherial tissue, wound margins, percent necrotic tissue, etc.) are confirmed with scaled graft measurement tools and/ or digital photography which are used by the clinicians and difficult to blind. These parameters are 'hard' endpoints, not open to interpretation, recorded at standard intervals during the study for both arms of the study. Therefore, we are in agreement with the authors that these do not require a blinded evaluator to ensure an introduction of bias. We believe allocation concealment is most important. **#5 Were the mean wound sizes at the start of treatment similar (no more than a 15% difference)**	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. For the sake of consistency, we have selected 15% as the threshold when difference in characteristics between

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			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' situation 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. As stated earlier in our comments, this factor can be adjusted for in analysis. **#6 Were the mean wound durations 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. Longer duration of a chronic wound has 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. **# 10. Was the study funded by an organization other than the skin substitute manufacturer?** The source of investment for a clinical study is not an automatic cause of bias or concern for the integrity of data generated. The Coalition 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. 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 funded by NIH or PCORI or AHRQ.	treatment groups may indicate a potential for bias. This figure is based on a consensus opinion of systematic review experts, but certainly other thresholds could be used. Assessment of risk of bias involves many judgments; we attempt to make ours transparent. We have removed the question regarding funding from our risk of bias assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.

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			Similarly, as the federal and state governments are limited in the funds that they can provide to conduct randomized controlled trial 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 manufacturers that have to fund these studies in order to obtain the clinical evidence that is needed to obtain approval/clearance to market the devices. 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.	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Results	The Coalition recognizes that by submitting our answers to AHRQ by section rather than in a full paper online, different reviewers may be reading different areas—however, since we believe we have not been given enough time to thoroughly respond in full to all of the questions, we would ask that the reviewers of this section to please read our comments in the Executive Summary since they pertain to this section also. We do have some specific comments as noted below. ***Specific Comments*** In answering Key Question 1, the authors list several products, such as AlloDerm Regenerative Tissue Matrix, Flex HD, Puros Dermis, Repliform, InteXen, and Permacol, which are not used/ cleared for the treatment of chronic wounds. In answering Key question 1 the authors erroneously describe Theraskin 1. Lines 1-4 should read. "TheraSkin is a biologically active, cryopreserved real human skin allograft, composed of living cells, fibroblasts and keratinocytes and a fully developed extra cellular matrix. TheraSkin does not contain any synthetic or animal materials." 2. P. 24. Please change the last sentence to "SWAI	Products not indicated for chronic wounds have been removed. Our product descriptions are taken from company Web sites or the description provided in FDA regulatory documents. We appreciate your clarifications. The first 510(k) clearance document referring to chronic wounds for Oasis is the 2006 date. We could not locate any earlier date for chronic wounds. The 2000 date probably refers to the Oasis Burn Matrix but we could not locate a clearance or approval document for this device on the FDA web site. Landsman et al., 2008 has been added to the report.

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			(Virginia Beach, VA) is registered with the FDA as an establishment providing HCT/P's." 3. P 24, line 6, word 3 should be "provided" not "distributed" In ***Table 8***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. In answering Key Question 2, the authors state that their searches identified 14 RCTs that met the inclusion criteria. However, one notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers. In ***Table 10***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Results: Key Question 2, Risk of Bias in the Evidence Base	***Quality of the Evidence Base*** In the ***Quality of the Evidence Base*** portion of this section, the authors state: "All four studies of Oasis were considered at high risk of bias because wound assessor blinding was not reported. Reporting of comorbidities was absent in three of the studies." It is not always possible to blind the wound assessor to wound care treatments, as the treatments often result in differences in wound appearance during the course of treatment. As such, there are objective wound evaluation techniques, such as wound dimensions and depth that are incorporated into the assessment of wounds. Additionally, there are publication limits (i.e. space constraints of the manuscript), which means that many of the unreported data fields are eliminated because they are insignificant in relation to outcome.	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We decided that the most critical of the questions for assessing risk of bias in these studies was "Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?"
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Results: Key Question 2, Study Design, Patient	***Page 44- Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics.*** *"Several important areas of study design and patient information of interest to this report were poorly*	Information on comorbidities, health status and prior treatments for chronic wounds would assist reviewers in assessing the comparability of populations within and across studies.

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		Enrollment Criteria, Description of Treatment, Patient Characteristics	*reported. Prior wound treatments were not reported in any of the studies and reporting of comorbidities was sparse*. " Chronic wounds may have been present for months up to over a year before entrance into a clinical study. Patients may have been seen by several clinicians over that time. It is virtually impossible to list all prior treatments for each subject in a wound healing study. This will vary widely across the patient population and has minimal value in determining the effect of the current treatment. Therefore it is not tracked and evaluated in chronic wound studies. A majority of clinical studies define exclusion criteria that ensure the use of another advanced treatment, prior to enrollment in the current study, must not have occurred within a certain timeframe before entering the study. This helps eliminates the cross-over effect of other treatment(s). Patients with chronic wounds typically have multiple medical conditions which contribute to the development of their wound. Co-morbidities are not specifically identified in chronic wound studies as a data point for analysis since only a few are directly linked to non-healing. However, medical conditions that may impede the healing process to such an extent that the patient would highly likely not respond to the study treatment are usually identified in the exclusion criteria (i.e. end stage renal disease, autoimmune compromised patient, uncontrolled diabetes, severe vascular insufficiency, etc.). The studies include these exclusion criteria to ensure patients' major health conditions are in relative control, to eliminate patient with reduced ability to respond to either the study treatment or the control.	

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Results: Key Question 2, Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics	Page 44- "*Wound duration and wound severity prior to enrolling in a study were also poorly reported. Patients were generally excluded from studies if their health was suboptimal, they were taking medication that would interfere with wound healing or their wounds were infected."* Removing the patients on medication which interferes with wound healing is appropriate in wound healing trials, since those patients would adversely affect the outcomes for any arm of the study. Unless all patients are taking the medication, it is not appropriate to include them in the study as this will impact the data results negatively. Removing patients with infected wounds from skin substitute clinical trials is medically appropriate since healing does not occur in the presence of infection. Many of the listed biological materials are required by the FDA labeling, to be applied only to a non-infected wound. It would be medically negligent to apply an active biological material to an infected wound knowing the tissue graft would fail.	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies.
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Results: Key Question 2, Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics	*Page 44- "Several studies also indicated they excluded patients who responded to usual care during screening periods (see studies of Apligraf, Dermagraft, and Oasis described below for details)."* Most studies in chronic wounds include a 2-3 week screening period with standard care to identify wounds that will progress to healing adequately with standard care. This is to ensure the wounds evaluated in skin substitute or other advanced treatment trials are truly non-responding 'chronic wounds'. This is essential to eliminate these patient's from the study that will heal without the need for an advanced treatment and that would not be a candidate in the 'real world' for advanced treatment.	We agree with the reviewer's comments. We added the following sentence: "This procedure insures that only patients with hard-to-heal chronic wounds are enrolled in the study."

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Discussion/ Conclusion	The Coalition recognizes that in submitting our comments to AHRQ online in the various sections rather than in one total paper, different reviewers may be reading different areas—however, since we believe we have not been given enough time to thoroughly respond in full to all of the questions, we would ask that the reviewers of this section to please read our comments in the Executive Summary since they pertain to this section also. However, we are copying below some of our responses in the Methods section since they are so relevant to the discussion and conclusions. We will first give you some our specific comments and then the information from the Methods section. ***Only five of 31 products listed in the report were examined in RCTs:*** 19 products listed in the report are not indicated or labeled for clinical treatment of chronic wounds and would therefore not have been identified in chronic wound studies. 6 of the 19 are wound dressings used to cover and protect the wound and are not biological cellular and engineered tissue alternatives. These products should not be included in the analysis. ***Only one of the 14 studies compared two skin substitute products (OASIS vs. Hyaloskin):*** This assumption is incorrect. OASIS is a bovine collagen matrix (biological skin substitute) which is surgically applied for tissue re-growth. Hyaloskin is a manufactured dressing with fibers of collage blended in the dressing center and is a cover dressing that is meant to be removed at selected time during wound management. This reference needs to be corrected. One notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers.	We have removed any products not indicated for chronic wounds. To generate our list of skin substitute products we started with the products listed under CMS codes Q4101 to Q4122, located the FDA product codes for these products, and looked for similar products within these FDA codes to generate a list of products. We included only those products indicated for chronic wounds and therefore not all of the products within an FDA product code would have been included in the report. Pressure ulcers are an important chronic wound and were considered for this report before the literature search was performed. The Landsman et al., 2008 study has been included.

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Discussion	***Only generally healthy patients were enrolled in studies.*** *The researchers noted patients with infected wounds, who used medications that could impede wound healing, had clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes were excluded.* The exclusion criteria for wound studies for diabetic patients and those for vascular/ arterial ulcers must be consistent with the (FDA) labeling and be compliant with medical appropriateness and coverage policy criteria. All of the cellular and engineered tissue alternatives are not indicated for use on an infected wound or a wound with inadequate vascular supply to support tissue growth. Malnutrition and uncontrolled diabetes will affect healing and therefore must be corrected before a skin substitute would be medically appropriate. In almost all Medicare and private coverage policies, they include criteria for coverage which are medically appropriate. Some examples are: • Applied to wounds reasonably expected to heal and not applied to wounds demonstrating such hostile host environment that destruction of the substitute is highly likely. • Applied to wounds that are clean and free of infection. Applied only to wound with adequate circulation/oxygenation to support tissue growth/wound healing as evidenced by physical examination with presence of acceptable peripheral pulses and/or Doppler toe signals and/or ankle–brachial index (ABI) of no less than 0.65.	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies. We have added to the text with regard to PMA regulated products included in this report: “The indications for use of these products is also more specific compared to products regulated under the 510(k) process. The wounds must be non-infected, greater than one month in duration, and not responded to conventional treatment.”

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Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	**Methodology of the Systematic Review** The methodological approach of this review has several major flaws: (1) selection of studies; (2) outcomes; (3) bias assessment; and (4) reporting. *Selection of studies* 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.[1,2] The percentage of "real world" patients excluded in such studies in wound care can be high.[2] RCTs are appropriate for establishing an effect under controlled conditions but are problematic when solely used to translate outcomes to "real-world" patients with chronic wounds because many patients do not fit the populations used in RCTs.[3] A good example of why some promising wound care products do not work well in all wound care 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"[4] or as a combination of the following three factors: (1) best research evidence; (2) best clinical experience; and (3) consistent with patient values.[5] In other words, the approach does not only look at 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	This report and questions were requested by CMS. The scope of the report was limited, and evidence from RCTs was thought more likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited. The Landsman and DiDomenico studies mentioned by the reviewer have been added to the report.

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			data on the risk, benefits, and costs of new and emerging technologies."[6] Because the authors of this systematic review chose only to examine RCTs published in the per-reviewed literature, much of the evidence on cellular and engineered tissue is missing, and thus the conclusions in terms of coverage of these products are therefore skewed. Furthermore, it is a puzzling why the authors apparently searched the gray literature but did not report on it. Why do this in the first place? Typically, Cochrane reviews look for abstracts, unpublished material, ongoing clinical trials, and so forth, so as to minimize publication bias, particularly when conducting meta-analysis, which was not done in this review. Granted, it can be very difficult to analyze such studies published as abstracts or research letters, but their inclusion is important, even if detailed analysis is not possible. Furthermore, there is no excuse not to search for evidence published in the peer-reviewed literature if that evidence is not published in English. Given the extensive effort that was put into searching, the authors could have found studies that would have had English abstracts, and then decided upon their relevance and had them translated. Not doing so is another form of selection bias. We also believe that many studies should have been included in this section. For example - The O'Donnell systematic review of randomized controlled trials of wound dressings for chronic venous ulcers (. J Vasc Surg 2006;44:1118-25.) 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 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. Two other studies should also be included since they	

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			are "head to head" studies of two "skin substitute" products: • 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 • 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	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	*Outcomes* The authors of this report chose to ignore many valuable outcomes that are linked to partial wound healing, in part because they chose to ignore observational trials, although sometimes this information is reported in RCTs. This is important because healing chronic wounds often requires many repeated, sequential, or overlapping treatments to completely heal a wound,[1,7] and this approach cannot be easily accomplished in an RCT.[8] For example, a venous leg ulcer would have to receive adequate compression, and might be treated with silver-impregnated dressings to reduce infection before receiving Apligraf to ensure that the wound is not clinically infected . There is an increasing body of evidence that partial wound-healing outcomes, such as time to reach 50% reduction wound area, are valid and clinical useful endpoints that can be used in real world wound care patients to determine whether the wound is clinically responding to a given treatment regimen.[9-16] In ignoring these types of outcomes and focusing only on RCTs, the reviewers seem to have entirely dismissed evidence-based practice altogether.	The most important patient-oriented outcome is complete wound healing and is therefore the focus of this report.
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	*Bias assessment* The Coalition is concerned of ECRI's condemnation of the comparative efficacy studies with respect to bias.	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN,

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			The authors should note that many of these studies were designed with respect to the FDA requirements and thus can be very difficult to conduct these studies in a blinded fashion. We note that the reviewers chose a non-validated approach to assessing bias assessment, which does not seem to have been reported in the literature. While some of the elements listed are certainly crucial, definitions of yes, no, or not reported are missing. For example, by what criteria did the reviewers judge that a study used appropriate randomization methods or concealment of treatment group allocation? Second, the authors seem to have singled out wound size/duration as and number of comorbidities the only important baseline parameters, suggesting 15% as the split point. How did they arrive at these specific criteria? 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. 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. Finally, there was no GRADING reported. GRADE is becoming one of the most important techniques by which the synthesis of the evidence is evaluated in terms of the quality of evidence across studies for each important outcome; which outcomes are critical to a decision; the overall evidence across these critical outcomes; the balance between benefits and harms; and the strength of recommendations.[17] Instead, the reviewers used the EPC approach, which is conceptually similar to the GRADE system of evidence rating; it requires assessment of four domains: risk of	Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text has been added to define “Yes,” “No,” and “Not Reported” in the risk of bias assessment. We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. Individual studies are evaluated for risk of bias on an outcome-by-outcome basis. Grading the strength of evidence is a judgment about all studies for a given population, intervention, comparison and outcome, taking into account the risk of bias within individual studies, the consistency of findings across studies, the precision and magnitude of the effect, and the directness of the evidence for the question at hand. We have added text to explain

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			bias, consistency, directness, and precision. Additional domains to be used when appropriate include dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias. Strength of evidence receives a single grade: high, moderate, low, or insufficient.[18] This would have been a reasonable approach had it been followed in a thorough fashion. Instead there are only one or two sentences in the entire 121-page report devoted to directness and consistency, and precision was entirely ignored at the expense of pages on risk of bias. We would submit that according to ECRI's own procedures and criteria that this systematic review was poorly done. Consequently, its conclusions must be regarded as uncertain.	this. Unfortunately, there were few instances in which more than one study used the same products in comparable populations and measured the outcome of complete wound healing. We have added tables to the report to add clarity to the presentation of results and strength of evidence.
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Methods	*Reporting* The gold standard for reporting systematic reviews are the PRISMA guidelines. In this review, several items were missing (e.g., method of data extraction, and summary measures presented as differences in means and risk ratios). Moreover, no rationale was given for not conducting meta-analysis, as this is usually a key part of any systematic review. **References** 1. Serena T, Bates-Jensen B, Carter MJ, et al. Consensus principles for wound care research Obtained using a Delphi process. Wound Repair Regen 2011;in press. 2. 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. 3. van Rijswijk L, Gray M. Evidence, research, and clinical practice: a patient-centered framework for	The PRISMA checklist is a useful tool but is not a standard component of the Technology Assessment reports for CMS program. The original scope of the report did not include quantitative analysis. Risk differences, relative risks and odds ratios are presented in the final report. The studies included in this report are extremely diverse in terms of populations, wound types, interventions and comparators. The original scope of the report did not include meta-analysis, but we have added details about studies that illustrate the reasons we did not combine many of them in a meta-analysis and have added the two meta-analyses that were performed.

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			progress in wound care. Ostomy Wound Manage 2011;57:26-38. 4. Gray JA. Evidence-based Health Care: How to Make Health Policy and Management Decisions. London: Churchill Livingstone, 1997. 5. Institute of Medicine (2001). Crossing the Quality Chasm: A New Health System for the 21st Century, Washington, DC: National Academy Press. 6. Tunis SR. A clinical research strategy to support shared decision making. Health Aff (Millwood) 2005;24:180-4. 7. Sussman C, Bates-Jensen B. Wound care. A collaborative practice manual for health professionals. 3rd ed. Philadelphia, Pa: Lippincott, Williams & Wilkins, 2007:500. 8. Carter MJ, Warriner RA 3rd. Evidence-based medicine in wound care: time for a new paradigm.Adv Skin Wound Care 2009;22:12-6. 9. Bolton L, McNees P, van Rijswicijk L, et al. Wound healing outcomes using standardized assessment and care in clinical practice. J Wound Ostomy Continence Nurs 2004;31:65-71. 10. Parnell LK, Ciufi B, Gokoo CF. Preliminary use of a hydrogel containing enzymes in the treatment of stage II and stage III pressure ulcers. Ostomy Wound Manage 2005;51:50-60. 11. Snyder RJ, Cardinal M, Dauphine´e DM, et al. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage 2010;56:44-50. 12. Coerpe S, Beckert S, Ku¨ per MA, et al. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single-center cohort of 704 diabetic patients. J Diabetes Complications 2009;23:49-53. 13. Sheehan P, Jones P, Caselli A, et al. Percent	

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			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;26:1879-82. 14. Phillips TJ, Machado F, Trout R, et al. Prognostic indicators in venous ulcers. J Am Acad Dermatol 2000;43:627-30. 15. van Rijwijk L. Full-thickness leg ulcers: patient demographics and predictors of healing.Multi-Center Leg Ulcer Study Group. J Fam Pract 1993;36:625-32. 16. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatol 2000;142:960-4. 17. Carter MJ. Evidence-based medicine: an overview of key concepts. Ostomy Wound Manage 2010;56:68-85. 18. Owens DK, Lohr KN, Atkins D, et al. ECRIseries paper 5: grading the strength of a body of evidence when comparing medical interventions—agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol 2010;63:513-23.	
Anonymous Reviewer 4	Coalition of Wound Care Manufacturers	Tables	In ***Table 3***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. In ***Table 5***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted. In ***Table 8***, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original approval date was 2000. In ***Table 10***, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.	The first 510(k) clearance document referring to chronic wounds for Oasis is the 2006 date. We could not locate any earlier date for chronic wounds. The 2000 date probably refers to the Oasis Burn Matrix but we could not locate a clearance or approval document for this device on the FDA web site. Landsman et al., 2008 has been added to the report.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	General	While this technology assessment is an extensive review of the wound care literature to evaluate advanced wound care products, there are several areas that we would like to offer comments to clarify the information that is provided by AHRQ. Additionally, due to the short review time frame (which included two public holidays), we would like to be able to include additional feedback as we receive comments from reviewers.	No response needed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Executive Summary	This section provided an overview of the entire document and what ECRI Institute hoped to accomplish. However, there are several sections for which we would like to provide some clarifying information. ?In the Background portion of this section, the authors stated: "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process." This statement is incorrect and misleading in several respects. First, products regulated under 21 CFR 1271, Human cells, tissues, and cellular and tissue-based products (i.e., HCT/Ps) may or may not be regulated as drugs or devices, depending on the various requirements. For instance, some manufacturers who minimally manipulate autologous tissues are not regulated as drugs or devices and do not need to demonstrate safety or effectiveness to begin marketing their services or products. On the other hand, certain HCT/Ps are required to meet all of the applicable requirements of drug or device manufacturers. Further, the FDA has stated in warning letters that making certain claims about HCT/P-regulated products can cause them to be 510(k) or PMA products even though the origin and composition is identical.	Describing regulatory information provided in FDA documents is an important part of this report. Changes to the text suggested by the FDA reviewer have addressed these concerns.

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Anonymous Reviewer 5	Cook Biotech Incorporated	Executive Summary	Secondly, device premarket requirements (e.g., PMA, HDE and 510(k)) are risk-based, not product origin-based. For example, FDA requires that PMA (premarket approval) applications be submitted for devices that have been identified as high risk. Under section 513(a)(1)(C) of the Food, Drug and Cosmetic Act, Class III devices are defined as devices for which insufficient information exists to place them into Class I or Class II and are ?for use in supporting or sustaining human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.? Therefore, all cellular-based devices have been placed into Class III by FDA because they ?present a potential, unreasonable risk of illness or injury.? On the other hand, Class II devices, which typically require 510(k) clearance, have sufficient information about their safety and effectiveness that a manufacturer need only demonstrate that the devices are substantially equivalent to other devices.	Describing regulatory information provided in FDA documents is an important part of this report. Changes to the text suggested by the FDA reviewer have addressed these concerns.

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Anonymous Reviewer 5	Cook Biotech Incorporated	Executive Summary	Finally, PMA and HDE devices should not be lumped together. A PMA device manufacturer is required to demonstrate a reasonable assurance of safety and effectiveness, while an HDE device manufacturer must demonstrate a reasonable assurance of safety only. Later portions of the Executive Summary appear to recognize some of these distinctions (e.g., the difference between PMA and HDE requirements). We also recognize that the report has formulated this summary text in response to a key question formulated by the investigators, What are the U.S. Food and Drug Administration (FDA) regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361[21 CFR 1270 & 1271]?? However, it is unclear how this question about regulatory status bears upon the purpose of the report: "The purpose of this review is to provide information to CMS for consideration in HCPCS coding decisions. The review will facilitate CMS' evaluation of HCPCS coding for skin substitutes by providing CMS with relevant studies and information for consideration of coding changes." (page 12) Given that the regulatory classification has no bearing on the amount of data available for assessing safety and effectiveness or the relative safety and effectiveness of one product versus another, it seems more accurate and appropriate to (1) answer the question by clearly describing the various regulatory requirements and (2) listing which products are subject to which requirements, without attempting sweeping, inaccurate summaries and then (3) proceed to the analysis of existing data without respect to the product?s regulatory requirements.	Describing regulatory information provided in FDA documents is an important part of this report. Changes to the text suggested by the FDA reviewer have addressed these concerns.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Methods	In the Methods of the review portion of this section, ECRI Institute commented that as part of the review, they developed Key Questions to answer, which included ?What are the U.S. Food and Drug Administration (FDA) regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361[21CFR 1270 & 1271]?? However, as noted above, this question is irrelevant for the evaluation of device effectiveness. Again, as noted above, the FDA device classification system is risk-based; the classifications do not automatically guarantee that a device is a safe and effective or that one device is more safe or effective than another device. Thus, it is entirely possible for a device cleared by FDA under a 510(k) to be as, or more, safe and/or effective than a device approved under a PMA. The executive summary only comments of the 3-letter classifications that are used to designate the different categories of products and specific terminology that is used in the FDA indication statement.	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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. This report specifically examines the use of skin substitutes for treating the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (including venous ulcers and arterial ulcers). Treatment of burn wounds with skin substitutes is outside the scope of this report.
Anonymous Reviewer 5	Cook Biotech Incorporated	Executive Summary	In the Evidence for Skin Substitutes portion of this section, ECRI Institute commented that 'These products use animal tissue collagen or synthetic material to create an extracellular matrix that acts as a wound covering and scaffold for tissue invasion and regrowth. They do not contain human cells and therefore do not have a natural source of growth factors or cytokines involved in initiating the wound healing process.' This statement is not true: while these animal-derived products do not contain human cells, they may still contain natural sources of animal-derived growth factors or cytokines (or other animal-derived non-collagen components) that are involved in the wound healing process.	The FDA reviewer has commented on the importance of growth factors and cytokines in wound healing. In response to the FDA reviewer we have added a discussion of growth factors and cytokines to the Background. In addition the following sentence has been added at the end of the paragraph cited by the reviewer from Cook Biotech: "The actual extent to which any one growth factor or cytokine is essential for wound repair has not been determined."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Executive Summary	In Table 3, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original clearance date was 1998.(K973170 4/30/98) Additionally, 510(k) devices are cleared, not approved.	We have made the change to the report.
Anonymous Reviewer 5	Cook Biotech Incorporated	Executive Summary	In Table 5, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers was omitted.	We have added this study to the table.
Anonymous Reviewer 5	Cook Biotech Incorporated	Introduction/ Background	This section provided an overview of wound healing and the general wound care landscape for treatment/management of chronic wounds. However, again, there are several sections upon which we would like to provide some clarifying information. In the Complementary or Competing Products portion of this section, the focus does not seem to be on products; instead the focus seems to be more upon factors that need to be controlled in any treatment algorithm for all wounds. In the Usual Care for Chronic Wounds portion of this section, the authors state: “Standard of care? (SOC) was commonly used in the studies included in this report when referring to the control group wound care or base wound care to which a skin substitute was added. Standard of care is also frequently used in presentations on manufacturer Web sites. However, as described above, usual care or standard of care is not a consistent term that describes an agreed upon set of procedures to be used when treating chronic wounds.” Standard of care (SOC) is an industry vernacular that is used to describe the prescribed treatment that is most currently accepted to be effective, which means that this is the treatment that is most currently used. Further, SOC must be agreed upon by the study participants ahead of study initiation and be relevant and acceptable to their practices.	We have removed the section Complementary or Competing Products and included its information under Usual Care for Chronic Wounds.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Background: U.S. Food and Drug Administration Regulations Governing Skin Substitute Products	In the U.S. Food and Drug Administration Regulations Governing Skin Substitute Products portion of this section, the authors provide an expanded explanation of the regulatory categories; however, as above, there is no explanation as to how this relates to this review. The section opens with the misleading statement (per our comments above): "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of the four categories described below depending on the origin and composition of the product.? The statement should be revised accordingly. As described above, the statement, "Therefore, wound care products regulated under the 510(k) process will typically require less evidence that they promote wound healing compared to products regulated under the PMA process." is misleading because, on the one hand, Class II devices have well-established safety and effectiveness profiles, and, on the other hand, copious clinical data may exist on individual products. Additionally, the discussion of these categories is inconsistent with the Executive Summary statement: "Skin substitute products are regulated by the U.S. Food and Drug Administration (FDA) under one of four categories depending on the origin and composition of the product: Human derived products regulated as HCT/Ps, human and human/animal derived products regulated through premarket approval (PMA) or humanitarian device exemption (HDE), animal derived products and synthetic products regulated under the 510(k) process."	An FDA reviewer has provided input on the regulatory section of the report. Changes were made in response to the FDA's comments which are similar to the comments made by this reviewer.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Methods	This section provided a description of the methods that were used to obtain and evaluate the information to evaluate the different products. In the Search Strategy portion of this section, it was stated that: "Systematic search of the following data based unlimited by date for secondary publications (e.g., systematic review, Health Technology Assessments): The Cochrane Database of Systematic Review (Cochrane Reviews), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment and Database (HTA)." However, there does not appear to be an accurate summary of the search method such that they can be reproduced by third parties (e.g., search terms, listing of all exclusion criteria) and there do not appear to be any results from the searches that were conducted in these databases.	For this report, we are only providing the strategy in Ovid syntax (used to search MEDLINE and EMBASE) for the years from 1996 through 2011 for all of the searches. Results from the searches of the other databases were sent directly to the analysts to determine inclusion or exclusion.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Methods: Risk of Bias Quesitons	In the List of Quality Assessment Questions portion of this section, the list of questions included: "Was the wound assessor blinded to the patient's, treatment group. The inclusion of these questions in ECRI Institute's analysis was described in the Explanation of Quality Assessment Questions as: "The FDA guidance document on wound treatments suggests that blinding should be employed when feasible. Blinding of patients to wound care treatment is not always possible because of visible differences in the treatment devices, dressings, or wound care routine." In practice, it is almost always nearly impossible to blind the wound assessor to wound care treatments, as the treatments often result in differences in wound appearance during the course of treatment, can leave debris of the products behind, or have other special characteristics that give clues to their identities. As such, characteristically objective wound evaluation techniques, such as wound dimensions and depth, measured with calibrated instruments and documented by photographic techniques are typically incorporated into the assessment of wounds.	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Methods: Risk of Bias Quesitons	In the List of Quality Assessment Questions portion of this section, the list of questions included: "Was the study funded by an organization other than the skin substitute manufacturer?" The inclusion of these questions in ECRI Institute's analysis was described in the Explanation of Quality Assessment Questions as: "Funding of studies by a device manufacturer either directly or through support or employment of study authors has the potential to bias study results." Such unsubstantiated innuendo is completely inappropriate in a professional report. Insofar 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 such trials, it is generally left to device manufacturers to fund clinical studies to obtain valid scientific evidence to support approval/clearance or simply to responsibly market the products. In fact, the governments have no incentive to bring new products to market, only businesses do. The issue of potential investigator bias is taken very seriously by device manufacturers. It is important to understand that all clinical studies must be reviewed by institutional review boards at each investigative site. Furthermore, significant risk studies are subject to thorough scrutiny by the FDA, including disclosure of financial conflicts of interest in marketing applications, and studies for PMA approval include audits of individual investigative sites as well as audits of the complete data set used in the analysis of the study. Additionally, a recent independent systematic review of all wound studies found on the venous stasis ulcers (O?Donnell et al, 2006) found that only two RCTs met all the quality criteria for a properly controlled study. Both of these **[comment cut off as is]**	We have removed the question regarding funding from our risk of bias assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Methods: Strength of Evidence	In the Strength of the Evidence Base portion of this section, the authors state: "Determining the risk of bias in the individual studies in an evidence base is the first step in determining the overall strength of an evidence base. An evidence base consisting of studies with a high risk of bias implies a low strength of evidence." However, in evaluating all of the literature that exists regarding the skin substitutes that are addressed in this technology assessment, all of the independent systematic reviews are dismissed due to the fact that they are review articles and the evaluation of systematic review databases, such as Cochrane Reviews, are conducted but excluded, removes publications that provide the highest level of clinical evidence for effectiveness of products. Further, a high risk of bias, even if present, no more guarantees a low strength of evidence than does a conflict of interest guarantee that an investigator would falsify data. This is simply a non-sequitur.	The assessment of strength of the evidence base and of bias follow the approaches used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text has been added to define "Yes," "No," and "Not Reported" in the risk of bias assessment. We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. Individual studies are evaluated for risk of bias on an outcome-by-outcome basis. Grading the strength of evidence is a judgment about all studies for a given population, intervention, comparison and outcome, taking into account the risk of bias within individual studies, the

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				consistency of findings across studies, the precision and magnitude of the effect, and the directness of the evidence for the question at hand. We have added text to explain this. Unfortunately, there were few instances in which more than one study used the same products in comparable populations and measured the outcome of complete wound healing. We have added tables to the report to add clarity to the presentation of results and strength of evidence.
Anonymous Reviewer 5	Cook Biotech Incorporated	Results	This section provided the results from the review of products and literature. In answering Key Question 1, the authors list several products, such as AlloDerm Regenerative Tissue Matrix, Flex HD, Puros Dermis, Repliform, InteXen, and Permacol, which are not used/ cleared for the treatment of chronic wounds, and should be eliminated from this discussion.	Products not indicated for chronic wounds have been removed from the report.
Anonymous Reviewer 5	Cook Biotech Incorporated	Results: Key Question 1	In Oasis Wound Matrix (Cook Biotech, Inc.), the authors state: Oasis Wound Matrix (Cook Biotech, Inc., West Lafayette, IN) was cleared for marketing under the 510(k) process in July 2006 (K061711) and is indicated 'for the management of wounds including: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers, chronic vascular ulcers; tunneled, undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound deshiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds.' The original clearance date was in April 1998 (K973170), with additional indications added in 2000.	This change has been made to the document. Information on indications was not available in the FDA databases for the earliest clearance dates. Therefore the earliest clearance dates for which summary information is publicly available have been included in the report.
Anonymous Reviewer 5	Cook Biotech Incorporated	Results: Key Question 1	In Table 8, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original clearance date was 1998. Additionally, 510(k) devices are cleared, not approved.	This change has been made to the document.

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Anonymous Reviewer 5	Cook Biotech Incorporated	Results: Key Question 2	In answering Key Question 2, the authors state that their searches identified 14 RCTs that met the inclusion criteria. However, one notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers (See comment in References).	The Landsman et al., 2008 study is now included in the report.
Anonymous Reviewer 5	Cook Biotech Incorporated	Results: Key Question 2	Further, we believe Key Question 2 itself is flawed as topical growth factors are far from "usual care" when it comes to these wounds.	Key Question 2 has been changed to compare skin substitutes to any type of wound care as a comparison rather than trying to define a usual care for comparison. Key Question 2 has been changed to: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures
Anonymous Reviewer 5	Cook Biotech Incorporated	Results: Key Question 2	In Table 10, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted.	The Landsman et al., 2008 study is now included in this table.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Results: Key Question 2	In the Quality of the Evidence Base portion of this section, the authors state: "All four studies of Oasis were considered at high risk of bias because wound assessor blinding was not reported. Reporting of comorbidities was absent in three of the studies." As mentioned above, it is rarely possible to blind the wound assessor to wound care treatments, as, among other things, the treatments often result in differences in wound appearance during the course of treatment. Instead, there are objective wound evaluation techniques, such as wound dimensions and depth that can be incorporated into the assessment of wounds. Additionally, as many clinical study authors are keenly aware, there are publication limits (i.e. space constraints of the manuscript), which force the elimination of many of the unreported data fields because they are insignificant in relation to study outcomes.	After reviewing several comments and giving further thought to this issue, we recognized that assessor blinding is not critical for determining the outcome of complete wound healing, the most important outcome we addressed. While we consider assessor blinding a method for reducing potential for bias, we decided that it should not be given so much weight in this assessment given our focus on complete wound healing. Two of the OASIS studies are now considered low risk of bias and the other two are considered moderate.
Anonymous Reviewer 5	Cook Biotech Incorporated	Results: Key Question 2	In the Study Design, Patient Enrollment Criteria... section it is worth noting that not all studies enrolled patients with wounds of the same size, even though comparable healing rates were achieved across studies. For example, Tables 39-43 show that the studies for OASIS Wound Matrix often allowed larger wounds and had median wound sizes that were 2, 5 or even 20 times the median size (sq. cm) of those allowed in other studies, and this important parameter, among others, was completely overlooked in the narrative of this analysis.	We have mentioned in the report that "Wound duration and wound size before enrolling in a study were also poorly reported." Part of our bias assessment also looks for differences in wound sizes within studies.

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Anonymous Reviewer 5	Cook Biotech Incorporated	Discussion/ Conclusion	This section provided the overall conclusions for the assessment. Here, the authors reiterated that: "Of the included studies, only one had a moderate risk of bias while all others were considered at a high risk for bias, primarily because these studies did not report blinding of the wound assessor." Practically-speaking, it is rarely possible in wound healing studies to blind the wound assessor to wound care treatments, and objective wound evaluation techniques, such as wound dimensions and depth, must be incorporated into the assessment of wounds.	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element.
Anonymous Reviewer 5	Cook Biotech Incorporated	Discussion/ Conclusion	"Also missing from this evidence base were studies that compared the various types of skin substitute products. Only one of the 14 studies compared two skin substitute products (OASIS vs. Hyaloskin)." One notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers.	Landsman et al., 2008 is now included in the report.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Discussion/ Conclusion	"While these results are consistent (all studies reported a better healing rate when treated with a skin substitute) and suggest that skin substitutes could be used in the treatment of diabetic foot ulcers and venous leg ulcers, the comparisons were made to relatively simple usual care approaches such as saline-moistened gauze. Only four of the studies used a more advanced wound dressing product. Comparisons with other advanced wound care products in terms of efficacy and cost are needed to determine where and when skin substitutes should be used." Again, the comparison arms are very carefully chosen by sponsors and investigators to reflect current states of medicine, real-world practices, and meaningful benchmarks; are reviewed by IRBs and often regulators ahead of initiation; and more often than not reflect a cost- and reimbursement-neutral alternative for these patients. This is the most reasonable and appropriate approach. Further, one notable study that was missed was Landsman et al., 2008 that compared OASIS Wound Matrix to Dermagraft in the treatment of diabetic foot ulcers.	The information in this draft paragraph has been modified and incorporated into several new paragraphs in the conclusion section. The term "advanced wound care product" has been removed from the report. Landsman et al., 2008 is now included in the report.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Executive Summary	In Table 3, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original clearance date was 1998. Additionally, 510(k) devices are cleared, not approved. In Table 5, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted. In Table 8, the approval date for OASIS (Cook Biotech, Inc.) is listed as 2006. However, the original clearance date was 1998. Additionally, 510(k) devices are cleared, not approved. In Table 10, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted. In Table 11, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted. In Table 12, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted. In the tables in Appendix B and C, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted.	These changes have been made to the document. Landsman et al., 2008 is now included in the report.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 5	Cook Biotech Incorporated	Appendices	In Appendix B, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted. In Appendix C, Landsman et al, 2008, OASIS Wound Matrix vs. Dermagraft for the treatment of diabetic foot ulcers (See comment in References) was omitted from all tables referring to Oasis Wound Matrix. ---------References---------- In References, the citation 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.? needs to be added.	Landsman et al., 2008 is now included in the report.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page iii	Regarding the list of Skin Substitute Products on Page iii: FDA does not refer to any product or class of products as “Skin Substitutes,” because each product (Biologic, Human Tissue, or Medical Device) is missing one or more key elements of human skin. Most Medical Devices used in wound repair are called Wound Dressings. A few cellular wound repair products may also be identified as “Skin Constructs.”	In response to the comments from the FDA, we removed the headings with FDA regulatory information and inserted headings to describe the material used to create the products in each group: Products derived from human donor tissue, minimally processed; Products derived from living human and/or animal tissue and cells; Acellular animal-derived products, and Biosynthetic products.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page iii	The list under “Animal Derived Products Regulated under the 510(k) Process” is incomplete. Review of 510(k)s with the Product code KGN yielded 67 records. The list of “Synthetic Products Regulated under the 510(k) process” (i.e., 5 products) may also be incomplete, based on how the authors defined the term “Skin Substitutes.”	We have reviewed all of the entries in code KGN and added them to the list.

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Project Name: Skin Substitutes for Treating Chronic Wounds
Project ID: HCPR0610

Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page v	Page v provides a list of products regulated as HCT/P. This list is incomplete, because any product containing human tissue (including those regulated under the Medical Device authorities) are still considered "HCT/P." Hence a more accurate title might be "Human-Derived Products regulated solely under the 21 CFR 1271." Stated alternatively, products regulated solely under the Human Tissue Regulations (21 CFR 1271) are a subset of all HCT/Ps, because there are other HCT/Ps regulated under the PMA and BLA premarket review process.	We changed the header of this section to "Human-Derived Products Regulated as HCT/P Solely Under the 21 CFR 1271." We also changed table headings to match this wording.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Executive Summary	Regarding the first 7 pages of the Executive Summary whose page numbers are ES-17. The summary presents information on: 1) the rationale for developing Skin Substitutes, 2) the properties of an "ideal Skin Substitute," 3) broad categories for the composition of Skin Substitutes and 4) the topic-specific search terms for identifying publications and approved/cleared products. The summary does not present a clear definition of what a Skin Substitute is for the purpose of this report or how it differs from a "Wound Dressing." This is important, because FDA does not have a class of products denoted as "Skin Substitutes." Therefore, what elements must or must not be present to meet this report's definition of a Skin Substitute? What elements must be present to define a synthetic Skin Substitute (page 11) for the purposes of this report? Is it appropriate to seek conclusions about a class of FDA products that does not exist?	It was not our intent to create a formal definition for skin substitute products. The following has been added to the Executive Summary to explain how we created our list of skin substitute products: "For this report, we have not created a definition for a skin substitute product. Instead we used the products listed under CMS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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."

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Executive Summary	The report does not speak to the most important aspects of wound repair: 1) maintaining a moist wound healing environment and 2) compliance with recognized methods for promoting chronic wound closure (e.g., off-loading and/or compression). If there were ways to improve these two issues in wound repair, the incidence and severity of many chronic wounds might be significantly reduced.	We have revised the report in several places to emphasize the importance of a moist wound healing environment and other methods known to promote the healing of chronic wounds.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Executive Summary	The following statement is incomplete, "an HDE is similar to PMA application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose." This statement should be revised to include the following text: HDE approval is based on evidence of probable benefit in a disease population occurring at a frequency of less than 4,00 patients per year in the U.S.	We have added the following language to the report: "Wound care products regulated under the PMA process are indicated for treating a subset of chronic wounds, those wounds with more than 30 days' duration that have not adequately responded to standard wound care. The 510(k) products are indicated for managing chronic wounds and no restrictions are put on wound duration or prior treatments." We also added "HDE approval is based on evidence of probable benefit in a disease population occurring at a frequency of less than 4,000 patients per year in the U.S."
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Executive Summary	The discussion of comparative outcomes for PMA and 510(k) regulated products does not clarify that PMA products are indicated for a subset of all chronic wounds (e.g., patients with baseline wound durations greater than 1 month and who failed to demonstrate a significant reduction in wound size after 2 weeks of standard care). Hence, comparisons of PMA and 510(k) wound care products may not reflect all patients with chronic wounds, but instead a subset of more serious patients.	Additional text has been added to the report to cover these differences.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page ES-1	States, "They do not contain human cells and therefore do not have a natural source of growth factors or cytokines involved in initiating the wound healing process." It might be important to follow this statement with comments such as, the true value of cytokines/growth factors in any wound dressing remains to be identified. While growth factors and cytokines are often cited as important for wound healing in "skin substitutes," there are may issues that suggest that these proteins may not be as critical as manufacturers claim. For example, 1) the limited number of cytokines approved for wound healing indications and the fact that normal wound healing requires: 2) the delivery of the correct combination of stimulatory and inhibitory cytokines and growth factors, 3) to the correct anatomical location, 4) at the correct phase of the wound healing process, 5) for the appropriate amount of time.	We have added this new sentence: "The actual extent to which any one growth factor or cytokine is essential for wound repair has not been determined." A discussion of growth factors and cytokines has been added to the Background section under Phases of Normal Wound Healing.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page 102	Regarding the pages in the report identified as page 102, the definitions of "Publication Type" do not included the information provided in the "Summaries of Safety and Effectiveness Data (SSEDs) that are issued at the time of PMA approval. Review of this information may have value. Such information should meet the cited requirements for data preparation and documentation. It also reflects data which underwent Bioresearch Monitoring audits.	We obtained the Summaries for Apligraf and Dermagraft and revised the tables and adverse event data where necessary.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Executive Summary	Regarding comments on page 1, the following statements need to be revised (see in bold): "Human tissue can be obtained from human donors, processed, and used exactly in the same role, skin for skin, tendon for tendon, bone for bone, etc. These uses are regulated as human tissue intended for transplantation (HCT/Ps)" as long as the proposed clinical use and manufacturing methods are consistent with definitions of "Homologous Use" and "Minimal Manipulation" cited in 21 CFR 1271.	This change was made as indicated.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	ES-2	Human tissue and cells may also be used as a source of cells for culturing to produce cellular derived material for wound healing. These products may be regulated under the BLA (PHS Act) or PMA /HDE (FD&C Act), depending on their composition and primary mode of action.	This change was made as indicated.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Results	A number of medical products intended for use in treating wounds are derived from animals. Porcine and ovine tissues and skin is processed into sheets for use as Skin Substitutes. Bovine fetal tissue is a source of skin cells that are grown in culture to produce skin substitutes. These products may be regulated under 510(k) process if there is an appropriate predicate device with an equivalent composition and Intended Use and that the proposed product does not raise any different types of safety or effectiveness questions. When a product does not meet these criteria, it may be reviewed in BLA (PHS Act) or PMA /HDE (FD&C Act) applications, depending on the composition and primary mode of action.	This change was made as indicated.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Results	"Some skin substitute products are made from synthetic material that mimics skin properties. These products are also regulated under 510(k) process." These products may be regulated under 510(k) process if there is an appropriate predicate device with an equivalent composition and Intended Use and that the proposed product does not raise any different types of safety or effectiveness questions. When a product does not meet these criteria, it may be reviewed in BLA (PHS Act) or PMA /HDE (FD&C Act) applications, depending on the composition and primary mode of action.	This change was made as indicated.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page 4 and other pages in the document	Page 4 discusses "Human Derived Products Regulated Through Premarket Approval Process." This discussion needs to clarify that the presence of living cells in Apligraf, Dermagraft and Epicel makes them Combination Products (i.e., with device and biological components) whose Primary Mode of Action, led FDA to conclude that they should be regulated under the Medical Device Authorities. Thus, they are not Class III Medical Devices, but instead Combination Products.	New text was added to the revised document to explain that these are combination products.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page 4 and other pages in the document	Regarding the Animal-Derived Products Regulated Through the 510(k) Process (page 4), I have not compared the list of products presented herein to all cleared Wound Dressings that might fit in this category. Hence this review should not be perceived as confirmation of the accuracy of the product list. I would not be surprised to find that there are other products and hence this list might be better considered as a series of examples, rather then as an all inclusive list.	Product code KGN was examined and additional items were added to the table of animal-derived products regulated through 510(k).

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Results	It seems appropriate to discuss the fact that Wound Dressings cleared under the 510(k) process (or Class I exempt products) are considered to function by "providing a moist wound healing environment." Because the importance of a moist wound healing environment is generally recognized as essential in promoting healing for many different types of wounds (at the body's optimal rate), such products are commercially distributed with a broad Indication for use. For example, "partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds," (page 6) without extensive clinical investigation. For products seeking claims beyond providing a moist wound healing environment, a legally marketed predicate device may not exist and hence clearance through the 510(k) process may not be possible. Therefore determination of whether a PMA or 510(k) premarket application is appropriate is based upon both product composition and claims of product performance.	Text covering these points was added to the revised document.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Background	Similar to the discussion immediately above, it should be noted that Surgical Mesh devices are defined in 21 CFR 878.3300 as "intended to be implanted to reinforce soft tissue or bone where weakness exists." Hence in the discussion of any wound dressing also cleared as a Surgical Mesh, claims of reinforcing soft tissue or bone where weakness exists, relate to device use as a Surgical Mesh and not a Wound Dressing.	We have removed all products that are considered surgical meshes and not indicated for chronic wounds.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Key Question 1	Similarly regarding Hyalomatrix (pages 9-10), part of the cleared indication for use, "as a temporary space-occupying material and as an adjunct for surgical repair in septoplasty, otoplasty, rhinoplasty and various ENT and head and neck surgical procedures involving cartilage tissue," reflects its use as an "Ear, nose, and throat synthetic polymer material" (Procode KHJ) and not as a Wound Dressing.	Hyalomatrix KC (code MGP) and Hyalomatrix (code FRO) are both 510(k) cleared and indicated for management of both venous and arterial leg ulcers and diabetic ulcers.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page 12	Page 12 identifies Orcel in the category of products not yet available in the US for Treating Wounds. The paragraph also correctly states that an HDE was approved in February 2001 for use in patients with mitten hand deformities due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures for covering wounds and donor sites created after the surgical release of hand contractures. This paragraph does not: 1) state that an Orcel PMA was also approved on September 20, 2001 for treatment of fresh, clean split thickness donor site wounds in burn patients and 2) as a PMA-approved device, physicians may use Orcel off-label on chronic wounds.	Text has been added to describe this potential off-label use of Orcel.
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Table 8	A point of clarification, Table 8 presented on pages 15-18 identifies "Approval Dates" for several Wound Dressings cleared through the FDA process. There are no approval dates for any product cleared through the 510(k) process. The verb "cleared" is used to reflect a different level of FDA review.	This has been corrected. The column now says "Clearance."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 6	U.S. Food and Drug Administration (FDA)	Page 23	Page 23 states that "All three studies of Apligraf/Graftskin were considered at a high risk for bias because wound assessor blinding was not reported." This statement is correct. However, because the results of each wound treatment appear differently, masking of these studies may not be possible.	After reviewing several comments and giving further thought to this issue, we recognized that assessor blinding is not critical for determining the outcome of complete wound healing. While we consider assessor blinding a method for reducing potential for bias, we decided that it should not be given so much weight in this assessment given our focus on complete wound healing.
Anonymous Reviewer 7	NA	General	I am concerned about three methodologic issues. I was originally asked to serve as a peer reviewer. I, however, have a conflict of interest. My conflict was the receipt of about $2000 last year to serve as a consultant to one of the companies that manufactures and markets one of the products under review. The consulting activity concerned the design of comparative effectiveness studies. First the authors of this review claim to have tried to create a common grouping for these wound care products. Unfortunately, as is true for many devices, using FDA classifications are not always helpful. The groupings are not alike based on the mode of action of the products, material components, or how they are clinically used. If the goal is to create a generalizable assessment of the products then the authors need to do a better job of understanding wound care and how these products are used and not how the FDA decided to categorize them. Many of the products in the listing would not be used for all wounds and several are very rarely used. Finally, based on FDA practices many of these products did not need to provide evidence of comparative efficacy to gain approval. They, therefore, do not have this level of evidence.	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. To generate our list of skin substitute products we started with the products listed under CMS codes Q4101 to Q4122, located the FDA product codes for these products, and looked for similar products within these FDA codes to generate a list of products. We included only those products indicated for chronic wounds and therefore not all of the products within an FDA product code would have been included in the report. The groupings we created for this report are only intended to be used within this report and serve the purposes of the report only.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 7	NA	Methods: Key Question 2	Second, the authors claim to want to compare these products to usual care. I have worked with several large national and international databases with respect to wound care. I have also helped design several efficacy studies for novel wound care therapies. I have served as a reviewer for the FDA and NIH with respect to wound care. I have and am conducting comparative efficacy studies of wound care therapies. I am an editor of the Cochrane wound group. I have worked on guideline committees on the treatment of wounds for several different academic and non-profit groups. The usual care group that was established by these authors is not a standard care arm but an advanced care arm. It should be properly identified. Many of these products are expensive, not frequently used, not easily available, and all also lack the type of evidence requested by these authors to show efficacy/effectiveness. Many aspects of the claimed usual care arm do not represent first line of care but second line care. This arm could represent a fair comparison if the goal was to compare like products but is should be clearly described by the authors and the authors should demand an equal amount of evidence as demanded below before this arm is codified as usual care. The authors also need to understand that not all wounds are treated the same and the comparison arm would need to vary by wound type. If the authors would like to compare advanced treatments, they need to make sure that they compare across similar wounds, with similar wound care practices and to be consistent with their methods use a mixed treatment comparison meta-analysis approach. Their likely goal of conducting comparative efficacy research is meritorious but would have required different methodology and is in contrast to the groupings created and commented above.	Key Question 2 has been changed to: “For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures…”

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 7	NA	Methods	Third I am concerned about the author's condemnation of the few comparative efficacy studies with respect to bias. Many of these studies were design with respect to FDA requirements. It can be very difficult to conduct device studies in a blinded fashion. The authors do not report any of their own analyses to indicate information bias occurred and do not make estimates about the magnitude of this bias, if it did occur. Do the authors realize that in many of the randomized clinical trials, initial clinical reports showed an increased reporting of cellulitis in the skin substitute arm. The early reports of cellulitis in fact, were errors based on clinical observation likely related to tissue rejection or skin substitute cell death. A finding that was not understood until after the studies had been analyzed. The outcome, a healed wound, was often reported several weeks after it had been applied and had no longer been present in the wound bed for many weeks making it less likely that a biased investigator would remember group assignment. Finally, in one study the maximal effect was noted in a sub-group analysis based on data not previously published. Are these the expectations of biased reporting?	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias.
Bates, Damien	Organogenesis Inc.	General Comments	PMA supplement for 2000 added diabetic foot ulcers as an indication	This indication was added to Table 7.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	General	1) The Draft Report has Limited Usefulness for Clinicians or Developing Coverage and Reimbursement Policies. Most third party payers develop coverage policies which define when an item or service is considered medically necessary and thereby, eligible for reimbursement. Determining medical necessity is frequently based on whether the item or service is expected to improve the net health outcomes of beneficiaries suffering from a particular illness or injury. For some payors, the question is whether an item or service improves net health outcomes for a particular condition as compared to other items or services. We are concerned that readers of the draft TA might incorrectly conclude that Apligraf has not been shown to improve net health outcomes in patients suffering from chronic wounds. In fact, Apligraf has been shown to improve net health outcomes.	We have revised the presentation of the study findings, calculated effect sizes, and graded the strength of evidence.
Bates, Damien	Organogenesis Inc.	General	Second, as discussed in more detail later in this letter, the draft TA does not include any discussion of several important indicators of the quality of the randomized controlled trials (RCTs) included in the trial (e.g., whether the trial was an FDA registration trial, the number of subjects included, whether the study was powered to draw specific conclusions, etc.) and instead appears to focus on a single quality indicator - the risk of bias due to unblinded wound assessment.	We acknowledge that some studies could have used blinded wound assessors but did not report this in the publications. The assessment tool questions for judging risk of bias used in this report closely follow the recommendations made in Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However,

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing. Individual studies are evaluated for risk of bias on an outcome-by-outcome basis. While adequate sample size determined by power calculation is an important aspect of clinical trial design, it is less of an issue in research synthesis. Inadequate power in a single study may be overcome when meta-analysis is possible. If not, it is accounted for in the determination of precision of results (i.e., a small sample will have a wider confidence interval).
Bates, Damien	Organogenesis Inc.	Discussion/ Conclusions	In order to improve the usefulness of the technology assessment to clinicians and to more accurately inform coverage and reimbursement policies, we recommend that the authors include the following statement in the penultimate paragraph of the Discussion and Conclusions on pages 50-51, “There is substantial evidence from RCTs available to clinicians on the use of PMA-approved skin substitutes.”	The following text was added to the Discussion and Conclusions: In contrast, products such as Apligraf and Dermagraft, regulated under PMA, that contain a human cellular component combined with a acellular component are indicated for chronic wounds that have not healed for more than 30 days. Therefore, the wounds treated by Apligraf or Dermagraft have not responded to other treatments such as gauze or to the products regulated under the 510(k) process. Because of the requirements placed on the PMA process, products such as Apligraf and Dermagraft also have more clinical evidence from RCTs supporting their efficacy compared with products regulated under the 510(k) process. Products using the 510(k) process rely on similarity to predicate products to support their efficacy.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	General	2) The Draft Is A Descriptive, Non-Comparative Review of the Clinical Data That Could Lead the Reader to Draw Incorrect Conclusions About the Relative Quality of the RCTs. We are also particularly concerned that, while the authors clearly differentiate among various "skin substitute" products with respect to answering Key Question #1, they combine the RCT clinical data for each product in answering Key Questions 2 and 3. Specifically, the RCTs that met the inclusion criteria were not compared to each other in terms of quality. This is discussed in more detail below. We are further concerned that the limited discussion of these data in the answers to Key Questions 2 and 3, are purely descriptive, not analytical, and that key trial design and results are not included in the descriptive discussion. The absence of a separate analysis of each product's clinical data gives a misleading impression that the clinical data for each product is a similar level of bias and is of equal "low" quality. We strongly disagree with any such conclusions regarding the Apligraf® data.	When assessing the quality of the RCTs included in this report and the strength of the evidence base no special consideration was given to whether a product was regulated under PMA or 510(k).
Bates, Damien	Organogenesis Inc.	General	In our comments, we identify specific sections of the current draft where we believe the analysis and conclusions are either incomplete or incorrect. We are also submitting in summary format additional information collected in the clinical trials that resulted in the three Apligraf® publications cited in this draft TA, hereafter referred to as the Edmonds, Veves and Falanga publications (see Appendices 1-12). We note that the detailed data upon which these publications were based were not included in the publications because of space and word limitations. However, these data are important because they address some of the concerns raised in the draft TA. Based on these additional data and the comments herein, we recommend that the authors make a number of revisions as described below.	We acknowledge that important information on the design and conduct of RCTs is often poorly reported. We encourage journals to recognize the necessity of making this information available in print or another form. We greatly appreciate that Organogenesis has provided these data for use in this report.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Specific Comments ES-2 and Page 5	A. The category "Skin Substitutes" is too broad. Comment: While payers may combine coverage policies for a number of different "skin substitutes" into a single document, they typically address the treatment risks and benefits associated with the use of each type of product separately and do not attempt to compare products that are not similar in make up or indications for use. Specifically, three categories of products have been combined, cell-based interactive wound healing products (PMA products), collagen and synthetic wound dressings (510k Products), and harvested and processed human tissue products (HCT/Ps). By assessing all products that may be described as "skin substitutes" in the aggregate as a single category, as the draft report does for Key Questions 2 and 3 the "denominator" (i.e., number of products) used in the analysis is inflated, and could lead the reader to discount the depth and quality of available studies on specific products and/or product types. For example, there are only three PMA products identified by this report of which two had multiple RCTs performed, whereas only one of the many human tissue products identified had an RCT. Therefore, the evidence base is much more robust for PMA products then it is for human tissue products. In addition, the aggregation of all products into a single category called "skin substitutes," which ignores differences in regulatory status (PMA, 510(k), HCT/P) and labeled indications (even though the indications are included in two of the tables), could mislead readers into believing that the products are interchangeable and that head-to-head trials can be easily performed and interpreted. This is not the case. Specifically, the clinical outcomes produced by the application a PMA product like Apligraf® have been reported to FDA as part of the approval process and are included in the FDA-approved Prescribing Information.	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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. This report is designed to make the product distinctions noted by the reviewer. We have emphasized that little information is available on the efficacy of human tissue products regulated under HCT/P. Products not indicated for chronic wounds have been removed from the report. Our assessment of risk of bias and strength of evidence is designed to indicate which studies or groups of studies provide the most reliable evidence for making conclusions about the efficacy of any wound care product for complete wound healing. Therefore if studies of PMA products are better quality studies these assessment tools should indicate that they are.

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			This is not the case for HCT/P and 510(k) cleared products for which clinical data are typically not presented to FDA. Therefore, performing and interpreting head-to-head trials of PMA products against non-PMA products is fraught with difficulty. Moreover, the report includes several 510(k)-cleared devices that are not indicated for use with any wounds. Products cleared under FDA product code FTL are indicated for soft tissue repair (e.g., hernia repair, bladder prolapse, and tendon support). The report also includes a product cleared under code KMF which is for a "liquid bandage" not a dressing. Products coded by FDA under FTL and KMF should not be part of the report. Recommendation: Revise the report by eliminating those products that are not dressings indicated for use on chronic wounds, and assigning products to different categories based on their FDA regulatory status, and separately analyze the clinical data for each category. The report should also be revised to acknowledge that the quality of evidence for PMA products is much more robust than for other products.	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	ES-15, Page 5, Page 45	B. "Usual care" protocols for management and treatment of chronic wounds vary significantly. This makes precise comparisons of the relative efficacy of the use of "skin substitutes" difficult. Comment: In general, current standard of care or usual care for chronic wounds includes elimination of fibrotic/necrotic tissue by debridement, maintenance of a moist wound environment, elimination of exudate, and off-loading (DFUs) or compression therapy (VLUs). A single standard of care for chronic wounds is not well defined or validated in the literature and can vary by medical specialties, geographic area, specific wound centers, etc. The authors critique the existing body of clinical research with respect to the appropriate comparison to "usual care" (eg, pgs. ES-15, ES-17, 46, 49). The authors question their use of simple gauze as usual care. A multi-disciplinary advisory panel that was chosen to develop specific guidelines for the treatment of venous leg ulcers, diabetic foot ulcers, and pressure ulcers established that maintaining a moist wound healing environment, as can be accomplished with saline-moistened gauze, is an important guideline across all three wound types (Robson, 2006, Wound Repair Regen; Steed, 2006, Wound Repair Regen; Whitney, 2006, Wound Repair Regen). Therefore, saline-moistened gauze represents an acceptable standard of care. Recommendation: The authors should acknowledge that the FDA has agreed that the control treatment in several registration trials should be saline-moistened gauze and that all statements questioning the use of saline-moistened gauze as a control be removed from the document.	While saline-moistened gauze may represent a replicable comparator, many studies have shown that this approach is minimally effective and other treatment approaches are more effective. We were asked to clarify Key Question 2 by rewording it as follows: "For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures:…"

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	ES-14, ES-16, Pages 44, 47, 50	C. The draft report's "Risk of Bias" assessment does not take into account the rigorous evidence evaluation already conducted by FDA on some of the studies listed in the review. Comment: In the draft report, the reviewers apply a "Risk of Bias" scale that assesses risk by counting the number of "no" or "not reported" responses to a list of specific Quality Assessment Questions. This scale creates an artificial construct that is not sensitive to the differing levels of evidence required to market products through each of the regulatory pathways identified in the report. It is misleading because it does not take into account the rigorous evidence review that FDA has already conducted on PMA products before they are approved for the market. As a result, several well-designed, randomized controlled trials that meet reviewers' criteria for inclusion in this analysis are incorrectly considered to have a "high risk" of bias. Specifically, the authors cite lack of blinding of wound assessors as the reason for assigning a "high risk" of bias to most of the RCTs. In fact, in the three Apligraf® RCTs, steps were taken to mitigate and minimize the risk of bias on this exact point. We have submitted additional data on this issue in Appendices 1-2 and we discuss it in more detail below. Recommendation: We urge the reviewers to add a statement acknowledging that the Edmonds, Veves and Falanga RCTs do not have a "high risk" of bias and that these trials were subject to careful scrutiny by FDA (Veves, Falanga) or European regulatory reviewers (Edmonds). As a result, these trials should be reclassified to "low risk" of bias.	Individual studies are evaluated for risk of bias on an outcome-by-outcome basis. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element and have revised our assessment of the risk of bias. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. Additional text has been added to define "Yes," "No," and "Not Reported" in the risk of bias assessment. Whether a product is regulated under PMA or 510(k) is not a consideration when judging study quality as these are "proxies" for the study characteristics we are assessing.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Results: Key Question 1	D. Description of Apligraf® In providing an overview of the different types of "skin substitutes" discussed in the draft report, reviewers assert that "Whether natural or synthetic, the biomaterial provides an artificial extracellular matrix that allows for infiltration of surrounding cells." While we understand that the authors are trying to describe common features of "skin substitutes," we note at least one error: Apligraf first received pre-market (PMA) approval from FDA in 1998 and then again in 2000 for the following indications: ". . . Use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure." Comment: Apligraf does not provide an artificial extracellular matrix that allows for infiltration of cells. Instead, the product is a living, bilayered skin substitute that is believed to stimulate the patient's own cells to regenerate tissue and heal the wound through a multi-modal cascade that includes the secretion of growth factors, cytokines, and matrix proteins. Recommendation: Revise the draft by including the following statement: "Apligraf does not provide an artificial extracellular matrix that allows for infiltration of cells. Instead, the product is a living, bilayered skin substitute that is believed to stimulate the patient's own cells to regenerate tissue and heal the wound through a multi-modal mechanism that includes the secretion of growth factors, cytokines, and matrix proteins."	The term "artificial" was removed from the text but was retained in the search strategy. Apligraf's indication for diabetic foot ulcers has been added to the document. The following text was added to the report's description of Apligraf: "Apligraf is believed to stimulate the patient's own cells to regenerate tissue and heal the wound through mechanisms that may include the secretion of growth factors, cytokines, and matrix proteins."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Methods: Key Question 2	E. Definition of Usual Care Comment: Key Question 2 of the report asks whether skin substitutes are more effective than usual care, where usual care is parenthetically defined as "synthetic dressings, growth factors, skin grafts, or other treatments used as a control." However, standard or usual care is not well defined by the specialty societies or validated in the literature. In general, the current standard or usual care includes elimination of fibrotic/necrotic tissue by debridement, maintenance of a moist wound environment, elimination of exudate, and off-loading (DFUs) or compression therapy (VLUs). Saline-moistened gauze dressings ("wet-to-moist") are considered acceptable standard of care, but the use of growth factors and skin grafts is not typically considered standard or usual care. Recommendation: The authors should delete the following parenthetical reference at Page ES: ". . . Synthetic dressings, growth factors, skin grafts, or other treatments used as a control. . ."	Key Question 2 has been changed to: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures
Bates, Damien	Organogenesis Inc.	Conclusions in the Executive Summary (pgs. ES-15-17)	F. Conclusions in the Executive Summary (pgs. ES-15-17) Comment: As we discuss in more detail below, we strongly disagree with the conclusions the authors make about the risk of bias in the Apligraf® articles and the strength of evidence for the effectiveness of Apligraf® in treating chronic wounds. Recommendation: In accordance with our other comments and the additional data submitted in the appendices to these comments, we request that the authors revise their assessment of risk of bias in the Apligraf® studies to "low risk" of bias and that they revise their assessment of the strength of evidence to "high."	With the revision of the risk of bias assessment, the studies by Edmonds, Falanga, and Veves are now considered low risk of bias.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Introduction and Background, Pages 9-11	G. Differences Between PMA, 510K, and HCT/P Regulatory Pathways Comment: While the draft report accurately describes differences among the three regulatory pathways currently used to secure US marketing clearance for "skin substitutes," it does not explicitly discuss the significantly different thresholds for clinical evidence associated with each pathway: To obtain PMA approval for a "skin substitute", the manufacturer must submit "valid, scientific evidence" so that FDA can determine whether there is reasonable assurance that the device is safe and effective. FDA considers RCTs to be the gold standard for producing valid, scientific evidence. Clinical studies supporting a PMA submission conducted in the US are subject to GCP regulations. A study conducted under an approved IDE requires: A detailed clinical protocol that has been reviewed by FDA and found to be scientifically sound Written procedures for monitoring the study to assure compliance with the clinical protocol and accuracy and completeness of the data collected Routine and expedited reporting of annual progress and important safety events, and, Registration on ClinicalTrials.gov and reporting of results (this is a relatively new requirement that was not in effect at the time of several of the clinical trials included in this report) FDA may audit study sponsors, IRBs, and clinical investigators involved in an IDE/IND clinical study. A device cleared for US marketing through the 510(k) process must also demonstrate that the device is as safe and effective (ie, is substantially equivalent) as a legally marketed device that is not subject to a PMA (ie, a predicate device). Demonstration of substantial equivalence requires an applicant to prove that the	With input from the FDA reviewer, we have revised the descriptions of the requirements for PMA, 510k and HCT/P. The assessment tool questions for judging risk of bias used in this report closely follow the recommendations made in Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			product has the same technological characteristics and indications for use as the predicate device. Clinical data demonstrating safety and effectiveness compared to the predicate device is not a requirement of the 510(k) process. It is our understanding that clinical data was not required for any of the wound dressings noted in the draft TA that have been 510(k) cleared for wound management. HCT/P registration does not require submission of any clinical data because the HCT/P is intended only for "normal function." Clinical studies of "skin substitutes" cleared for market as 510(k) or HCT/P products are frequently conducted after market entry and have major flaws in study design, conduct, analysis and/or reporting. Recommendation: We recommend that the authors introduce a new criterion in the Quality Assessment Questions to account for the differences in the type of evidence associated with each regulatory pathway (PMA, 510(k), and HCT/1).	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Results, Key Question 2; Pgs. 48, 50, and ES-16	H. Excluding Patients with Comorbidities from Randomized Controlled Trials (RCTs) Comment: The draft review notes that patients with comorbidities are often excluded from RCTs studying the use of "skin substitutes" in chronic wound therapy. As a result, "The studies that are available are also not generalizable to the broader patient population that is not as healthy…." We agree that it would be ideal to study chronic wound healing in a "real world" patient population with multiple comorbidities, varying drug regimens, poor adherence to therapy, etc. However, randomized controlled trials are designed to maximize internal validity (i.e., reduce the risk of bias). As a result, patients with comorbidities, on multiple concurrent medications, etc. typically do not meet study inclusion criteria because they risk confounding study results. For example, we know that certain medications, (e.g., immunosuppressives) have negative effects on wound healing and can make it difficult to determine with certainty whether study outcomes are the result of the target therapy or result from side-effects of drugs taken by the patient over the course of the trial. Recommendation: The authors should add the following statement to the TA: "Performing RCTs on patients with multiple comorbidities or chronic conditions is difficult and other trial designs should be considered in order to obtain additional clinical data on use of skin substitutes in these patients.	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies. We agree that data on sicker patients may be available in observational studies; however, the scope of this report was more limited.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Results, Key Question 2, Pages 5, 48, 60, ES-16	I. Excluding Patients with Infected Ulcers Comment: Similarly, the draft assessment notes that patients who present with infections are also generally excluded from study participation. It is well known that treating wound infections is an integral part of good wound care. The authors' own assessment notes that common principles that apply to all wounds include: "Removal of necrotic tissue…maintenance of moisture balance …measures to prevent or treat wound infections, therapies to correct ischemia in the wound area…" It is good clinical practice to treat infections and stabilize co-morbidities (eg, blood sugar) before application of skin substitute products. In addition, we note that Apligraf is contraindicated for use in clinically infected wounds. Therefore, exclusion of patients with infections is appropriate and should not be positioned as a weakness in study design. Recommendation: The authors should add a statement to the TA recognizing that excluding patients with wound infection from clinical trials of skin substitutes may be appropriate and that clinicians should carefully review the instructions for use of skin substitutes to determine whether use in such patients is contraindicated.	We have added this statement to the text of the report: "Since Apligraf and Dermagraft are specifically not indicated for infected wounds (see Table 7) studies of these treatments would not include patients with infected wounds at the time of starting treatment with the skin substitute."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Introduction, Page 5	J. Treatment of Chronic Wounds vs. Burn Wounds with Skin Substitutes Comment: The authors assert that "Skin substitutes are now more important in the treatment of chronic wounds [as compared to burns] because of the vastly larger number of patients with chronic wounds compared to burn wounds." However, it is also true that, because not all skin substitutes engraft (ie, a temporary biological dressing to improve healing by secondary intention), they are not appropriate for the treatment of full-thickness acute wounds created after tangential excision of the burn eschar. Recommendation: The authors should add a statement to the TA saying that some skin substitutes may not be appropriate for the treatment of full-thickness acute wounds created after tangential excision of burn eschar."	We were asked to consider only patients with chronic wounds in the report.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Introduction, Page 6	K. Use of Skin Graft to Treat Chronic Wounds Comment: The "Skin Grafts" section of the draft report gives a brief overview of the use of skin grafts to treat chronic wounds, but we note that use of skin grafts on chronic wounds is associated with markedly reduced "take rates" when compared to acute wounds that exhibit nearly 100% graft take. For example, a retrospective analysis by Kirsner et al. found that, while > 90% of chronic leg ulcers had initial graft take at 7-10 days, only 52% of ulcers were healed, 26% partially healed, and 22% of chronic leg ulcers had recurred at 11 months. A recent Cochrane review also found that there is insufficient evidence to indicate that skin grafts are any better or worse than simple dressings. Discussion of this point should be included in the report. Recommendation: The authors should cite the above data and add a statement to the TA saying that skin grafts may not be an appropriate treatment option for certain patients with chronic wounds.	We added the following to the discussion of skin grafts in the introduction: "A recent Cochrane Review points out that insufficient evidence from RCTs was available to indicate whether skin grafting increased the healing of venous ulcers."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Introduction	L. 510(k) Regulated Products Comment: In the draft report's description of the 510(k) regulatory clearance process, the authors note that "Wound care products regulated under the 510(k) process will typically require less evidence that they promote wound healing compared to products regulated under the PMA process." PMA-regulated products must present data to demonstrate safety and effectiveness from a well-designed randomized controlled trial, whereas 510(k)-regulated products are only required to submit a report establishing substantial equivalence with a pre-marketed device. In the case of the products discussed in this draft TA, typically no clinical data is submitted before market clearance and we are not aware of any FDA requirement to submit such data. Recommendation: We suggest that the phrase "will typically require less evidence" be changed to "will not typically require clinical evidence to establish efficacy in wound healing, as compared to products regulated under the PMA process where substantial clinical evidence is always required." This change is particularly important because the draft report did not identify a single randomized controlled trial examining the use of skin substitutes for treating pressure ulcers. Yet, most of the "skin substitute" products regulated under the 510(k) process are indicated for use in management of pressure ulcers.	We have changed the sentence as suggested by the reviewer.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Methods Page 18	Quality Assessment Questions (QAQ) The discussion of the Quality Assessment Questions used to rate the quality of evidence reviewed in the draft report raised a number of concerns. Specifically, A. Blinding (QAQ 3) Comment: While this draft technology assessment observes that patient blinding is not always possible, it suggests that, at a minimum, an objective wound assessor can and should be blinded to patient treatment. In clinical trials, a number of methods are frequently used to minimize any potential for bias in evaluating treatment outcomes. These include: use of clinical photographs for a blinded evaluation, and corroborating the Investigator's assessment of wound healing by comparison with wound tracing data obtained by another wound care provider. In fact, such methods were used in the Veves and Falanga trials. We have submitted additional data on those trials in Appendices 1 and 2, corroborating this. Therefore, these trials minimized this risk for bias and the authors should revise the draft TA, in all applicable places, that the Veves and Falanga papers have a "low risk" for bias. Recommendation: The authors should add a statement to each applicable location in the TA stating that "there are methods, such as use of clinical photographs and use of wound tracing data, that can reduce bias due to non-blinded wound assessment." We also recommend that QAQ 3 be re-worded as follows: "Did the clinical study adequately address the potential for bias in the assessment of wound healing?" Lastly, we recommend that the authors revise their assessment of risk of bias in the Veves, Falanga, and Edmonds papers to "low risk" of bias.	After reviewing several comments and giving further thought to this issue, we recognized that assessor blinding is not critical for determining the outcome of complete wound healing. While we consider assessor blinding a method for reducing potential for bias, we decided that it should not be given so much weight in this assessment given our focus on complete wound healing. We do consider identical treatment protocols an essential element in a low potential for risk study of wound treatments. Therefore, we assigned a high risk-of-bias to a study if this criterion was not met or was not reported.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Quality assessment question 10	B. Funding of Studies Comment: The source of funding for a clinical study is an important consideration in evaluating bias; however, this factor should not be evaluated apart from the overall purpose of the study: Clinical studies that are designed to generate data to support a PMA application are almost exclusively funded by manufacturers. These studies are conducted under an FDA-approved IDE and, as such, follow the principles of Good Clinical Practice. These include multiple measures to reduce bias, such as Presenting a detailed clinical protocol for reviewed and approval by FDA and the IRB Prospectively designed hypothesis and appropriate statistical methodology for assessment Requirements for monitoring the conduct of the study and quality of the data. A study conducted under an approved IDE requires a detailed clinical protocol that has been reviewed by FDA and found to be scientifically sound, includes written procedures for monitoring the study, requires routine and expedited reporting of annual progress and important safety events, and, with some exceptions for initial feasibility work, requires registration and results to be reported on www.ClinicalTrials.gov (this latter requirement is relatively new and was not in place when many of the trials reviewed in this draft technology assessment were conducted). Additionally, FDA has the ability to audit Sponsors, IRBs, and Clinical Investigators involved in an IDE/IND clinical study. We acknowledge that there may be rigorously designed, executed, and reported RCTs that are not conducted under an IDE/IND, but we suggest that the type of regulatory oversight is an objective criterion that provides meaningful information for assessing the overall quality of a clinical study.	We have removed the question regarding funding from our quality assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			While we agree that industry-sponsored studies may have an increased potential for bias, but it is inappropriate to group together all company-sponsored studies and imply, as the draft TA does, that they all have the same potential for bias. In fact, some company-sponsored RCTs may actually have significantly lower risk of bias than investigator-initiated studies because of the oversight and auditing of FDA and other regulatory authorities perform over registration trials. Recommendation: The authors should add a statement to the draft TA saying that "Manufacturer-funded clinical trials conducted under the oversight of the FDA or other regulatory authorities, especially trials conducted under IDE where the FDA has reviewed and approved the trial protocol, have a low risk of bias. The authors should also add a new QAQ or replacing QAQ 10 with the following question: "Was the study subject to oversight by relevant regulatory authorities (eg, was the study used for FDA-approval?)"	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Methods	C. Additional Quality Assessment Questions Comment: We are very concerned that the authors appear not to have considered a number of very important trial design and performance considerations in their quality assessment questions. These include, but are not limited to, the number of subjects in the trial, whether the study was adequately powered to make the conclusions it made, whether proper statistical methods were employed, whether the evidence supported the conclusions, and whether the results were statistically significant. Without inclusion of these and other important considerations, we believe that it is impossible to properly characterize the quality, risk of bias, and clinical usefulness of an RCT. Recommendation: The authors should include additional QAQs addressing the considerations raised in this comment and any others pertinent to a complete critical assessment of the RCTs discussed in the TA. Alternatively, if the authors do not accept our recommendation, they should include a statement acknowledging that these issues were not evaluated and that it is not possible to draw any conclusions or inferences concerning the quality and bias of the RCTs discussed in the TA.	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias and the method of determining the strength of evidence used in this report closely follow the recommendations made in these two reports. Additional text has been added to define “Yes,” “No,” and “Not Reported” in the risk of bias assessment. After reviewing several comments and giving further thought to this issue, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Results Key Question 2 Page 44	A. Quality of Evidence Base Comment: The issues cited in the technology assessment that resulted in an assessment of a "high risk" for bias in the three Apligraf® studies are addressed in detail in comments provided to Table 19. Briefly, both studies reported in Falanga and Veves utilized post-hoc analyses to address the potential for treatment bias in the open-label studies and information regarding comorbidities were prospectively collected during each study, but were not reported in the corresponding article due to journal-imposed manuscript word-count limitations. We are providing this additional data in Appendix 5 to this letter. Recommendation: It is correct that all Apligraf® studies were funded by the manufacturer, but important to also note that they were conducted under regulatory authority oversight, specifically an approved IDE (Falanga and Veves) or individual approvals from the EU countries and AUS (Edmonds). As previously discussed, regulatory authority oversight is an important surrogate measure of the quality and soundness of the study. The authors should add a statement to the draft TA stating that the strength of evidence for efficacy of Apligraf® is "high."	The assessment of these studies has been revised with the focus on complete wound healing.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Page 44-45	B. Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics 1) Exclusion of Patients Responding to Usual Care Comment: The report suggests that excluding patients who respond to usual care during screening periods or who are in suboptimal health is a negative. It is important to note that these studies were FDA registration studies and were RCTs which operate under the premise of maximizing internal validity. These studies deliberately exclude potential confounders such as significant medical conditions so as to best assess the effect of the treatment. The run-in period was necessary to exclude those patients that would heal with standard of care and thus the patients in these trials represent a much harder to treat or "real world" population, since skin substitutes are used as a supplement to standard care where it is known that the standard of care failed to heal the wound. A trial design with a run-in period may actually underestimate the value of a product like Apligraf® because all the patients enrolled in the trial have hard to treat wounds that will not respond to standard of care. Recommendation: We suggest deleting the statement "Several studies also indicated they excluded patients who responded to usual care during screening periods" as it may be perceived by the reader as a negative aspect of study design, and replace it with the statement "Use of a run-in period assures that all patients in the trial have hard-to-heal wounds and may more accurately demonstrate the value of skin substitutes in wound healing."	We added the following sentence to the end of the indicated paragraph: "This procedure insures that only patients with hard-to-heal chronic wounds are enrolled in the study."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Results: Key Question 2	2) Institutions Involved in Apligraf® EU/AUS Clinical Trial (Edmonds) Comment: The statement "One study recruited patients in the European Union and Australia but did not report the method of recruitment or institutions involved" is inaccurate. The list of participating institutions is listed as an Appendix within the Edmonds article (pg. 17). Recommendation: The authors should correct this error by deleting the statement above or revising it to say that the study "did" report the method of recruitment.	The statement "but did not report method" has been removed.
Bates, Damien	Organogenesis Inc.	Results: Key Question 2	3) Period of Evaluation for Apligraf® DFU and VLU Clinical Trials Comment: The statement in the draft TA "Two of the studies examined patients with diabetic foot ulcers for 12 weeks and one study examined venous leg ulcers for 12 months" describes the period of evaluation of efficacy for the diabetic foot ulcer study (12 weeks for efficacy, 6 months total study duration), but only the total study duration for the venous leg ulcer study (6 months for efficacy, 12 months total study duration). It is unclear and potentially misleading. Recommendation: For clarity, we suggest the authors re-state the sentence as: "The two diabetic foot ulcer studies evaluated the efficacy of Apligraf® for 12 weeks with a total study duration of 6 months. The single study in venous leg ulcers evaluated the efficacy of Apligraf® for 6 months with a total study duration of 12 months."	The sentence has been changed to: "Two studies examining patients with diabetic foot ulcers evaluated efficacy at 12 weeks during a study duration of 6 months and one study examining venous leg ulcers evaluated efficacy at 6 months during a study duration of 12 months."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Results: Key Question 2	4) Proportion of Patients with Type 1 vs. Type 2 Diabetes Comment: Data regarding diabetic type was not explicitly provided in the Veves article, however the draft TA stated, "At baseline, the two groups were similar regarding demographics, type and duration of diabetes, and ulcer size and duration (Table 1)." Table 1 presented HbA1c levels, not the actual type and duration of diabetes. However, the data for type of diabetes in this study is provided in the Apligraf Prescribing Information (Table 6 in Appendix 12). In the Apligraf group, 36.6% and 61.6% of patients had type 1 or type 2 diabetes, respectively. Two patients in the Apligraf group did not have type of diabetes specified. In the Control group, 27.1% and 72.9% of patients had type 1 or type 2 diabetes, respectively. Recommendation: Based on this information we suggest that the statement "One study evaluating diabetic foot ulcers did not specify diabetic type" be removed from the draft.	The sentence mentioned by the reviewer has been removed. The information on patients with type I and type II has been added to the evidence tables.
Bates, Damien	Organogenesis Inc.	Results: Key Question 2	5) Wound Severity Comment: The concept of "wound severity" includes multiple clinical parameters and may vary among types of chronic wounds. It has been well-established that both ulcer duration and ulcer area are important prognostic indicators of healing. In general, large baseline ulcer size and longer ulcer duration predict poor healing. Additionally, wound grading scales, such as Wagner Classification for Diabetic Foot Ulcers, University of Texas Wound Classification System for Diabetic Foot Ulcers, or IAET, are utilized to characterize the chronic wound with regard to tissue depth, and in the case of the University of Texas scale also considers infection, and ischemia. All three Apligraf studies collected clinical data on baseline ulcer duration and area, which served to describe the wound	We added the following sentence: "None of the three studies reported a wound severity score but did provide information on wound duration and wound size."

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			severity. In addition, the IAET Staging scale was collected for VLUs and reported in the Falanga article (pg. 297) and the Apligraf prescribing information includes IAET staging information (Table 4). In the Apligraf group, 48.5% and 51.5% of ulcers were Stage II or Stage III, respectively. In the Control group, 50.9% and 49.1% of VLUs were Stage II or Stage III, respectively. For the two diabetic foot ulcer studies (Edmonds and Veves) the inclusion criteria for the studies specified non-infected, non-ischemic full-thickness neuropathic diabetic foot ulcers, which correspond to either a Wagner grade 2 or University of Texas grade 2-A. There was no value in capturing staging information in the clinical study since the study pre-specified a homogenous population. Recommendation: The authors should revise the draft TA to state that the three Apligraf studies did report wound severity and revise the current statement in the draft from “None of the studies reported wound severity” to “None of the studies, other than the Apligraf studies, reported wound severity.”	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Results: Key Question 2	6) Efficacy of Skin Substitutes Comment: In the results section of the draft TA under the subheading "Efficacy of Skin Substitutes" (pg. 46), the following statement is inaccurate with regards to the types of dressings used in the Apligraf DFU and VLU study control groups: "In the two studies of diabetic foot ulcers the control dressings were a non-adherent gauze dressing (healing rate at 12 weeks was 52% vs. 26%) and saline-moistened gauze (healing rate at 12 weeks was 56% vs. 38%). The third study compared Apligraf to an Unna boot for treated venous leg ulcers." Recommendation: We suggest updating this section to reflect the correct dressings, as stated below: "The following dressings were used in the Apligraf DFU and VLU studies: • Veves: Saline moistened Tegapore (3M Health Care), covered with a layer of saline moistened gauze (Kendall Health Care Products), dry gauze, and petrolatum gauze wrapped in Kling (Johnson & Johnson Medical) (Veves 2001). • Edmonds: Mepitel (Mölnlycke Health Care AB), a porous wound contact layer consisting of a flexible polyamide, was applied as a primary non-adherent dressing. Secondary dressings included saline moistened gauze, dry gauze, and a bandage held in place with tape. • Falanga: Non adherent primary dressing (Tegapore, 3M Health Care), gauze bolster, zinc oxide impregnated paste bandage (Unna boot) and self-adherent elastic wrap (Coban, 3M Health Care)."	These changes were made to the report's evidence tables describing Control Wound Treatment.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Discussion, Conclusions and Recommen-dations	A. Relative Quality of the RCTs and Risk of Bias Comment: This document constitutes a laudable effort in providing a descriptive analysis of the existing RCT literature addressing the efficacy of skin substitutes. Additionally, it places a great deal of emphasis on establishing the differences between the commercially available products according to FDA classification (PMA, HCTP/c and 510Ks). However, the report's conclusions are limited by only focusing on describing certain aspects of study conduct and reporting criteria while ignoring important parameters that also affect and differentiate RCTs in terms of quality. These include, sample size, powering, statistical analysis, p values, confidence intervals, independent observer assessments and prospectively defined efficacy outcomes. Furthermore, discussing, and coming to conclusions about these trials, as a single group implies that all were of similar quality. We disagree with any such conclusion - implicit or otherwise. Perhaps because a number of important parameters related to the quality, design and reported outcomes of the RCTs were not included in discussion of answer to Key Question 2, all the RCTs discussed in the draft TA also are grouped together as having a "high risk of bias" whether they were overseen by the FDA or not. We believe such grouping is inappropriate. In our view, the most important arbiter of bias is whether a trial is performed under FDA oversight, a fact which is not included in the draft TA. We reiterate that all three Apligraf studies included in this draft were registration studies conducted under regulatory oversight. As previously discussed, a study conducted under an approved IDE requires a detailed clinical protocol that has been reviewed by FDA and found to be scientifically sound, includes written procedures for monitoring the study, requires routine and expedited reporting of	Whether a product is regulated under PMA or 510(k) is only a proxy for the study characteristics we are assessing with the risk of bias assessment. The risk of bias assessment was developed with several considerations in mind. The FDA guidance document on treatment for chronic wounds informed our choice of factors to consider, as did the report providing guidance to the EPC program for reviews: Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/

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			annual progress and important safety events and, among other things, gives FDA the ability to audit sponsors, IRBs, and clinical investigators involved in an IDE/IND clinical study. We acknowledge that there may be rigorously designed, executed, and reported RCTs that are not conducted under an IDE/IND and received by FDA. However, regulatory oversight is an objective criterion and an important surrogate for assessing the overall quality and potential for bias of a clinical study. An example of how the analytic method used in the TA can be misleading because of the overemphasis placed on potential bias related to non-blinding the wound assessor is the fact that the only study in the category of "Moderate Risk of Bias" (risk of bias being the sole indicator of quality of literature) is the Krishnamoorthy study. Aside from the fact that this study was actually an open label study (thus bias was not avoided by the blinding of the assessor requirement), the study was not powered to detect significant differences between the four study arms, and the rate of healing in the control arm (15%) is much lower than that reported with standard of care for VLU at 12 weeks (up to 55%). Unfortunately, the "Moderate risk of Bias" classification leads the reader to think that the quality of this study is superior to those, such as the Apligraf studies, that were powered to detect a significant difference between study arms. Lastly, we note that, as currently written, the same level of bias is assigned to all RCTs (except for one) irrespective of how many QAQs are reported as an "N" or a "NR." Referring to Tables 19-24, it is difficult to understand how the Naughton trial with 9/10 "N's" or "NR's" has the same level of bias as the Edmonds or Veves trials with 3/10 "N's" or "NR's." Assigning the same level of bias to these trials due to the extreme emphasis placed on blinding of the wound assessor	

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			while ignoring factors such as FDA oversight, is hard to understand as an analytic method and even harder to accept as a valid way of assessing bias. Recommendation: The draft TA should be revised to acknowledge the importance of FDA oversight in minimizing bias and the authors should revise their estimates of bias accordingly. The authors should also revise the draft TA by providing a more complete overall assessment of the clinical trials in order to allow readers to more accurately assess the relative quality and bias of the RCTs included in the TA. Additional factors to include in the analysis are sample size, power, statistical analysis, p values, confidence intervals, independent observer assessments, and prospectively defined efficacy outcomes.	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	General	B. Considering all Skin Substitutes as a Single Group Comment: The authors' decision to evaluate the RCT clinical data on all skin substitutes as a single group provides the potential to mislead the reader in several ways. As previously described, it leaves the impression that the risk of bias and the quality of all the RCTs is similar. It also leaves the misimpression that these products are interchangeable. There are also other problems with taking this approach. For example, the draft TA does not differentiate between: • Products that didn't have clinical trials that met the ECRI inclusion criteria from those products that did. The inference is that a low quality evidence base is equivalent to no evidence base at all. Furthermore, no distinction is made between those skin substitutes that have multiple sources of bias and dramatically exceed the threshold for high risk of bias from those that have just enough sources of bias to barely exceed the threshold for "high risk of bias". • Individual products that have entirely different "weights of evidence" in terms of, among other things, total number of studies; pervasiveness of bias across studies, total number of subjects treated; efficacy data; statistical validity, etc., are grouped together. One specific example: the authors do not differentiate between a study that has 11 patients per study arm to one that has 100 per study arm or more. Recommendation: The authors should group skin substitutes by FDA regulatory classification and provide a more critical, product-specific analysis of the quality and risk for bias of each RCT.	New tables have been added that summarize the results for complete wound healing, risk of bias assessment, and strength of evidence for each study.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Executive Summary Tables	A. Table 2 Comment: The draft TA incorrectly describes Apligraf Recommendation: The authors should replace the Product Description of Apligraf with the following description from the Apligraf Prescribing Information: "Apligraf is supplied as a bilayered skin substitute: the epidermal layer is formed by human keratinocytes and has a well differentiated stratum corneum, the dermal layer is composed of human fibroblasts in a bovine type I collagen lattice."	The product description Table 2 and Table 7 have been changed.
Bates, Damien	Organogenesis Inc.	Executive Summary Tables	B. Tables 2 and 7 Comment: Apligraf also received PMA approval for treatment of DFUs in 2000. Recommendation: The following diabetic foot ulcer indication (taken from the Apligraf Prescribing Information) should be added to the "FDA Specific Indication for Chronic Wounds" column for Apligraf/Graftskin: "Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure."	This change has been made.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Appendices	A. Use of Product Prescribing Information for Supplemental Information for Apligraf Comment: In the comments/suggestions below, we suggest using the Apligraf Prescribing Information as the source document for several pieces of data. The Apligraf Prescribing Information details the results of the registration clinical trials published in the Veves and Falanga articles. However, enrollee numbers in the Falanga article and the Apligraf Prescribing information do not match, so we are providing the following explanation to prevent confusion. The data in the Falanga article and the data in the Apligraf PMA/Prescribing Information are from the same RCT. The Falanga article reports on a per protocol population (those subjects meeting inclusion and exclusion critieria, n = 275; 146 Apligraf, 129 control). As reported in Falanga, there were 293 individual patients treated in the trial, however 4 patients were randomized into the study a second time (different wounds, different treatment group), therefore the Adverse Event reporting in the Apligraf Prescribing Information reports on 297 patients. The PMA approval is based on an intent-to-treat efficacy population of n=240 (130 Apligraf, 110 control). Of the 293 patients in the study, 53 patients from a single clinical site were removed from the efficacy analysis under joint agreement by FDA and the manufacturer. Additionally, for the four patients randomized twice, only the first randomization is included in the n=240 analysis. It is important to note that statistical significance for the primary efficacy endpoint of time to complete wound closure (Cox's proportional hazards regression analysis) was obtained with both populations (p=0.003, Falanga (n=275) and p=0.0023 PMA (n=240)) demonstrating the robustness of the data. Recommendation: Please revise the appropriate tables in accordance with the information provided above.	Thank you for providing this information.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Table 19, QAQ 3	B. Was the wound assessor blinded to the patient's treatment group? Comment: Given the significant challenges with conducting a blinded clinical study with skin substitutes as discussed in the technology assessment, the current wording of QAQ 3 and the weighting of QAQ 3 in the categorization of overall risk-of-bias fails to discriminate between clinical studies that adequately addressed the potential for bias, through either a blinded wound assessor or other means (i.e., blinded photographic assessment) and those that do not. Both the Falanga and Veves articles reported results of Phase 3 studies that were submitted to FDA as part of PMA submissions for marketing approval. The potential for bias was a significant regulatory concern and was addressed to FDA's satisfaction for each study. For the DFU study (Veves), FDA requested additional information during the PMA approval process to corroborate the wound closure assessment with wound tracing information (Appendix 1). For the VLU study (Falanga), FDA requested copies of all photographs from all subjects in the efficacy cohort and, additionally, Organogenesis conducted a blinded photographic review. The methodology and results of the blinded photographic review are provided as an attachment (Appendix 2). Based on the information provided in Appendices 1 and 2, we suggest that the "NR" be changed to "Yes" for Quality Assessment Question #3 for both the Falanga and Veves articles. Recommendation: The authors should add a statement to each applicable location in the TA stating that "there are methods, such as use of clinical photographs and use of wound tracing data, that can reduce bias due to non-blinded wound assessment." We also recommend that QAQ 3 be re-worded as follows: "Did the clinical study adequately address the potential for bias in the	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we realized that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods such as photography and planimetry when assessing wounds for intermediate outcomes, but we have focused the review on the outcome of complete wound healing.

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			assessment of wound healing?" Lastly, we recommend that the authors revise their assessment of risk of bias in the Edmond, Veves and Falanga papers to "low risk" of bias.	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Table 19, Question 6	C. Were the mean wound group durations at the start of treatment similar (no more than a 15% difference) between groups? Comment: Information regarding baseline ulcer duration was reported in Falanga et al (Table 1) as categorical data (< 6 mo, 6 mo to 1 yr, 1-2 y and > 2 y). There was a > 15% difference between Apligraf and Control groups within wound duration categories. However, it is important to note that even with a randomized study, there are rare occasions when randomization does not result in substantially similar groups, and the differences in the underlying groups impact the interpretation of the results. In these kinds of circumstances, additional statistical models (eg, Cox's proportional hazards regression analysis) should be assessed to better estimate the "true" treatment effect, independent of the issues of the uneven distribution of subjects in the randomization process. Such an event occurred in the VLU study: a much larger proportion of long duration wounds were randomized into the Apligraf group, and since long duration wounds are more difficult to heal, this significantly impacted the interpretation of study results. The Cox model that was used in this study was able to correct for the uneven distribution of subjects from the randomization, and thus it allowed for a more accurate estimate of the true treatment effect of Apligraf compared to control. As reported in Falanga, the results of this clinical trial are reported using the Cox model and therefore the potential for bias associated with imbalanced treatment groups was addressed. Recommendation: Therefore, the authors should change the answer to this question to "No" and they should also acknowledge that this did not introduce bias into the results of this study.	No changes were made. The studies of Apligraf are considered to have a low risk of bias.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Table 19, Question 7	D. Were the number of comorbidities similar (no more than a 15% difference) at the start of treatment between groups? Comment: Information regarding baseline comorbidities were not included in the articles, due to space limitations. All three articles report the results of registration studies designed to support approval by FDA. In these studies, information regarding comorbidities was collected and reported in the Clinical Study Reports provided to FDA. The statistical tables for baseline comorbidities are provided for each study (article) in Appendices 3, 4, and 5. In all 3 studies, the proportions of comorbidities were similar (no more than a 15% difference, with the exception of "allergies" in the Veves study) between groups. Recommendation: The authors should change the "NR" to "Yes" for QAQ 7.	Table 19 was changed to reflect reporting of similar baseline comorbidities.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Table 29	E. Comment: All three Apligraf studies had entry criteria for wound surface area (measured in cm2), not wound volume (measured in cm3). These data are included in the column for wound surface volume. Entry criteria for the 3 studies were as follows: Edmonds: 1-16 cm2 Veves: 1-16 cm2 (this is incorrectly listed as ≥1cm2 in Table 29) Falanga: The minimum wound surface area was not reported in the article but was prespecified in the clinical protocol (Appendix 6). To be eligible for the study the venous leg ulcer must have been greater than ½ x ½ inches and not greater than 4 x 8 inches in area. The clinical protocol also specified that the ulcer was of at least 1 month duration, which had not adequately responded to conventional ulcer therapy, as stated in the Apligraf Prescribing Information (Section 7A – Study Design). More extensive information on comorbidities collected and reported in the clinical trial was provided in the comments to Table 19. Recommendation: The authors should change the heading “Minimum Wound Volume” to “Minimum Wound Surface Area” to comport with the data that was reported as cm2. We also suggest removing the column “Minimum Wound Surface Area” as it would be duplicative if the suggested change above is made.	The suggested changes were made to surface area and wound volume columns of Table 29.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Table 34	F. Comorbidities Treatment Comment: Table 34 contains a "Comorbidities Treatment" column that is listed as "NR" for all three Apligraf studies. While the articles do not report on specific treatment of comorbidities, a rigorous clinical study intended for registration includes careful and close monitoring of the subject's overall health status. This often includes management of comorbidities. Routine laboratory testing and spontaneous adverse event reporting ensure careful and close monitoring of the subject's overall health status. Additionally, while not reported in the Veves article, the following instructions were included in the clinical protocol (Appendix 7) regarding glucose control: Daily glucose measurements will be performed until study week 12. All patients will monitor their blood glucose twice a day through the use of a glucometer. A Fasting Blood Sugar determination will be obtained in the morning, and a post-prandial Random Blood Sugar measurement will be taken in the evening. Daily glucose level determinations will be recorded by the patient in the patient log, and glucose control will be recorded on the appropriate case report form at each weekly visit. If the blood sugar level goes beyond the Investigator's specified range for the patient, the patient will be instructed to contact the Investigator immediately. No specific attempts to improve glucose control will be made during the study unless clinically indicated. Any changes in glucose management will be documented in the CRFs. Recommendation; The authors should change the "NR" for the Edmonds and Falanga articles to "routine laboratory testing and spontaneous adverse event reporting." We also recommend changing the "NR" for the Veves article to "intervention to improve glucose control when clinically indicated, routine laboratory testing, and spontaneous adverse event reporting."	The suggestions were made to Table 34. Thank you for the additional information.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Table 34	G. Skin Substitute Treatment Column Comment: For the Falanga article, the description in this column states that "…self-adherent plastic wrap…"was used to immobilize the Apligraf. This is incorrect - elastic wrap was used. Recommendation: The authors should change this statement to "self-adherent elastic wrap (Coban)". The same self-adherent elastic wrap was utilized in both groups.	This change has been made to Table 34.
Bates, Damien	Organogenesis Inc.	Table 39	H. Comment: The data in this table is not recorded consistently. For some trials the data on comorbidities is reported as "diabetes" in the aggregate without separation into type of diabetes, while for other products it is reported as Type I or Type II diabetes. This data should be reported consistently for all trials. All three Apligraf trials reported comorbidity data by Type of Diabetes - therefore this level of specificity should be included in this table for consistency. Recommendation: The authors should make the following revisions: For the Edmonds article, please include the type of diabetes under comorbidities. This data is included in the Edmonds article (Table 2 pg. 15). Also for completeness please add a parenthetical to clarify that the completion rate was at 6 months (similar to how the Falanga study was reported). For the Veves article, please include the type of diabetes under comorbidities. This data is included in the Apligraf Prescribing Information (Table 6). Also for completeness, please add a parenthetical to clarify that the completion rate was at 6 months (similar to how the Falanga study was reported).	The suggested changes have been made to the appropriate tables in the report.
Bates, Damien	Organogenesis Inc.	Table 44	I. Comment: The table does not appear to be consistent. For example, for some studies there is a "Comfort (mean VAS score)" or "Other wound healing outcomes" row, but this is not consistent across individual studies.	The NR was removed for median time to wound closure for the Edmonds study. Hospitalization data were added to the table. The comfort row and the other wound healing outcomes row were removed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Recommendation: The authors should clarify the table by adding columns for p-value, confidence interval, and statistical test for all outcome measures (eg, P>0.05; log-rank test) so that this information is more clearly available to the reader. Specifically, for the Edmonds article, the authors should change "NR" to "Not Applicable (N/A)" for median time to wound closure for the control group. As detailed in the table, no median time was reported for the control group because there was a <50% rate of closure, therefore the rate of closure wasn't relevant and it wasn't a reporting failure to not report the data and N/A is more appropriate. In a study of neuropathic diabetic foot ulcers, pain relief is not a relevant clinical outcome, therefore, we suggest changing this field to "not applicable", rather than "NR". For the hospitalization row, the article reports on serious adverse events (SAEs) as defined by ICH guidelines, which also includes hospitalizations. We are providing additional data regarding hospitalizations in this study (Appendix 8). This field should be changed from "NR" to 30.3% (10/33) for Apligraf and 23.1% (9/39) for Control through the 6-month study duration. For the Veves article, for consistency across data tables, the row "other wound healing outcomes" should be eliminated or, in the alternative, the "NR" designation should be deleted. In a study of neuropathic diabetic foot ulcers, pain relief is not a relevant clinical outcome, therefore, this field should be changed to "not applicable", instead of "NR". For the Falanga article, the median time to wound closure information, especially the sub-group information, is hard to read as currently presented since the Skin Substitute and Control data for each subgroup do not horizontally align. Wound pain and exudate data were collected during the clinical trial, but were not	The rows in the Falanga study have been corrected. Pain and exudate data were added to the table.

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			reported in the article. We are providing statistical tables from the PMA application in Appendix 9. Based on this information the table should be modified as follows: • Pain/discomfort o Definition and method of determining outcome: recorded as none, mild, moderate, extreme at Study Visits Day 3-5, Weeks 1, 2, 3 and 4 and Month 6. o Skin substitute results: statistically significant improvement over baseline at all visits starting at Week 1; o Control results: statistically significant improvement over baseline at all visits starting at Week 1. No statistically significant improvements were seen between treatment groups at any visit. • Exudate o definition and method of determining outcome: recorded as none, mild, moderate, severe at Study Visits Day 3-5, Weeks 1, 2, 3 and 4 and Month 6. o Skin substitute results: statistically significant increase in exudate over baseline at Day 3-5 and a decrease at Month 6; o Control results: statistically significant decrease in exudate over baseline at Month 6 only. At Week 2 there was statistically significantly more exudate in the Skin Substitute group compared to control; no other statistically significant results were seen between groups at any other timepoint.	

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bates, Damien	Organogenesis Inc.	Table 49	J. Comment/Recommendation: For the Edmonds article, please see Appendix 10 for complete information regarding adverse events in this trial, because the Edmonds article only reported on SAEs. The table should be revised accordingly to be consistent with the article. For the Veves article, there is an asterisk behind the p-value in the Graftskin Osteomyelitis cell for osteomyelitis that does not correspond to the table footnote text, therefore the table should be revised by removing the footnote and correcting the reference to the asterisk. Furthermore, there was 1 death in the control group (myocardial infarction) that was not reported in the Veves article (Attachment 11). This death is not reported in the Prescribing Information because there were no deaths in the Apligraf group, and because the adverse event table (Table 2) only includes AEs ≥1% in the Apligraf group. The table should be revised accordingly. For the Falanga article, please see Table 1 of the Apligraf Prescribing Information for more comprehensive safety information and update Table 49 accordingly.	The suggested changes were made and the Apligraf PMA summary information was used to update the adverse event information in Table 49.
Bordon, Diana	Integra LifeSciences Corporation	Executive Summary, ES-7, Key Question 1, 5th paragraph	Executive Summary, ES-7, Key Question 1, 5th paragraph Human and Human/animal derived products are not the only skin substitutes regulated through PMA or HDE. Skin Substitutes that make specific claims of treating specify types of wounds may be regulated through PMA and require multi-center, randomized clinical trials for evidence of safety and effectiveness. FDA has approved PMA indications for devices in the MGR classification that are animal derived products without a human component.	We did not identify any products that were only animal in origin and regulated under PMA. We acknowledge that there may be other products not identified by our searches with similar characteristics and indications to those included in this report. The reviewer did not provide names of any additional products we should have included.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Bordon, Diana	Integra LifeSciences Corporation	Page 10, 510(k) Submission, last sentence of 2nd paragraph	Page 10, 510(k) Submission, last sentence of 2nd paragraph 510(k) wound dressings are generally not cleared for the indication to "promote" wound healing. This would be a PMA indication that would require multi-center, randomized clinical trials for evidence of safety and effectiveness. Because 510(k) devices do not typically require clinical data to support clearance, these devices are indicated only to manage or support wound healing, not promote wound healing or treat a specific type of wound. 510(k) devices do not require clinical data, are considered substantially equivalent and therefore get a general indication for management of wounds in general.	The FDA reviewer suggested additional text to clarify the regulatory distinctions between PMA and 510(k) when dealing with wound care products.
Bordon, Diana	Integra LifeSciences Corporation	Page 27 paragraph 2	Page 27 paragraph 2 INTEGRA® Dermal Regeneration Template was first approved for marketing by the FDA under the Premarket Approval process in March of 1996, not April of 2001.	Early summaries were not available on the FDA's website. We used the 2001 and 2002 documents to provide the indications most relevant to chronic wounds.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Brame, Bud	LifeNet Health	Methods	AHRQ Should Consider Published Clinical Evidence Beyond Randomized Controlled Trials (RCTs) In its draft assessment, AHRQ relies solely upon randomized controlled trials that met other pre-determined criteria. While RCTs typically represent high-level evidence, it is important that analyses also include the relevant real-world clinical application of the technology. Prospective and retrospective studies, when properly designed, can provide substantial evidence of safety and clinical efficacy. These should include well-designed prospective single arm and retrospective studies that otherwise meet inclusion criteria for analysis. Finally, while RCTs that compare a technology against the standard of care is reasonable for some technologies and indications, it is not an effective study design for the treatment of chronic wounds, particularly in cases that involve patients who are not generally in good health, another criticism of available studies contained in the assessment. Skin substitutes generally are indicated for use when the standard of care regimen fails. Therefore, utilizing the RCT design comparing a technology versus standard of care in patients who previously failed the same standard of care unnecessarily places the patient at risk to further damage and yields results that are equally impactful to those from single arm studies.	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be “skin substitutes” and the regulatory pathways they may take. The second reason for writing this report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Brame, Bud	LifeNet Health	Methods	The Assessment Does Not Consider Clinical Studies Currently In Process While it is important to base analyses upon published clinical evidence, it is equally critical to acknowledge clinical studies currently underway which, based upon the study design, merit future consideration. This technology assessment will be used by stakeholders in the future for medical coverage policy development. The final draft should reference clinical studies under development for future considerations of clinical efficacy by health insurance organizations and other stakeholders. One such study involves DermACELL in the treatment of chronic wounds in the lower extremities of the diabetic patient. This 40 patient prospective single arm study comparing to a literature control evaluates clinical efficacy of DermACELL, with specific analyses related to the rate of wound closure, time to closure, and number of grafts required to achieve closure. The single arm design with literature control was selected specifically to address key questions similar to those considered by AHRQ for this technology assessment.	A table of ongoing RCTs has been added.
Brame, Bud	LifeNet Health	Results	DermACELL Description Sterile acellular human dermis allograft with a readily available Extracellular Matrix (ECM) processed with the patented MatraCell technology, which provides a collagen scaffold to supports the patient's own cellular in-growth.	Changes were made to the text describing DermACELL.

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Brame, Bud	LifeNet Health	Discussion/ Conclusion	Not all Skin Substitutes are Created Equally In the draft assessment, AHRQ notes the difficulty of extrapolating results from one study (and one technology) to other technologies in the space. However, in its categorization of technologies, it neglects to note the inherent differences between human-derived products and other technology type - those derived from human and animal components and synthetic technologies that attempt to act like human-derived products. Human-derived products are the gold standard for application because they naturally interact with the wound site and wound bed. Non-human derived and synthetic products are attempting the mimic the natural interaction of human tissues and materials they are attempting to mimic the human-derived allograft. Therefore, it is entirely reasonable that clinical studies are needed to ensure that the interaction between the non-human or synthetic technology mimics that of natural human tissue-derived products.	Thank you for your comments.
Curry, Christian	Soluble Systems	General	AHRQ needs to consider at least two additional studies related to Skin Substitute Efficacy for Treating Chronic Wounds 1. Evidence for the efficacy of TheraSkin was not considered in the analysis because the study by Landsman et al 2010 is not an RCT (Table 18. Page 71). We agree that clinical studies must be well designed to provide information of sufficient quality to serve as a basis for decision making. A well designed Randomized Clinical Trial (RCT) certainly provides the necessary information. However, not all RCTs are well designed (as noted by AHRQ). And RCTs are not the only study design which yield high-level evidence, particularly in chronic wound care where, by definition, Standard of Care has failed. This analysis, by only considering studies with RCT designs, ignores this consideration.	Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited. An RCT of TheraSkin compared to Apligraf (DiDomenico et al. 2011) was included in the report.

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Curry, Christian	Soluble Systems	General	In screening for only randomized trials the technology assessment fully overlooked studies such as Landsman et al. We also propose that the Landsman study provides compelling evidence supporting the efficacy of skin substitutes (TheraSkin) for both DFUs and VLUs. In fact, a review of the study design may lead to a conclusion that the study provides a better level of evidence than several of the RCTs accepted for review.	Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited. An RCT of TheraSkin compared to Apligraf (DiDomenico et al. 2011) was included in the report.
Curry, Christian	Soluble Systems	General	a. The AHRQ analysis concerns the use of Skin Substitutes for Chronic Wounds. By definition, these are wounds that have not progressed with standard treatments. In line with this, most AB/MACs will not cover the use of Active Biological Skin Substitutes (TheraSkin, Apligraf, Dermagraft) until 4-6 weeks of unsuccessful treatment with standard therapy. Thus, any RCT that uses Standard Treatment as a control is choosing to test their product against a therapy that has already proven a failure. For example, the Apligraf and Dermagraft pivotal RCTs use as control the very same therapy (mostly saline moistened gauze) which had failed to heal the test wounds in the pre-test period. Using a control which has already failed is perhaps ethically inappropriate and certainly is not much of a challenge for the test product to achieve better results.	We agree with the reviewer's comments.
Curry, Christian	Soluble Systems	General	**The TheraSkin study design that this Assessment should consider is a Consecutive Retrospective study of 188 patients**. This design eliminated the ethical issue of continuing to subject patients to a failed therapy (putting these patients at an inappropriate level of risk). In effect, this design also blinded the treating practitioners to even the fact of the study and helped insure real world results.	Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Curry, Christian	Soluble Systems	General	We agree with the assessment that blinding minimizes bias by eliminating the possibility that analysts, evaluators, and/or patients can be affected by expectations they may have that the intervention in question will or will not work. The participants (physicians, staff, and patients) in the Landsman study did not know the treatment would be evaluated as a clinical trial. Although they knew the product they were using, their focus was to heal the patient and they had no knowledge of a future study. All participants were blinded to any expectation other than practicing what they believed was best clinical practice, and behaved exactly as they would in a clinical setting with the ultimate goal of healing a chronic wound. For example, the TheraSkin Study sample had wounds that were reflective of the average size actually experienced by practitioners, while the biologically active RCT?s accepted for review had wounds which were much smaller. In essence, TheraSkin chose instead to conduct an all or nothing design. Either TheraSkin would heal the non-progressing wound, or it would not. At 12 weeks, 60% of DFU and 61% of VLU wounds were fully closed by TheraSkin. These were wounds that failed to progress with standard of care prior to the application of TheraSkin for an average of 12 weeks and 18 weeks for DFUs and VLUs respectively.	Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Curry, Christian	Soluble Systems	General	2. The Technology Assessment Draft appropriately calls for studies comparing skin substitutes. We recommend considering an RCT peer-review published in mid-2011 by DiDomenico et al., (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.) To our knowledge, this is the only RCT which provides a direct comparison against an established skin substitute therapy (TheraSkin vs. Apligraf). Neither Apligraf or Dermagraft have published any studies comparing their efficacy to any other biologically active product (i.e., contain living cells such as human fibroblasts and keratinocytes). Direct comparison studies are important not only to guide treatment decision, but, given the vast differences in product cost and average number of applications, can have major implications for resource allocation.	The DiDomenico study (2011) has been added to the report.

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Curry, Christian	Soluble Systems	General	Categories of Skin Substitutes We recommend that AHRQ: 1. Eliminate discussion of any products noted within the current draft as Not A Skin Substitute for Chronic Wounds. Of the 40 or so products listed in the Draft, many are not designed for or marketed for healing Chronic Wounds. For example, many of the products are designed for Burns (Acute Wounds), Soft Tissue Repair (Acute Wounds), or are Wound Covers (Dressings). 2. Change the way the various products are categorized. In the current draft, FDA regulatory status is used to categorize products. Yet the reasons for variation in FDA treatment have little, if anything, to do with the way in which practitioners view treatment options. Practitioners are increasingly viewing skin substitutes as 1. Biologically Active (living cells as a part of the product), 2. Acellular (generally a collagen matrix) that is of either a) human and or b) animal origin. FDA imperative is to structure a regulatory framework that does a good job of assuring quality, safety, and claimed efficacy. Practitioners are concerned with patient response to a therapeutic stimulus. Efficacy questions would seem to be best asked in the Practitioner context.	We have removed any product not indicated for the treatment of chronic wounds. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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. No changes to the organization of the products were made. We are not proposing an official classification system.
Curry, Christian	Soluble Systems	ES	The Executive summary attempts to put a definition on the ideal skin substitute stating that ideal skin substitute should adhere to the wound bed and provide the physiological and mechanical function of normal skin while not being rejected by the host. It is true no skin substitutes are likely to meet this definition, because the only product would be an autograft.	We have revised the paragraph that mentions "the ideal skin substitute."

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Curry, Christian	Soluble Systems	ES	Throughout the Executive Summary and the assessment references to the ideal skin substitute as a temporary biologic dressing. Using the term dressing with a skin substitute is not an accurate reflection of their mechanical and physiological characteristics. First, surgical dressings for wounds do exist and are discussed later in the document in the Background Section pages 6 through 8. Wound dressings unequivocally are not skin substitutes. They are designed maintain a moist environment at wound interface without maceration, remove excess exudate, provide mechanical protection, act as a barrier, be easily removed without trauma, leave no foreign particles in wound, and be non-toxic, non-allergenic and non-sensitizing.	We have removed the phrase “ideal skin substitute.”
Curry, Christian	Soluble Systems	ES	Depending on the type a skin substitute utilized by a practitioner, the skin substitute will provide a number of different factors to a wound. An acellular skin substitute can provide a number of the same qualities of a wound dressing but also provide scaffolding whether natural or synthetic for host cells to propagate within a wound. Biologically active skin substitutes such as TheraSkin, Apligraf, and Dermagraft provide living allogeneic cells to a wound in addition to a natural or synthetic scaffolding or extracellular matrix. The Bioengineered Skin Substitutes culture cells in vitro while TheraSkin, through its cryopreservation process is able to maintain the important characteristics of healthy human skin. TheraSkin’s living cells at application consist of biologically active human fibroblast and keratinocytes in two forms replicative and apoptotic.	We thank the reviewer for this input.

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Curry, Christian	Soluble Systems	ES	Also, it was assumed in the Executive Summary that products which have received the FDA product code MGR are the only ones which contain human fibroblasts and keratinocytes. As noted above, TheraSkin, which is regulated by the FDA as an HCT/P, also contains human fibroblasts and keratinocytes which are capable of producing growth factors and cytokines.	We have made this change to the TheraSkin description.
Curry, Christian	Soluble Systems	Results	On page 24 the description of TheraSkin should be: 1. Lines 1-4 should read. ?TheraSkin is a biologically active, cryopreserved real human skin allograft, composed of living cells, fibroblasts and keratinocytes and a fully developed extra cellular matrix. TheraSkin does not contain any synthetic or animal materials.	This change has been made to the document.
Curry, Christian	Soluble Systems	Results	2. P. 24. Please change the last sentence to ?SWAI (Virginia Beach, VA) is registered with the FDA as an establishment providing HCT/Ps	This change has been made to the document.
Curry, Christian	Soluble Systems	Results	3. P 24, line 6, word 3 should be provided not distributed.	This change has been made to the document.
Curry, Christian	Soluble Systems	Results	As noted in the General Comments Section, RCT by DiDomenico et al., (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.) should be included in both the tables and the discussion and be noted as the only head to head study of biologically active skin substitutes.	The DiDomenico et al. study (2011) has been added to the report. There are currently two studies that compared skin substitute products (OASIS versus Hyaloskin and Apligraf versus TheraSkin).
Curry, Christian	Soluble Systems	Discussion/ Conclusion	The Discussion and Conclusion notes that the kind of information needed by clinicians trying to decide which product to use is only available when comparing two skin substitute products. As noted in our other comments the study from DiDomenico et al. compares two biologically active skin substitutes TheraSkin and Apligraf.	The DiDomenico et al. studyhas been added to the report.
Curry, Christian	Soluble Systems	Tables	TheraSkin is not listed in the keywords section of Table 15 or in the search statement in Table 16.	TheraSkin is listed in the keywords section and search statement.

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Curry, Christian	Soluble Systems	Appendices	TheraSkin is not listed in the keywords sections of Table 15 or in the search statement in Table 16.	TheraSkin is listed in the keywords section and search statement.
Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	AHRQ Technology Assessment Program: Advanced BioHealing, Inc. (ABH), A Shire Company, is committed to improving the lives of patients through the development of advanced regenerative medicine technologies. Having focused our energies on diabetic foot ulcers (DFUs) and the Dermagraft® treatment option, we applaud the effort by the Centers for Medicare and Medicaid Services (CMS) to: (1) gain a greater understanding of these types of medical products, devices and treatments that are regulated by the U.S. Food and Drug Administration (FDA); (2) emphasize the value of high quality clinical data to support its coverage and payment decisions; and (3) attempt to infuse this field with clarity to ensure that each and every Medicare and Medicaid patient suffering with a DFU has access to the proper technology to treat these very challenging and life-debilitating wounds. CMS may be aware that Dermagraft was developed by Advanced Tissue Sciences (ATS) out of La Jolla, California. A trailblazer in the field of advanced wound healing, ATS was among the early pioneers, developing the first cryopreserved advanced wound healing technology in the 1990s. Regulated by the FDA as a Class III high-risk medical device, Dermagraft was approved by the FDA through the premarket approval application (PMA) process in September 2001. Among the FDA product classifications evaluated by AHRQ's Technology Assessment (TA), Class III high-risk devices are subject to the most rigorous review, being required to produce substantial evidence of clinical effectiveness and safety from robust clinical trials pre-approved by the FDA.1 We are proud of the fact that more than 28 percent of the published studies the TA relied upon to evaluate the	Thank you for your comments

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			field were evaluating Dermagraft. And with more than a decade of experience healing wounds, accompanied by an exemplary safety record, Dermagraft is an advanced technology that has met or exceeded the highest quality standards established by the FDA. It is with this long history of data-driven, patient-centric care with high quality outcomes that we offer our comments.	
Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	Medicare's Responsibility Medicare's primary responsibility, as the single largest public health insurance agency, and as required by the Social Security Act, is to ensure that its beneficiaries receive medically reasonable and necessary care. 2 This means ensuring that the correct items and services are being provided in a timely manner to Medicare beneficiaries based upon the physician's medical judgment of the condition to be treated and the patient diagnosis. In the context of evolving, new, and cutting-edge technologies, what is reasonable and necessary is measured against the recognized standard of care at the time such decision must be made. ABH welcomes this approach.	No response needed
Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	More specifically, CMS does this by developing coverage and payment policies, at either the local level, through the local coverage decision (LCD) process, or at the national level, through the national coverage decision (NCD) process. There is a time and place for both of these processes. We believe the LCD process is working well, but could be improved with more precise and consistent information being made available to local medical directors. Making certain that the proper advanced wound healing technology is available for the physician's use on any particular patient is paramount. Which medical device is considered proper for any given patient requires an understanding of the intended use of the device and	No response needed

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			how that intended use has been demonstrated to be effective for the patient in question. It is important for all stakeholders to have this same level of knowledge and understanding: the FDA, CMS, private insurers, physicians, and patients. We do not believe it is Medicare's responsibility, however, to choose among competitive products which ones it will cover and then pay for use. We also question the Medicare Program's statutory authority to do so. We understand that there are limited funds to pay for the Medicare population's health care, however, the decision about which item or service should be made available to the patient is one which must be made between the physician and patient. To do otherwise, would be putting the federal government, and in this case CMS, in the position of practicing medicine. Furthermore, if CMS were to inject comparative effectiveness research into its coverage and payment decisions, then it would be doing so in conflict with federal law and the intent of Congress. When the President signed the American Recovery and Reinvestment Act of 2009, which was intended, in part, to accelerate the use of comparative effectiveness research to better inform medical decisions, he codified into law statutory limitations on the authority of the Federal Coordinating Council for Comparative Effectiveness Research. Specifically, the law states, "Nothing in this section shall be construed to permit the Council to mandate coverage, reimbursement, or other policies for any public or private payer."3 We know that the entire issue of the proper use of CER in coverage and payment decision was hotly debated before this provision was signed into law. If CMS were to take such action based upon this TA, then we believe it would be doing so in direct conflict with the intent of Congress.	

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Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	Additionally, as CMS is likely aware, since the Council began its work, the appropriate design and implementation of comparative effectiveness studies is under significant debate at this time and appropriate techniques and measurements have not yet been identified as a standard due to the complexity of conducting and interpreting these types of studies. Yet this is what the TA is, in essence, recommending to CMS. Its conclusion is clear: "Comparisons with other advanced wound care products in terms of efficacy and cost are needed to determine where and when skin substitutes should be used (emphasis supplied).4 While we recognize that head-to-head comparative effectiveness studies may be considered one of several sources of meaningful data, we do not believe it is the government's role to mandate such analyses. Rather, manufacturers should have the discretion to embark upon such analyses, or other types of studies that they believe can effectively inform CMS coverage and payment decisions.	Thank you for your comments. The conclusions section has been revised. The absence of comparative studies leaves a gap.

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Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	For instance, we recently supported an economic model study (abstract enclosed) conducted by The Lewin Group to evaluate the outcomes and cost effectiveness of Dermagraft compared to conventional care of DFUs in the Medicare population.5 Using a Markov model, the investigators concluded that Dermagraft was more effective than conventional care,6 both in terms of outcomes and cost. More specifically, 76% of the DFUs were healed with Dermagraft, compared to 50% treated with conventional care. The median time to heal was 19 -20 weeks when using Dermagraft versus 51 -52 weeks for Medicare beneficiaries treated with conventional care. Regarding costs, the average expected cost to Medicare per patient was less when Dermagraft was used compared to conventional care. Specifically, measured over a one year period, the annual cost per patient was $23,080 versus $28,505. Recognizing that no product, including Dermagraft or conventional care, heals all DFUs, Dermagraft was more cost effective than conventional care for Medicare beneficiaries when measured on a per healed ulcer basis: $30,344 versus $56,516. Lastly, it is worth noting that when Dermagraft was used, compared to conventional care, cost neutrality for the Medicare program was achieved at six months.7 This economic model is an example of the type of post-FDA approval data analysis that can add valuable peer-reviewed comparative data for CMS and its local medical directors by using CMS' Medicare claims information and is specifically designed to make well-informed coverage and payment decisions.	No response needed.
Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	FDA Status ABH agrees that the TA's review and description of the FDA classifications is utilized by companies interested in promoting their products for advanced wound healing. Our one exception to the overview provided is the	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for

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			distinction made in the 510(k) category between "animal derived products" and "synthetic products." All of these products are subject to the same regulatory framework and standards for 510(k) clearances, regardless of the source material used. We believe the distinction is unnecessary, can create confusion, and ask that as CMS considers the TA, that it not make this distinction. It is true that these three categories --HCT/Ps, 510(k)s, and PMAs --are subject to a range of FDA oversight; and we have provided them in order from the most modest regulatory requirements to the most stringent, with PMA approved products facing the most stringent oversight by the FDA. While the regulatory standards for each of these classifications differ in a number of ways, the most significant for purposes of this TA, is the type, standard, and level of clinical data required or not under each classification. For Class III medical devices, this includes the requirement for adequate and well controlled clinical studies to establish the safety and effectiveness of the product for improved wound healing, usually requiring a comparison against what is recognized to be the standard of care treatment for the indication studied. Sufficient valid scientific evidence that provides reasonable assurance that the device is safe and effective for its intended use or uses is required and evaluated by the FDA prior to licensure. And this matters most given the fact that a product's FDA status ultimately defines that product's intended use and the claims its manufacturer can make in the marketplace about the product's wound healing capabilities.8 We believe that the FDA status and the intended use framework that applies to each must be a key determining factor as to when and how Medicare covers and pays for the technology. To review, we have provided the three FDA classifications, coupled with their intended use, and claims made statements:	the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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.

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			FDA Classification Intended Use Claims Made HCT/P Homologous to the human tissue Homologous claims only9 510(k) Same intended use as the predicate device and is as safe and effective as a legally marketed device Improved wound care; claims based upon management of the wound, without improving the incidence or timing of wound closure relative to standard care. Thus, wound closure is evaluated as a safety outcome for all products with a wound care claim (no impediment of healing), demonstrated by laboratory testing (i.e., biocompatibility testings).10 PMA Based upon the substantial scientific evidence demonstrated in well controlled clinical trials Improved wound healing; claims are based upon clinically meaningful and objective clinical trial data regarding the incidence of complete healing, acceleration to complete healing, facilitation of surgical wound healing, or quality of healing. 11	

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Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	Within this particular framework, the FDA only requires valid scientific clinical data to be generated to support a Class III high-risk PMA device. 510(k)s must demonstrate substantial equivalence to a predicate device with supportive laboratory data and often without requiring clinical data (some 510(k) products are required to generate limited clinical "field" data to show that the product works as intended).12 HCT/Ps are regulated by the FDA as banked tissue, but are not otherwise subject to either the 510(k) or PMA processes. We recognize and understand that the FDA and CMS have different missions and different regulatory requirements to meet their obligations. "Safe and effective" is not equivalent to "reasonable and necessary." However, both agencies make their respective regulatory judgments against the recognized standard of care.13 We believe this is appropriate and reasonable, particularly for both agencies to **14** continue to embrace this common framework.	This information is presented in the report.
Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	Methods: Key Question 2	Defining the Standard of Care ABH believes the Technology Assessment misses an opportunity for clarity by posing what is referred to as Key Question 2. It reads: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers) are skin substitutes more effective than usual care (synthetic dressings, growth factors, skin grafts, or other treatments used as a control) in promoting wound healing for the following outcome measures. 15 The question, imprecisely worded, suggests that some of the very products which are the subject of the TA, are the "usual" treatment options for chronic wounds. To make the appropriate coverage and payment decisions, CMS should evaluate the products against the acknowledged standard of care.16 When considering DFU-management, the acknowledged standard of care	Key Question 2 has been changed to: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures.

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			consists of proper examination and ulcer assessment, sharp surgical debridement to remove necrotic and/or hyper-keratinized tissue, a dressing appropriate for the characteristics of the ulcer (typically a moist to dry dressing), and offloading with appropriate footwear to alleviate pressure on the ulcer.17 Key Question 2 is also written to presume comparative effectiveness data are needed to help CMS make its coverage and payment decisions. As discussed above, comparative effectiveness data are not always required nor easily obtained. CMS may decide to encourage their development to enhance its decision-making, but ultimately the choice should be left to the company seeking appropriate coverage and payment for its technology. Moreover, it is also important to note that "comparative effectiveness" in and of itself does not establish a standard of evidence. For instance, randomized controlled trials as well as retrospective data analyses can generate comparative effectiveness data. Our study, referenced above, conducted by The Lewin Group is another example. When a manufacturer; therefore, chooses to design a comparative effectiveness trial or analysis, CMS and the local medical directors will still be required to evaluate the level or value of the evidence produced.	

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Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	Methods: Key Questin 2	Other inaccurate points in Key Question 2: Presumes that the effectiveness of the "usual" treatment options is well established or documented. Uses the phrase "skin substitute," which is a term that evolved in the marketplace and is vague and should not be relied upon by CMS when trying to define these products. States that the mentioned products are "usual." These products are not the norm. Therefore, ABH is convinced that the more appropriate question to ask should be: Are advanced wound healing technologies more effective than the recognized standard of care to promote wound healing?	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as “skin substitutes” and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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. Key Question 2 has been changed to: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures.

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Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	Other Alternatives The TA advocates for the use of comparative effectiveness studies to inform CMS coverage and payment policy. As noted, we do not believe such data should be required or easily can be studied or provided. While we appreciate the fact that they may add value to CMS's decision making process, we believe very few studies of this nature will be conducted. The very fact that the TA distilled 118 citations down to 14 studies is telling. Rather than emphasize the need for different data, we recommend the following approach, which may be a more simplified alternative to what the TA recommends, as a more immediate way to gain clarity: 1. Define the recognized standard of care for chronic wounds (we have provided one as an example that we believe is well-documented for DFUs). 2. FDA should widely publicize and distribute one set of definitions of HCT/Ps, 510(k)'d products, and PMA technologies, including intended use statements and claims made statements to CMS, MACs, and local medical directors. 3. Manufacturers within this space must abide by their respective FDA status, meaning that marketing claims must be consistent with the intended uses and labeling cleared or approved by the FDA, e.g., an HCT/P should not be marketed or covered and paid for as a biologically active PMA-approved technology.	No response needed

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Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	4. CMS should publish its hierarchy of evidence to best inform its coverage and payment policies; this hierarchy should contemplate studies needed for FDA approval or clearance as well as studies done outside the framework intended to educate and inform CMS and its agents about the value of its product for coverage and payment purposes. 5. To facilitate patient access to these evolving technologies, maintain and encourage the continued use of the LCD process. Medicine is practiced locally and we support the development of coverage policies at the local level. ABH would like to thank you in advance for considering these comments and recommendations in the constructive manner in which they are offered. We welcome any opportunity to work closely with AHRQ and CMS on this and other important patient access issues. Please feel free to contact me directly if you would like additional information or have any questions. Respectfully, Therésa K. Dixon, M.B.A., M.S. Vice President, Government Affairs & Health Economics Advanced BioHealing Inc., A Shire Company Direct: 813.741.3234 Mobile: 813.395.3067 Email: tdixon@abh.com Enclosure	No response needed
Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	Methods	Abstract Submission to the ADA 71st Scientific Sessions Cost effectiveness of a human fibroblast-derived dermal substitute for the treatment of diabetic foot ulcers in Medicare and commercially insured populations Yiduo Zhang, PhD, MA, MHS and Paul Hogan, MS, ABD The Lewin Group, Falls Church, VA	Conference abstracts are not included in this report.

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			A Markov model was developed to compare cost-effectiveness of a human fibroblast-derived dermal substitute (HFDS, Dermagraft) to conventional care (CC) in the treatment of diabetic foot ulcers (DFUs). The model simulated health status over 52 weeks of a cohort of 10,000 patients with a DFU treated either with HFDS or CC. Weekly health state transition probabilities were directly derived from results of a published U.S. clinical trial (N=245). Health states were verified by medical review and included healed, unhealed not infected, cellulitis, osteomyelitis and three types of amputations (toe, foot [includes TMA], below-knee). Due to similar costs, bone resections were collapsed with toe amputation. Transition to bone resection/amputation occurred in 4.6% of HFDS and 11.4% of CC patients. Medicare costs were estimated from 100% of the 2009 Medicare claims data covering 480,447 DFU patients. Costs for a commercially insured population came from a 2009 proprietary claims database covering 34,889 DFU patients. Medical claims data from initial DFU diagnosis date were cumulated over 1 year for each patient. Actual payments based on the medical claims determined costs of each health state. Sensitivity analyses were conducted according to the ISPOR Task Force guidelines. The proportion of healed ulcers was 76% (HFDS) vs. 50% (CC), median time to heal was 19-20 weeks (HFDS) vs. 51-52 weeks (CC). Patients receiving HFDS had fewer infections and amputations. The average expected cost to Medicare per treated patient over 52 weeks was $23,080 (HFDS) vs. $28,505 (CC). The average estimated cost per healed ulcer was $30,344 (HFDS) vs. $56,516 (CC). Cost neutrality for HFDS was achieved at 6 months for Medicare payers and 8 months for private insurers. When using commercial reimbursement rates, HFDS provided similar but smaller cost effective ratios.	

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			HFDS treatment pays for itself in as early as 6 months from the payer's perspective. Additional costs for HFDS were offset by medical savings from accelerated wound healing and reduced DFU complications and amputations. Supported by: Advanced BioHealing Document ID: 1278ADA11D1LB Category: 13 Health Care Delivery -Economics Keywords: cost effectiveness, diabetic foot ulcer, Dermagraft #10901432_v1	
Dixon, Theresa	Advanced BioHealing, Inc. (ABH), A Shire Company	General	1. This is not the case with 510(k) products or those regulated as HCT/Ps. 2. Implicit is the agency's responsibility to ensure that it is paying for these products responsibly and not using payment decisions to restrict patient access to new technologies. 3. American Recovery and Reinvestment Act, P.L. 111-5, §804(g) (2009). 4. Synder DL, Sullivan N and Schoelles KM. Technology assessment report: Skin substitutes for treating chronic wounds [draft]. Agency for Healthcare Research and Quality 2011: 1-121. 5. Zhang Y, Hogan P. Cost effectiveness of a human fibroblast-derived dermal substitute for the treatment of diabetic foot ulcers in Medicare and commercially insured populations [abstract]. Diabetes. 2011; 60 (suppl 1). http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=87707. Accessed January 16, 2012. 6. Conventional care consisted of sharp debridement to remove necrotic or hyperkeratinized tissue whenever clinically necessary. Wound dressings consisted of a non-adherent interface, saline-moistened gauze to fill the ulcer, dry gauze, and adhesive fixation sheets. Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of	No response needed

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care 2003;26:1701-5. 7. Zhang Y, Hogan P. Cost effectiveness of a human fibroblast-derived dermal substitute for the treatment of diabetic foot ulcers in Medicare and commercially insured populations [abstract]. Diabetes. 2011; 60 (suppl 1). 8. The misbranding provisions of Federal Food, Drug and Cosmetic Act are implicated here. Phrases like "biologically active" and "wound management" are terms of art that should not be misused. 9. "Homologous use" is defined as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor." 21 CFR §1271.3(c). 10. FDA Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds --Developing Products for Treatment (June 2006). 11. Id. http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=87707. Accessed January 16, 2012. 12. The whole 510(k) review process is evolving and there is certainly a push from the FDA that certain 510(k)'d products will require clinical data to support their applications. To date; however, the 510(k)'d devices that are the subject of this TA are not supported by FDA-reviewed clinical data. 13. This comparison is made for drugs and Class III medical devices only. And as noted above, comparative effectiveness data are not required. ABH does not believe they should be required. 14. For FDA approval and CMS coverage purposes, we believe the medical device should only be shown to be as safe and effective or as reasonable and	

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			necessary, but not more so. Of course, however, manufacturers will want to produce such evidence to encourage adoption in the marketplace. 15. We are not restating the nine outcome measures identified in the TA. 16. Standard of care: A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance. (Definition of standard of care. MedicineNet). http://www.medterms.com/script/main/art.asp?articlekey=33263. Published June 6, 2004. Accessed January 16, 2012). 17. Boulton AJM, Kirsner RS and Vileikyte L. Neuropathic Diabetic Foot Ulcers. N Engl J Med. 2004; 351:48-55.	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Douglas, J.	Independent Researcher	General	Thank you for the opportunity to provide comment on the Technology Assessment Skin Substitutes for Treating Chronic Wounds. The investigators are to be commended for the thoroughness of their review of the current literature. In light of the conclusion of this Technology Assessment that the evidence base to address important questions about the efficacy of skin substitutes for the treatment of chronic wounds was limited, future assessments and policy decisions must address the ethical issues concerning the privacy of children whose healthy tissues are likely to be acquired by commercial interests in the cosmetic and medical product industries (due to presently unforeseeable technological advances in the field of genomics); the extent to which parents and legal guardians can give consent for the use of foreskin and other healthy tissue excised from minors in the in the cosmetic and medical product industries; and the provision of information to parents and guardians in exculpatory consent forms. Circumcision of male minors, in the absence of a clear and present immediate medical indication, is a controversial practice within the medical profession (KNMG 2010; Smith 2011), with questions having been raised in the professional literature about the very legality of allowing the circumcision of healthy boys at the expense of Medicaid (Adler 2011). Despite this, more than 1.14 million circumcision procedures were performed on male infants in U.S. hospitals in the year 2009 (AHRQ 2011).	Thank you for your comments regarding the use of children's healthy tissue for skin substitutes. We will forward your concerns to the Agency for Healthcare Research and Quality.
Douglas, J.	Independent Researcher	General	Foreskins excised from minors in the absence of a clear and present immediate medical indication, almost invariably present in a normal healthy state, and as such their excision and preservation contributes little to the study of the pathology of disease. Further, the most promising advances in the field of stem cell research, are to be found in stem cell lines derived from adult sources including dental pulp stem cells (Authur et al	Thank you for your comments. We will forward your concerns to the Agency for Healthcare Research and Quality.

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			2008), uterine stem cells (Bock 2011) and bone marrow stem cells (Wada et al 2011); as well as diagnostic and therapeutic application of the patient's own cells (HHS 2011; Paca et al 2011). Products derived from foreskins excised en masse from minors in the absence of clear and present immediate medical indications, are frequently utilised in the commercial medical product, and more especially cosmetics industries (Advanced Healing 2011; Organogenesis 2011; Pitman 2008; SkinMedica 2011). As observed by the OHRP (2011) 'Changing technology in the field of genomics has dramatically increased the amount and nature of information about individuals that can be obtained from their DNA'. Valid concerns therefore exist for the future privacy of children whose healthy tissues are likely to be acquired by commercial interests in the cosmetic and medical product industries - and may be retained indefinitely - due to presently unforeseeable technological advances in the field of genomics. Doubts exist about the appropriateness of utilising products derived from foreskin and other healthy tissue excised from minors in the absence of a clear and present immediate medical indication, in the cosmetic and medical product industries, on the basis of exculpatory consent forms signed by parents and legal guardians of minors, and whether it is appropriate for parents and legal guardians to give consent explicitly for these purposes. The provision of information to parents on circumcision consent forms about the storage, transfer, processing, sale or any other use of excised healthy foreskins in unstudied, however a study conducted by Schaefer et al (2011) to ascertain ?whether and to what extent U.S. IVF clinics inform egg donors that resultant embryos initially intended to be implanted for reproductive	

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			purposes may in fact be used for research instead concluded that Egg donors in the United States, including some who may have a moral objection to research and stem cell research, are not being informed that embryos created with their donated eggs may in fact be used for these purposes, suggesting that incomplete information is being provided to parents about the use of foreskin and other healthy tissue excised from minors in the absence of a clear and present immediate medical indication.	
Douglas, J.	Independent Researcher	General	Future assessments and policy decisions must address the ethical issues concerning the privacy of children whose healthy tissues are likely to be acquired by commercial interests in the cosmetic and medical product industries (due to presently unforeseeable technological advances in the field of genomics); the extent to which parents and legal guardians can give consent for the use of foreskin and other healthy tissue excised from minors in the in the cosmetic and medical product industries; and the provision of information to parents and guardians in exculpatory consent forms. References Adler P W (2011) Is it lawful to use Medicaid to pay for circumcision. J Law Med. 2011;19(2):335-53 Abstract available at http://sites.thomsonreuters.com.au/journals/2011/11/28/journal-of-law-and-medicine-update-december-2011/ Accessed: 2012-01-08 Archived by WebCite at http://www.webcitation.org/64YPGfMLo Advanced Healing (2011) Dermagraph Active Living Cells Overview Link http://www.dermagraft.com/about/overview/ Accessed: 2012-01-16. Archived by WebCite at http://www.webcitation.org/64jhakjim AHRQ (2011) Hospital Stays for Children, 2009. HCUP Statistical Brief #118 prepared by Yu, H. (RAND Corporation), Wier, L.M. (Thomson Reuters), and	Thank you for your comments. We will forward your concerns to the Agency for Healthcare Research and Quality.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Elixhauser, A. (AHRQ) August 2011. Agency for Healthcare Research and Quality, Rockville, MD Full-text available at http://www.hcup-us.ahrq.gov/reports/statbriefs/sb118.jsp Arthur A, Rychkov G, Shi S, Koblar SA, Gronthos S (2008) Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues in Stem Cells. 2008 Jul;26(7):1787-95. Epub 2008 May 22 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/18499892 Bock, R (2011) Uterine stem cells used to treat diabetes in mice NIH News Full-text available at http://www.nih.gov/news/health/aug2011/nichd-30.htm Archived by WebCite? at http://www.webcitation.org/64jhMI7v9 HHS (2011) Scientists Rejuvenate Cells From Elderly Department of Health and Human Services Health Highlights 1 November 2011 Full-text available at http://www.healthfinder.gov/news/newsstory.aspx?Docid=658486	
Douglas, J.	Independent Researcher	General	KNMG (2010) Non-theraputic circumcision of male minors Royal Dutch Medical Association Full-text available at http://knmg.artsennet.nl/web/file?uuid=579e836d-ea83-410f-9889-feb7eda87cd5&owner=a8a9ce0e-f42b-47a5-960e-be08025b7b04&contentid=77976 OHRP (2011) Regulatory Changes in ANPRM Comparison of Existing Rules with Some of the Changes Being Considered Office of Human Research Protections website Full-text available at http://www.hhs.gov/ohrp/humansubjects/anprmchangetable.html Accessed: 2012-01-16. Archived by WebCite at http://www.webcitation.org/64jh4cWek Organogenesis (2011) Apligraf: How Is It Made Link http://www.apligraf.com/professional/what_is_apligraf/how_is_it_made/ Accessed: 2012-01-16. Archived by WebCite at http://www.webcitation.org/64jhpT91Q	Thank you for your comments. We will forward your concerns to the Agency for Healthcare Research and Quality.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Paca SP, Portmann T, Voineagu I, Yazawa M, Shcheglovitov A, Pa?ca AM, Cord B, Palmer TD, Chikahisa S, Nishino S, Bernstein JA, Hallmayer J, Geschwind DH, Dolmetsch RE (2011) Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome Nat Med. 2011 Nov 27;17(12):1657-62. doi: 10.1038/nm.2576 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/22120178 Pitman, S (2008) Babies? foreskin dubbed as new anti-aging treatment Cosmetic Design Full-text available at http://www.cosmeticsdesign.com/Formulation-Science/Babies-foreskin-dubbed-as-new-anti-aging-treatment Accessed: 2012-01-16. Archived by WebCite at http://www.webcitation.org/64ji8mqbP Schaefer GO, Sinaii N, Grady C (2011) Informing egg donors of the potential for embryonic research: a survey of consent forms from U.S. in vitro fertilization clinics Fertil Steril. 2011 Dec 22. [Epub ahead of print] Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/22196714 SkinMedica (2011) Key Ingredients Link http://www.skinmedica.com/skin-care-products/skin-rejuvenation/tns-recovery-complex#tab2 Accessed: 2012-01-16. Archived by WebCite at http://www.webcitation.org/64jiK7Gdx Smith JF (2011) The professional imperative for obstetrician-gynecologists to discontinue newborn male circumcision Am J Perinatol. 2011 Feb;28(2):125-8. Epub 2010 Aug 10 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed?term=20700861 Wada N, Bartold PM, Gronthos S (2011) Human foreskin fibroblasts exert immunomodulatory properties by a different mechanism to bone marrow stromal/stem cells Stem Cells Dev. 2011 Apr;20(4):647-59. Epub 2010 Oct 12 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed?term=20712449	

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Ennis, DO, MBA, William J.	University of Illinois Hospital and Health Sciences System	General	As the Chief of the section of wound healing and tissue repair at the University of Illinois Hospital and Health Sciences System and the director of the nations only wound care clinical fellowship I applaud the attempt to bring clarity to the area of skin substitutes. Without increasing the evidentiary levels within the wound care community we will not be able to achieve our goal to become a recognized medical specialty. I have dedicated most of my career to that mission and am happy to see more comprehensive literature based reviews such as this AHRQ document. It is however critical that the overall findings of such a project are sound and consistent with other areas of medicine and with other similar type publications. While this document provides an excellent "cataloging" of skin substitutes and identifcation of their individual regulatory pathways, it falls short on the final conclusions as these studies are lumped together. I hope to make a few comments that will clarify my position over the next several sections of my ressponse.	No response needed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Ennis, DO, MBA, William J.	University of Illinois Hospital and Health Sciences System	Executive Summary	The executive summary provides a succinct overview of the proposed research questions and a clear methodology. The comments that the studies included healthy subjects is troubling. One of the well accepted problems with an RCT is that through strict inclusion/exclusion criteria, necessary to prevent confounding variable noise, there is some loss of generalizability of a study. Is this comment an endorsement for pragmatic clinical trials? Should all RCT's be married with effectiveness studies? The use of simple gauze is in fact an FDA requirement at the time many of the RCT's were conducted. In fact most of these studies had FDA oversite and the studies were designed based on those recommendations. It is not consistent to then state that gauze is not a form of standard of care. In fact sadly, in the United States moist gauze is still the number one dressing prescribed in hospital care despite a myriad of evidence for advanced moist healing products. In addition for a PMA type trial one would not perform a comparative effectiveness study as recommended by the comment that the skin substitutes should have been compared to one another.	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies. We recognize that studies comparing products are not typically conducted, but note that they would be helpful to clinicians.
Ennis, DO, MBA, William J.	University of Illinois Hospital and Health Sciences System	Introduction/ Background	Mostly a standard review of wound healing and wound products as a method to create a base of knowledge for the report. It should be noted however that the majority of dressings discussed were not commercially available at the time many of these PMA studies were conducted.	Thank you for your comment.

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Ennis, DO, MBA, William J.	University of Illinois Hospital and Health Sciences System	Methods	One of the big issues in this document is the issue of blinding. Many of these studies used photography with independent reviewers, agree not all of them noted that in their pivotol publications. The question of funding however is hard to understand. Who other than the company applying for a PMA would fund a pivotal trial?	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We have removed the question regarding funding from our risk of bias assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.
Ennis, DO, MBA, William J.	University of Illinois Hospital and Health Sciences System	Results	The results of RCT's are biased towards the specific inclusion and exclusion criteria. No one would deny this, however that is the FDA process that companies are to follow. Efficacy vs effectiveness trial arguments have always been around for all fields of medicine and certainly not just for wound care.	We agree with the reviewer's comments.

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Ennis, DO, MBA, William J.	University of Illinois Hospital and Health Sciences System	Discussion/ Conclusion	My overall impression is that this was an excellent review and the products were well researched. One of the concerns within the wound care community has and continues to be, the inconsistent interpretation, evidence requirements and processes across the continuum from FDA clearance to CMS payment to AMA CPT coding. The wound care community is well aware that there has been a limited amount of well controlled data for clinicians to make evidenced informed decisions and we can and should improve this deficit. By combining some of the strongest PMA level RCT data that we have with 510K data and products without data, clinicians will come away with a "biased" view that all of these products are the same and a deeper dive into this topic would not support that finding. Thank you for your time in reading my comments and I hope they provide some useful input to this process Sincerely William J Ennis DO,MBA Professor Clinical Surgery University of Illinois	We thank the reviewer for his comments.
Gibbons, MD Gary W. Medical Director	South Shore Hospital Center for Wound Healing and Hyperbaric Medicine	General	Chronic wounds are typically associated with many chronic illness like vascular disease, Diabetes, cancer explaining why they don't often heal with routine care. They are associated with high morbidity and costs both in terms of human sacrifice, resource utilization/dollars spent. While there are published evidence based guidelines for care for all chronic wound types, they are most often specialty driven and fragmented and lack multidisciplinary administration. There continues to be great variation in care even in the same community and region because providers compete instead of collaborate. But for Wound Centers like South Shore Hospitals the evidence is practiced for all wound types and still there is need for advanced modalities when standard algorithms don't bring closure. We follow the evidence pyramid where RCT's are at the top and the data for skin substitutes(human tissue products) that have PMA from the FDA are more robust as they have	Based on comments made by the FDA, we have added the following statements to describe the different regulatory processes: "Wound care products regulated under the PMA process are indicated for treating a subset of chronic wounds, those wounds with more than 30 days' duration that have not adequately responded to standard wound care. The 510(k) products are indicated for managing chronic wounds and no restrictions are put on wound duration or prior treatments." Also added An HDE is similar in both form and content to a PMA application but is exempt from the effectiveness requirements of a PMA. HDE approval is based on evidence of probable benefit in a disease population occurring at a frequency of fewer than 4,000 patients per year in the United States.

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			withstood the rigors of RCT's for their indicated use. The current draft does not recognize this and in fact is very misleading. The PMA products have the highest level 1A evidence and are the lowest biased in our medical world yet not recognized by the authors in this draft. To simply lump all of these products into one category does a dis-service to the treatment options that are truly evidence based and available to maximize our outcomes for chronic wounds especially those that are of venous or Diabetic etiology. While head to head trials now are difficult and costly there are trials out there and they need to be acknowledged and cited. I have great consern what the authors are promoting here and skin substitues aren't interchangeable and all don't work the same way. To me the way this is currently written could seriously jeapardize those of us who practice as centers of excellence as the potential use of advance therapies could be further restricted for all the wrong reasons. Saline moistened gauze was the standard for many of these studies but not wet to dry dressings. People are missing the point here. New products don't necessarily mean better quality and outcomes it is how the products are used to achieve the desired outcome. The same can be said for advanced therapies. The authors need to understand here that the real problem is getting providers to practice multidisciplinary evidence based wound care #1. Many new products and even advanced therapies are on the market because of tremendous media and industry promotion not having to undergo the rigors like two of the human tissue advanced therapies. We need to match quality clinical outcomes with fiscal responsibility and I fear as currently written this Draft will not support that foundation.	

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Gibbons, MD Gary W. Medical Director	South Shore Hospital Center for Wound Healing and Hyperbaric Medicine	Discussion/ Conclusion	If this Draft is meant to be a white paper for the advancement of the treatment of chronic wounds of any etiology the evidence needs to be reevaluated and scientifically driven including discussions with those of us who are most vested and dedicated to patients suffering from a chronic wound(getting them healed with the most appropriate and efficient use of resources. All products are not alike and any product used incorectly and inappropriately serves no one. And unfortunately, currently that is the state of the state of healing chronic problem wounds. Thank you for the opportunity to comment	
Hankin, PhD., Cheryl President and Chief Scientific Officer	BioMedEcon, LLC Health Economics and Outcomes Research	General	We note that reviewers examined skin substitute products that are currently regulated by the FDA for use within the U.S. by undertaking a search of 13 electronic bibliographic databases from 1950 to August 2011. 1 Unfortunately, Talymed™ (Marine Polymer Technologies, Inc., Danvers, MA), a skin substitute for the treatment chronic wounds which was cleared by the FDA for marketing under the 510(k) process in July 2010 (K102002) and granted a unique HCPCS code of Q4127 (Talymed, per sq cm) on 11/04/2011, was entirely omitted from this draft report. Furthermore, although results from a randomized clinical trial of Talymed™ were published in May 2011, this study was omitted from the systematic literature review presented in the draft report. Omission of Talymed™ results is especially concerning because the published study satisfies all criteria stipulated *a priori* by reviewers for inclusion in their systematic review. Talymed™ is indicated for the management of wounds including: diabetic ulcers, venous ulcers, pressure wounds, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, second degree burns, surgical wounds, traumatic wounds healing by secondary intention, chronic vascular ulcers and	Thank you for recommending inclusion of the Kelechi study (2011). This study has been added to the report since it meets study inclusion criteria.

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			dehisced surgical wounds and bleeding surface wounds, abrasions and lacerations." Talymed™ is included in FDA product code FRO (Dressing, wound, drug). Talymed™ is a sterile, bioactive, 3-dimentional, scaffold-like wound matrix membrane comprised of biodegradable shortened fibers (nanofibers) of poly-N-acetylglucosamine, which are isolated from microalgae. The active ingredient in Talymed is polysaccharide, which is produced by microalgae. Talymed™ is free of proteins, metal ions, and other contaminants. Microalgae-based Talymed™ does not carry the risk of adverse reactions to animal based proteins that can occur with human- and animal-derived skin substitutes. Talymed™ is placed on the open wound and covered with a transparent dressing. New wound matrix can be reapplied as necessary. Talymed™ is provided as a 5 x 5 cm and 10 x 10 cm patch that should be cut to fit wound size. Talymed's mechanism of action is unique among tissue scaffolds, which have been generally limited in their ability to sufficiently activate the wound healing cascade. 2,3,4 In vivo research indicates that at 3 and 6 months of follow-up in the healed wounds of genetically diabetic mice who received Talymed™ nanofibers at surgically-induced wound sites, no nanofibers or foreign body reactions were found, and the and the biodegradable properties of Talymed™ were found demonstrated. Cell metabolism and migration assay results of *in vitro*, cell-nanofibers interactions and in vivo wound healing kinetics of full thickness wounds in diabetic mice receiving Talymed™ nanofiber scaffolds, cellulosic control material, or no treatment are shown in the table below.5 [Table includes a description of Phases and Mechanism of Action]	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Hankin, PhD., Cheryl President and Chief Scientific Officer	BioMedEcon, LLC Health Economics and Outcomes Research	General	In an investigator- and assessor-blinded study, 82 patients with venous leg ulcers (VLUs) were randomized (via computer-generated, stratified, permuted block allocation of randomly varied block size) to receive standard care with Talymed™ [applied once only (N=20), bi-weekly (N=22), or once every three weeks (N=20)] or standard care alone (N=20)].6 The primary endpoint, the proportion of patients who achieved complete VLU healing at 20 weeks, compared healing rates of patients across these conditions. This study is exceptional among others that were reviewed insofar as: 1) the principal investigator, participating physicians who provided medical oversight, and study nurses who assessed wound outcomes were blinded to treatment allocation; 2) authors clearly specified methods used to randomize participants' baseline comorbid and wound-related (wound duration and size) characteristics; 3) results were provided for all randomized patients (intent-to-treat analysis); and 4) the study posed moderate risk of bias. In contrast, of the 14 studies included in the Draft Technology Assessment Report, 13 did not report any information on assessor blinding; information on differences in wound size, wound duration and comorbidities was uniformly poor; and 12 were funded by the manufacturer (the remaining 2 studies did not report funding source). At enrollment into the study, the average patient age was 61.5 years, average ulcer size was 11.2 cm2, mean VLU duration was 3 months, and the most common comorbid conditions were hypertension (74%), diabetes (61%), arthritis (46%), class III obesity (45%), and blood clotting disorders (23%). There were no significant group differences with regard to baseline demographic, comorbid illness, and VLU characteristics. At 20 weeks, the proportion of patients with completely healed VLUs was 45.0% (9/20), 86.4% (19/22), and	Thank you for the information on the study of Talymed™.

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			65.0% (13/20) for groups receiving standard care plus Talymed™ only once, every other week, and every 3 weeks, respectively, versus 45.0% (9/20) for those receiving standard care alone (P <0.01 for standard care plus Talymed™ every other week vs standard care alone). No significant treatment-related adverse events or reactions occurred during the study and none of the subjects experienced increased pain or edema. [Table titled Study Selection Criteria Determination: Kelechi et al., 2011] [Table titled Study Quality Risk of Bias: Kelechi et al., 2011]	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Hankin, PhD., Cheryl President and Chief Scientific Officer	BioMedEcon, LLC Health Economics and Outcomes Research	General	1 Evidence-based Practice Center: ECRI Institute EPC (Contract Number: HHSA 290-200710063). Technology Assessment: Skin Substitutes for Treating Chronic Wounds. Project ID: HCPR0610. December 22, 2011. 2 Fischer TH, Thatte HS, Nichols TC, et al. Synergistic platelet integrin signaling and factor XII activation in poly-N-acetyl glucosamine fibermediated hemostasis. *Biomaterials*. 2005;26:5433-5443. 3 Thatte HS, Zagarins S, Khuri SF, et al. Mechanisms of poly-N-acetyl glucosamine polymer-mediated hemostasis: platelet interactions. *J Trauma*.2004;57(suppl 1):S13-S21. 4 Pietramaggiori G, Yang HJ, Scherer SS, et al. Effects of poly-N-acetyl glucosamine (pGlcNAc) patch on wound healing in db/db mouse. *J Trauma.2008*;64:803-808. 5 Scherer SS, Pietramaggiori G, Matthews J. et al. Poly-N-acetyl glucosamine nanofibers: A new bioactive material to enhance diabetic wound healing by cell migration and angiogenesis. *Ann Surg*. 2009;250: 322-330. 6 Kelechi TJ, Mueller M, Hankin CS, Bronstone A, Samies J, Bonham PA. 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. *J Am Acad Dermatol.* 2011 May 25.	
Hughes, Jeff	TEI Biosciences Inc.	General	TEI Biosciences Inc. (Boston, MA), the manufacturer and distributor of PriMatrix Dermal Repair Scaffold (?PriMatrix?), respectfully submits comments in response to the AHRQ Report entitled ?Technology Assessment?Skin Substitutes for Treating Chronic Wounds - Draft December 22, 2011? (the ?Report?). On Page 50, the Report states that only five of the 31 skin substitute products identified for the Report were examined in RCTs and that the actual clinical evidence	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be “skin substitutes” and the regulatory pathways they may take. The second reason for the report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational

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			for the efficacy of skin substitutes in the treatment of chronic wounds is very limited since clinical evidence of effectiveness is not available for the majority of available skin substitute products. Also on Page 50, the Report states that: a) What is also missing from the evidence base were studies that compared the various types of skin substitute products b) Only one of the 14 RCT studies compared two skin substitute products c) This kind of [comparative] information is needed by clinicians trying to decide which wound treatment products to use d) Only four of the studies used a more advanced wound dressing product as a comparison e) Comparisons with other advanced wound care products in terms of efficacy and cost are needed to determine where and when skin substitutes should be used. We believe that many of the deficiencies listed above are addressed in the Dr. Karr 2011 study (reference 158 in the Report) (the ?Karr study?). This study was excluded by ECRI at the abstract level as it is not a RCT, but we respectfully request that ECRI reviews the study as it provides relevant and valuable information, including: a) A comparison between two skin substitute products by a single doctor with multi-year experience with both products b) A comparison between a PMA-approved product (Apligraf?) and a 510(k)-cleared product (PriMatrix) c) A comparison of these two products in both diabetic foot ulcers (DFUs) and venous stasis ulcers (VSUs) d) A significant difference in healing rates e) A significant difference in the cost of each therapy in treating the two wounds studied.	studies; however, the scope of this report was more limited.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Hughes, Jeff	TEI Biosciences Inc.	General	We believe these results bode well with the Report's goal of "helping health care decision-makers make well-informed decisions to improve the quality of health care services." The Karr study was published in Advanced Skin and Wound Care in March 2011.The Karr study meets nine of the eleven inclusion criteria outlined in the Report (pages 15 - 16). Population 1. Study must have enrolled human subjects, diagnosed with a chronic wound lasting more than 30 days without healing YES: The Karr study reports an average duration of more than 100 days for both DFUs and VSUs 2. Results for patients with different wound etiologies must be reported separately YES: The Karr study reports results for DFUs and VSUs separately and independently Intervention 3. Study must evaluate the efficacy of commercially available skin substitute product regulated by the FDA YES: Both PriMatrix and Apligraf are regulated by the FDA Study Design 4. Studies must be randomized controlled trials NO: The Karr study is retrospective 5. Studies must have enrolled at least 10 patients per arm YES: The Karr study has 4 arms with 13, 12, 11 and 12 patients, respectively, and 20, 20, 14 and 14 ulcers treated, respectively Outcomes 6. Study must have reported on at least one of the outcomes listed in Key Question 2 YES: The Karr study directly compares time to heal in each of the 4 arms 7. The reliability and validity of all instruments measuring relevant outcomes such as	Thank you for the information on the Karr study.

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			activities of daily and function or pain must have been address in the published literature NO 8. For all outcomes, we only considered time points for which at least 50% of the controlled participants contributed data YES: The Karr study reports data on 100% of participants included in the study	
Hughes, Jeff	TEI Biosciences Inc.	General	Publication Type 9. Study must have been published in English YES 10. Study was reported as a full-length peer-reviewed article YES We therefore respectfully request that the Karr study be included in the Report. In our opinion, it is the first and only large clinical investigation of the effectiveness of a PMA skin substitute product (Apligraf) against a 510(k) skin substitute product (PriMatrix) with the potential for significant reduction in the cost of treating DFUs and VSUs. A summary of the Karr study and results: This retrospective study addresses 68 ulcers in 48 patients; 40 of these are diabetic foot ulcers and 28 are venous stasis ulcers. The study is a head-to-head comparison of PriMatrix to Apligraf. Both treatments were found to be successful. DIABETIC FOOT ULCER GROUP (n=40 ulcers) Average Time to Heal -Apligraf 87 days -PriMatrix 37 days Average number of grafts -Apligraf 2 -PriMatrix 1.5 Average size of ulcer -Apligraf 6.4 sq cm -PriMatrix 10.2 sq cm VENOUS STASIS ULCER GROUP (n=28 ulcers) Average time to heal -Apligraf 63 days	Thank you for the information on the Karr study

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			-PriMatrix 32 days Average number of grafts -Apligraf 1.7 -Primatrix 1.3 Average size of ulcer -Apligraf 5.4 sq cm -Primatrix 10.2 sq cm	
Hughes, Jeff	TEI Biosciences Inc.	General	In conclusion, the author found both Apligraf and PriMatrix to be highly effective in the treatment of both DFUs and VSUs. Both products contain cells and growth factors upon application and exposure to patient?s blood that work to promote rapid regeneration of dermal tissue in patients with difficult-to-heal wounds and at high risk for complications including infection and amputation. This retrospective study of 68 ulcers in 48 patients found that on average, PriMatrix-treated patients healed faster than did those treated with Apligraf despite larger wound sizes. This shortened time to healing, while using less graft material, can improve patient outcomes with increased cost-effectiveness in the treatment of challenging chronic DFUs and VSUs. Thank you for allowing us to comment and for your reconsideration of this important study.	Thank you for the information on the Karr study

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Kirsner, Robert	Organogenesis Consultant	General	Overall, this was a well done and well presented analysis of skin substitutes. Several issues exist with the report. The premise of the report was to study skin substitutes. However, the terminology used may be confusing. Most would agree that skin substitutes would be those products that resemble skin or part of the skin histologically and would consist of both cells and extracellular matrix. Many of the products that the report concerned itself with do not have cells and does not resemble skin in structure. Since none of the products function by replacing skin but rather either stimulate healing by cytokine release, provide a substrate for cell migration or by yet to defined mechanism. Therefore, the terminology of the report is somewhat confusing and perhaps a more limited analysis of '**engineered skin constructs'** may be more appropriate terminology.	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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.
Kirsner, Robert	Organogenesis Consultant	Background	Adding to the confusion is the background sections of the report imply that the FDA regulatory process of characterization is based on product origin-based. However **I believe it is based on the proposed mechanism of action and/or potential risk.**	Based on input from an FDA reviewer these concerns are now addressed in the report.
Kirsner, Robert	Organogenesis Consultant	Methods	Also while this analysis was performed to evaluate the products on chronic wounds, **a number of the products listed are used for burn wounds as opposed to chronic wounds.** A more precise choice of products to be discussed and analyzed would be recommended.	All products not indicated for chronic wounds have been removed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Kirsner, Robert	Organogenesis Consultant	Methods	A second major issue relates to the methodology, which limits data analyses to Randomized Controlled Trial (RCT). While RCTs can be performed for a number of reasons, they are most often performed for registration purposes and used to demonstrate efficacy. Equally or perhaps more importantly is whether these products are effective and effectiveness research often uses other methodologies such as data base analyses, among others. Thus, the methodology employed prevented a broader analysis of available data.	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. Systematically reviewing and effectively analyzing the non-RCT literature for all of these products is beyond the scope of this report. To make the scope more manageable, we gauged the state of the evidence base by looking for high- quality studies in the form of RCTs. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.
Kirsner, Robert	Organogenesis Consultant	Methods: Key Question 2	A third issue relates to usual or standard care. Since a rigorous analysis was performed on this topic, it seemed unusual that such a cavalier and cursory discussion existed around the evidence base and quality of the evidence for standard care. For example, a RCT has never been performed to demonstrate the efficacy or effectiveness of debridement, but the authors easily accept it as standard care.	Key Question 2 has been changed to compare skin substitutes to any type of wound care as a comparison rather than trying to define a usual care for comparison. Key Question 2 has been changed to: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures.
Kirsner, Robert	Organogenesis Consultant	Methods	A fourth issue relates to the outcomes chosen. Given the limited data it would seem that the authors **might have analyzed other outcomes such as partial wound healing or using surrogate outcomes.** The outcome of complete healing is an FDA mandated outcome used for registration and this report seems in part to be limiting itself by using the FDA as a guidepost.	The most important patient-oriented outcome is complete wound healing and is therefore the focus of this report.

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Kirsner, Robert	Organogenesis Consultant	Methods	A fifth issue was the assignment of bias to a funded study. This appears to be a catch 22 situation as by limiting the studies to RCTs which are most often used for product registration it would seem that, almost by definition, studies would be funded by a manufacturer. It would therefore be superior to not allow manufacturer funding to be an automatic cause of bias or concern for the integrity of data generated. In a similar fashion faulting studies for, for example, because patients were excluded if their health was suboptimal, or they were taking medication that would interfere with wound healing or their wounds were infected also seems unfair. This is the typical design of efficacy studies meant for registration. Thus creating a methodology that selects for these types of studies and then criticizing studies seems unreasonable.	We have removed the question regarding funding from our risk of bias assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.
Marston, MD, William Professor and Chief, Division of Vascular Surgery; Medical Director, UNC Wound Healing Center	University of North Carolina School of Medicine	General	Thank you for the opportunity to review this Technology Assessment. This document will provide very important information for those working in the treatment of chronic wounds. Overall I find it a fair and balanced review of the current literature in this area. The description of the criteria for evaluation of the published clinical studies will provide much needed clarity for those striving to produce better studies to evaluate new treatment strategies in this area. The criticisms of the literature are valid and hopefully will stimulate improved study design moving forward. Please consider the following suggestions from my review of the document. Products you may wish to add to this review: Talymed, Marine Polymer Technologies Marine diatom derived skin substitute 510K approved HCSPCS code Q4127	We have added one study (Kelechi et al. 2011) to the report that compares Talymed plus standard care to standard care.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Marston, MD, William Professor and Chief, Division of Vascular Surgery; Medical Director, UNC Wound Healing Center	University of North Carolina School of Medicine	Background	Background**:** 1. Diabetic Foot ulcers Recent estimates have determined that over 50% of diabetic foot ulcers are now affected by peripheral arterial disease.[1-3] This progressive development of ischemic diabetic foot ulcers is important given the higher risk of limb loss and lack of products designed to treat this segment of the population which now constitutes the majority. Almost all of the randomized studies published to date have excluded ischemic DFUs from enrollment. Given the focus on the lack of applicability of the available studies to the larger population of patients with DFUs seen in clinical practice, this issue could be highlighted in further detail in this section. 2. Vascular/Venous leg ulcers In 15-20% of leg ulcer cases, arterial and venous insufficiency are both present and must be addressed to achieve successful wound closure. These patients are typically excluded from clinical trials.	Thank you for your comments on the background section. We have taken this information into consideration and revised our Tables to include any information provided in a publication that described the extent of peripheral arterial disease in the study patients. This topic is also mentioned in the Discussion section.
Marston, MD, William Professor and Chief, Division of Vascular Surgery; Medical Director, UNC Wound Healing Center	University of North Carolina School of Medicine	Methods	**Strength of Evidence:** It is noted that all of the studies in the evidence base reported some benefit of skin substitutes over the control so that consistency was demonstrated. However, there have been numerous significant RCTs performed in the chronic wounds over the last two decades that were conducted but never reported in the literature. A number of the products listed in this review and many that are not marketed in the US were evaluated in RCTs but when the outcomes were not achieved, no public report of this information occurred. This publication bias has been significant and should be highlighted to stimulate increased compliance with the recommendation that results from all such RCTs require publication for public evaluation.	We have added comments about publication bias. We noted the absence of studies of pressure ulcer wounds. In our examination of studies listed in ClinicalTrials.gov we did not identify completed but unpublished studies in recent years.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Marston, MD, William Professor and Chief, Division of Vascular Surgery; Medical Director, UNC Wound Healing Center	University of North Carolina School of Medicine	Results: Key Question 2	**Comparator wound dressings for standard treatment arms** 1. Simple gauze dressings vs more advanced wound care products: In the executive summary and elsewhere, studies on skin substitutes are criticized for using simple gauze dressings as the control therapy. This implies that comparisons are required to more advanced wound care products. In the section on wound dressings, very accurate descriptions of the classes of dressings commonly used on chronic wounds are provided. However, it should be mentioned that the evidence that any of these types of wound dressings result in improved clinical results in closing more wounds or affecting any of the other patient-relevant outcomes is very limited. A review of recent Cochrane database evaluations concluded the following: 1. The type of dressing applied beneath compression has not been found to affect ulcer healing.[4] 2. There is no evidence to suggest that foam wound dressings are more effective at healing foot ulcers in people with diabetes than other types of dressings.[5] 3. There is insufficient evidence to determine whether the choice of topical agent or dressing affects the healing of arterial leg ulcers.[6] 4. There is some evidence to suggest that hydrogel dressings are more effective in healing (lower grade) diabetic foot ulcers than basic wound contact dressings however this finding is uncertain due to risk of bias in the original studies.[7]	After a review of these comments, we have decided to remove any reference to “advanced wound care products” from the report. The criticism of using simple gauze has also been changed since only a few of the studies used this treatment as a control and this was mostly in studies of diabetic foot ulcers. We have instead commented more on the wide variation in study comparisons and the types of patients, generally more healthy than the general population seeking treatment, examined in the studies.

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Marston, MD, William Professor and Chief, Division of Vascular Surgery; Medical Director, UNC Wound Healing Center	University of North Carolina School of Medicine	Results: Key Question 2	Despite the proliferation of hundreds of so called "advanced wound dressings" that are proclaimed by their manufacturers to be better than a simple gauze dressing, the clinical studies on these products, if available, suffer from the same problems of bias, small sample size and lack of generalizability affecting the current literature on skin substitutes. While there are dressings that may have benefits in terms of longer wear time, better absorption of moisture, or reduced nursing requirements, there is limited credible evidence that the patient oriented outcomes described in this document are positively affected. Based on this information it seems incorrect to suggest that there are advanced wound dressings available that are generally agreed to have documented better outcomes than gauze dressings. In fact, it would probably be more accurate to remove the term "advanced wound dressings" from this document as this is a term introduced and popularized by dressing manufacturers to create additional demand for their products. The consideration of standard of care in chronic wound clinical trials has been carefully considered in many studies, particularly those for products proceeding through the PMA process. In some cases the FDA directed sponsors towards the use of gauze dressings given the lack of evidence for superiority of other dressings, generally in earlier studies initiated before 2000. More recently, studies of diabetic foot ulcers typically use hydrogel-type dressings as the comparator.	Any reference to "advanced wound care products" has been removed from the report.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Marston, MD, William Professor and Chief, Division of Vascular Surgery; Medical Director, UNC Wound Healing Center	University of North Carolina School of Medicine	Results: Key Question 2	**General comment, venous ulcers:** An issue that is frequently encountered in the design of venous leg ulcer studies concerns the diagnosis of venous disease. Debate frequently occurs between study designers and investigators on the need for definite diagnosis of venous insufficiency. While some studies have required abnormal venous anatomy or function on duplex ultrasound as a study inclusion criteria, others have not. Investigators treating venous ulcers at wound clinics without easy accessibility to duplex testing have argued that a venous ulcer can be diagnosed by history and physical examination alone. Those arguing for routine studies note that ulcers caused by lymphedema and obesity may mimic the clinical features of venous insufficiency and may confound study results given the different etiologies. In my opinion, we currently should treat patients with chronic wounds with a positive diagnosis to be sure that patients in venous leg ulcer trials actually have venous disease. If possible, this could be highlighted in this assessment by noting in the Tables whether the venous ulcer studies included actual venous diagnostics as entry criteria. References: 1.Morbach S, Lutale JK, Viswanathan V, Mollenberg J, Ochs HR, Rajashekar S, Ramachandran A, Abbas ZG: Regional differences in risk factors and clinical presentation of diabetic foot lesions. *Diabet Med* 2004, 21(1):91-95. 2.Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, Uccioli L, Urbancic V, Bakker K, Holstein P *et al*: Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia* 2008, 51(5):747-755.	We thank the reviewer for his/her general comment on venous ulcers. Six studies in the report were focused on treatment of venous ulcers and/or mixed venous/arterial ulcers. Of the six studies, only one study (Falanga et al. 1998) required evidence of venous insufficiency confirmed by air plethysmography or photoplethysmography. Additional comments regarding these limited patient inclusionary criteria in venous leg ulcer studies have been added to the report. Information on patient testing has been added to our Tables as well.

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			3.Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, Edmonds M, Holstein P, Jirkovska A, Mauricio D *et al*: High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia* 2007, 50(1):18-25. 4.Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA. Dressings for healing venous leg ulcers. Cochrane Database Syst Rev 2006 Jul 19:3:CD001103. 5.Dumville JC, Deshpande S, O'Meara S, Speak K. Foam dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2011 Sep 7;9:CD009111. 6. Nelson EA, Bradley MD. Dressings and topical agents for arterial leg ulcers. Cochrane Database Syst Rev 2007 Jan 24;(1):CD001836. 7. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2011 Sep 7;9:CD009101.	
Reyzelman, Alex	California School of Podiatric Medicine	Methods	This is in regard to the Graftjacket study authored by A. Reyzelman et. al. Questions were raised in this report in regards to the randomization procedures during the trial and not achieving a true blind. 1) Each site that enrolled subjects had sealed envelopes with pre-assigned study groups which was opened only when the subject met all of the inclusion and none of the exclusion criteria for the trial	We thank Dr. Reyzelman for providing us with this information. We have revised the assessment for this study.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Reyzelman, Alex	California School of Podiatric Medicine	Methods	2)Although true blinding was not possible with these type of trials, objectivity was obtained by using the acetate tracing for the diabetic foot ulcer size along with obtaining pictures with a date and initials marker.	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We captured methods of assessing wounds, but we have focused the review on the outcome of complete wound healing.
Silverman, MD Ron Chief Medical Officer	KCI	General	We commend the authors of this report for undertaking the difficult task of addressing the use of skin substitutes for treating chronic wounds. We appreciate the opportunity to be able to submit comments. This AHRQ Technology Assessment attempts to evaluate products derived from different sources, processed in different ways and follow different FDA pathways to market. This literature review attempts to categorize or segment the various products based on Regulatory approval pathway and by simple structural definitions (eg, natural or synthetic biomaterials, acellular products, and cellular products). This may not be the most clinically meaningful method for categorization. The wound healing cascade is a dynamic process, and each product provide different and potentially unique components targeted towards various stages of wound healing. Additionally, as stated in the report, these complex patients (with co-morbid conditions) generally are the population of patients developing chronic wounds, thus requiring unique assistance in bringing a wound to complete closure. Attempting to segment products by artificial or random (non validated) descriptors oversimplifies the category which leads to an inappropriate review of products used to treat patients suffering from chronic wounds.	We thank the reviewer for providing comments on the report. CMS requested this report to better understand the types of wound care products that are commonly referred to as “skin substitutes” and the regulatory pathways for the different types of products. We are not proposing an official classification system.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	General	An illustration of segmenting products too broadly is seen with the terminology biologic dressing. Burn literature demonstrates the use of skin substitutes as a modality to protect the skin on a temporary basis, and is thus termed as a biologic dressing. [this sentence after the comma is awkward] In chronic wounds, use of the term skin substitutes indicates a modality that offers components or structure to the various stages of the complex wound healing cascade as they aid in bringing the wound to complete closure. Transferring the burn terminology for skin substitutes to chronic wounds inaccurately represents the full scope of benefits these products provide to wound care patients	The term biological dressing has been removed from the report. For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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.
Silverman, MD Ron Chief Medical Officer	KCI	General	Many of the products listed in the report have proven clinical benefits in the acute care setting in the treatment of non-chronic wound indications such as surgical repair, surgical mesh or soft tissue reinforcement. Whereas, in chronic wounds, these same products are used as a tissue matrix to modulate the wound to the closure process. For example, Graftjacket Regenerative Tissue Matrix (RTM) can be used in rotator cuff tendon repair in acute injuries.1 In chronic wounds, Graftjacket RTM can be used as an acellular regenerative tissue matrix for the treatment of diabetic foot ulcers.2 The American Medical Association (AMA) has differentiated procedure codes for skin substitutes (now known in AMA documents, as skin substitute grafts) with a new CPT code series. These products are recognized differently across indications and are illustrated by procedure codes established in 2012. When these products are used to treat wounds, the appropriate codes are CPT 15271-15278. However when such products are used to secure soft tissue a different code	We agree with the reviewer's comments and have addressed this issue in the introduction and purpose sections of the report.

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			is appropriate CPT 15777. Again, the actual product used has not changed but rather the function or different clinical benefit is clearly recognized. In addition to the issue of forcing a broad categorization to the products, the report's critique of the clinical studies is also a concern. The statement in the report that most of the RCTs evaluated included healthy patients showed a basic unfamiliarity with the complexities of the chronic wound care population and therefore is clinically inappropriate. Treatment of chronic wounds is complex and normally "real world" patients are excluded from these evaluations to allow for consistency between treatment groups. Unlike acute wounds, chronic wounds do not progress through the normal phases of healing; they fail to proceed through an orderly repair process to produce tissue with anatomic or functional integrity.3 Therefore, this report does not include the fundamental information required to understand and evaluate various modalities associated with the chronic wound patient population and the complexities associated with treating chronic wounds. In general, the treatment of chronic wounds requires addressing the whole patient rather than just the wound itself. Chronic wound patients are usually compromised by one or more co-morbid conditions that usually affect wound healing. These co-morbid conditions may include diabetes, obesity, lack of nutrition, smoking, heart disease, etc, and must be addressed prior to determining a course of action for successful wound healing. For example, in the diabetic patient population, the contributing factors leading to a diabetic foot ulcer include uncontrolled diabetes, vascular insufficiency and peripheral neuropathy; this clearly demonstrates that a randomized control trial for the treatment of diabetic foot ulcers would by clinical definition, not be seen as a generally healthy population.	

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Silverman, MD Ron Chief Medical Officer	KCI	General	Our last general comment regarding the report is that we observed a section of reimbursement sources listed; however, the report did not explain the use of these sources in their evaluation of these products.	We have removed mention of reimbursement sources in the document.
Silverman, MD Ron Chief Medical Officer	KCI	TOC	We now offer the following suggested corrections and comments as appropriate in each section of the report by the directions provided on your website:Page v: Table of Contents Current: Graftjacket (Wright Medical Technology, licensed to KCI Medical) Correction: Graftjacket: Regenerative Tissue Matrix and Graftjacket Xpress (Manufactured by LifeCell Corporation, licensed to Wright Medical and licensed to KCI)	This change has been made to the document.
Silverman, MD Ron Chief Medical Officer	KCI	General	Comments: KCI is the exclusive distributor for Graftjacket RTM and Graftjacket Xpress in the wound care field pursuant to a distribution agreement with LifeCell Corporation and a trademark agreement (for the trade name Graftjacket with Wright Medical Technologies. The FDA establishment registration for Graftjacket listing KCI USA, Inc. as the responsible company for storage and distribution of Graftjacket confirms this fact. Document is available upon request. Wright Medical maintains the marketing and sales responsibilities for non-wound related indications, such as the orthopedic application of Graftjacket, RTM on rotator cuff tears and calcaneal tendon ruptures. There is no other business relationship between Wright Medical and KCI.	Changes have been made to product description where appropriate
Silverman, MD Ron Chief Medical Officer	KCI	ES	Background Paragraph 4 Current: The ideal skin substitute should adhere to the wound bed and provide the physiological and mechanical function of normal skin while not being rejected by the	This paragraph has been modified in the final report. The phrase“ideal skin substitute” has been removed.

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			host. This ideal situation is not likely to be provided by any current skin substitute. However, for chronic wounds a skin substitute should be able to provide a temporary biologic dressing that stimulates the host to regenerate lost tissue and replace the wound with functional skin. Proposed Language: A critical factor in wound healing is to accommodate the needs of the compromised wound environment. Therefore, it is important to have a modality (skin substitute) adhere to the wound bed and provide the physiological and mechanical function necessary to bring the wound to closure while not being rejected by the host. Each product provides different components to aid in bringing the wound to closure. Bioengineered tissues may offer dermal or epidermal cells; however, they typically require multiple applications. Human acellular matrices offer natural components providing structure and function of the native extracellular matrix that it is replacing.4 It is important to note that acellular dermal matrices may be processed by a variety of techniques that may damage the extracellular matrix to a greater or lesser extent, depending on the technique. When the architecture of the matrix is damaged, there is an increased inflammatory response that may lead to resorption of the material. The main structural component of skin is collagen which is highly conserved across species. Therefore, animal-derived products may provide similar benefits. It is important to take into consideration the immunologic response that results from placing xenogenic materials on a human wound, and whether or not the individual xenogenic product has addressed this immunologic issue through its processing technique. Comments: The term “ideal” implies that such a concept exists and	

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			would be appropriate for all wounds. This is inaccurate because every patient and every wound is different; thus, the term ideal does not fit this context. An effective acellular matrix would be one that closely approximates the structure and function of the native extracellular matrix it is replacing. As an example, Graftjacket RTM provides an intact, acellular matrix to the wound. The steps used to process the material are non-damaging, and therefore, Graftjacket RTM can support cellular repopulation and revascularization by host tissue with a minimal inflammation and rejection response.5,6	
Silverman, MD Ron Chief Medical Officer	KCI	ES	Background Paragraph 4 Current: However, for chronic wounds a skin substitute should be able to provide a temporary biologic dressing that stimulates the host to regenerate lost tissue and replace the wound with functional skin. Proposed Language: Skin substitutes in the treatment of burn patients are often used as gold standard for temporary coverage of open burn wounds when there are no available donor sites.7 However, for chronic wounds skin substitutes incorporate into the body and provide various components to the complex healing cascade. Examples include being implanted into the wound bed (single application) such as acellular matrices or being able to provide human cells (requiring multiple applications), such as bioengineered tissue, that stimulates the host to regenerate lost tissue and replace the wound with functional skin. Comments: There seems to be some confusion in the report regarding the use of human derived skin products originating in treatment of burn patients versus an understanding of human derived skin products in the treatment of chronic wounds. Throughout, the report	The term “biological dressing” has been removed from the report. Only products that are indicated for chronic wounds are now included in the report. We have also removed any products that would be considered wound coverings.

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			definitions appear that originated and are pertinent in the treatments of burns (such as the use of human tissue products as a biologic temporary covering) and further (consistently) apply these concepts to the treatment of chronic wounds. This is incorrect. With an acute burn, physicians are often faced with failing organs and/or massive amounts of devitalized tissue. Historically, physicians have relied on using patient donor sites, tissue banks for human donated skin or xenograft (porcine) skin as replacement options. With time and advanced technology methods, physicians now have numerous skin replacement options. Although this is a good situation for patients in need of tissue as a treatment option, the overall picture of the various technology options can be very confusing.8 Naturally occurring tissues consisting of cutaneous allografts, xenografts, and amniotic membranes have been used for many years to provide temporary coverage as biologic dressings in the treatment of burn patients. Of the available naturally occurring materials, cutaneous allograft is considered to be the gold standard for coverage of open burn wounds when there are no available donor sites. It has been hypothesized that the disadvantage of xenografts is that it does not establish vessel to vessel connections. Most xenografts are also rapidly rejected due to a strong xenogenic immunologic response. Consequently, even though xenograft skin is more readily available, it may be less effective as a biologic dressing. The limitations of the naturally occurring biologic dressings have focused attention on the development of skin substitutes consisting entirely of synthetic materials or a combination of synthetic materials and collagen. The ultimate limitation of any tissue product used as a biologic dressing is that it is only temporary. Historically when donor sites are scarce, the resulting	

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			therapeutic void has been filled by using cutaneous tissue as biologic dressings.7 In contrast the needs of a chronic wound can be quite different. There is not usually the critical acute loss of tissue and while infection is a concern to be aware of in chronic wounds, the greater need is to provide components to stimulate, facilitate or modulate healing. This is of course, a complex dynamic process requiring the addition of various components at different stages of the wound healing continuum. If the intent of the report is to categorize the products in two segments, either skin substitute or biologic dressing, it brings attention to the fact that any modality used as a dressing is temporary. A traditional wound covering of any origin is intended to provide a clean and moisture controlled environment to protect the wound from infection and harmful environmental agents, and to facilitate the formation of dermis. In non-burn wound healing circles, a wound covering does not provide human cells or natural human scaffold for cellular or vascular infiltration, is not typically capable of integrating into the host tissue, and further, does not typically require a secondary dressing, as it is indeed covering the wound. A wound covering, by definition, is removed from the wound after its intended length of treatment time and discarded. With the advancement in research and technology, the idea that a traditional wound covering is the best way to treat a chronic wound may not be true for complicated patients. For example, Graftjacket RTM is a dermal tissue graft (not a wound covering) that is incorporated into the host tissue, does require a secondary dressing, is not removed after healing, and does not function as a cover to prevent dehydration and protect the wound from infection or harmful environmental agents. Therefore, it is inaccurate to suggest that an acellular matrix	

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			(eg, Graftjacket RTM) be considered a wound covering. Rather, it is a scaffold that allows the body's own biologic activity to progress through the natural repair process.	
Silverman, MD Ron Chief Medical Officer	KCI	ES	Page ES1: Background Paragraph 5 Current: Skin substitutes can be divided into two broad categories: Biomaterials and cellular. Biomaterial skin substitutes do not contain cells (acellular), and are derived from natural or synthetic sources. Natural sources include human cadaver skin processed to remove the cellular components and retain the structural proteins of the dermis, and collagen obtained from bovine and porcine sources. Synthetic sources include various degradable polymers such as polylactide. Whether natural or synthetic the biomaterial provides an artificial extracellular matrix that allows for infiltration of surround cells. Cellular skin substitutes are distinguished by their origin: xenogeneic (from nonhuman species), autologous (from the patient), and allogenic (from another human). Keratinocytes and fibroblasts obtained from these sources are cultured in vitro to produce the cellular material used to make the substitute. Proposed Language: Skin substitutes can range from various origins and contribute different components to the healing of chronic wounds. Some of the products do not contain cells (acellular) and are derived from natural (human or animal) or synthetic sources. Natural sources include human cadaver skin processed to remove the cellular components and retain the structural proteins of the dermis and collagen simulating normal function or from animal sources, such as bovine and porcine sources. Synthetic sources include various degradable polymers, such as polylactide. Lastly, some skin substitutes may	We agree that dividing skin substitutes into two broad categories is too simplistic and have revised the report to reflect this. The suggestion that the products be divided into two broad categories was suggested by Dieckmann et al. in their review. Dieckmann C, Renner R, Milkova L, et al. Regenerative medicine in dermatology: biomaterials, tissue engineering, stem cells, gene transfer and beyond. Exp Dermatol 2010 Aug;19(8):697-706. PMID: 20545761

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			have a combined source to include human origin with synthetic factors as a supportive mesh structure. Human and animal acellular products attempt to simulate the necessary structure of an extracellular matrix. Addition of the acellular matrix to the wound provides a scaffold for normal cell migration into the wound, providing structural support.4 Providing such a necessary structure is also aligned with the need for only one application. Cellular products, on the other hand, typically contain epidermal and or dermal cells cultured on a synthetic or biologic mesh or lattice.9 Cellular matrices act as delivery vehicles for growth factors and some ECM components to the wound and thus often require multiple applications. Comments: The suggestion that the products be divided into two broad categories is flawed. The products reviewed differ in more than these two categories. Cellular material can be derived from human or animal sources. Cellular material can have additional synthetic materials in its final form. The term biomaterial also does not accurately describe the products. These products (skin substitutes) provide multiple benefits to compromised patients suffering from chronic wounds. We suggest that the products be evaluated on their contributions to the wound healing process and the proven clinical benefits..	

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Silverman, MD Ron Chief Medical Officer	KCI	ES	Page ES2: Background Paragraph 2 Current: Human tissue can be obtained from human donors, processed, and used exactly in the same role, skin for skin, tendon for tendon, bone for bone, etc. These uses are regulated as human tissue intended for transplantation (HCT/P). Proposed Language: Human tissue can be obtained from human donors, processed, and used for the same role, skin for skin, tendon for tendon, bone for bone, etc. As such, human tissue is used in repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues; thus, an HCT/P performs the same basic function or functions in the recipient as in the donor. Comments: FDA defines Homologous use as ?the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. 21 C.F.R. 1271.3(c). Therefore, claims of wound repair and tissue replacement can be permissible claims for skin substitute products regulated as HCT/P's, provided that such claims are supported by valid scientific evidence. For example, acellular human dermis may be used to repair or replace damaged or missing skin in a diabetic foot ulcer.	Per recommendations by the FDA, this section has been revised.

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Silverman, MD Ron Chief Medical Officer	KCI	ES	Page ES2: Background Paragraph 3 Current: Establishments producing products regulated as HCT/Ps are required to register with the FDA and list their HCT/Ps products but they are not required to demonstrate the safety or efficacy of their HCT/Ps products. Proposed Language: HCT/Ps are regulated under section 361 of the Public Health Service Act (PHSA) and 21 CFR Part 1271. HCT/Ps are not subject to premarket regulation by FDA. However, the applicable regulations include requirements for procurement, processing, storage and distribution of human tissue and are intended, among other things, to ensure the safety of U.S. HCT/P's. Manufacturers of HCT/Ps are required to register their establishments, list their products, and are subject to periodic FDA inspection in much the same manner as manufacturers of other medical products.	The FDA has provided input into the Background section of the report regarding HCT/Ps.
Silverman, MD Ron Chief Medical Officer	KCI	ES	Page ES4: Methods of Review Paragraph 2 Current: In addressing questions 2 and 3 the guidance document prepared by FDA In 2006 was used and clinical outcomes was broadly grouped in two categories- 'improved wound healing and improved wound care'. Comments: Web link for reference is inactive. In the reference source provided in the report, the June 2006 FDA guidance document, we found many inconsistencies with the context of many topics within the AHRQ report. Specific inconsistencies include: indication statements, standard of care, definitions of endpoints such as treatment and management, as well as distinction definition of temporary dressing as supported below: 1) The indications for use considerations: the guidance	We agree that generalizing results from one wound type to another is difficult given differences in wound pathophysiology and patient condition. The studies reviewed in this report used a wide variety of control treatments (standard of care and other treatments) that also make generalizations more difficult. Therefore we chose not to generalize any findings beyond the actual wound type and specific wound care product. The term standard of care and usual care are also discussed in the report as these terms also cannot be generalized across wound types We have recorded data on several important wound healing outcomes in our evidence tables. However, we considered complete wound healing the most important patient-oriented outcome in the report.

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			document is consistent with the AHRQ ECRI report, in that because wounds differ in their pathophysiology, is difficult to generalize results obtained from a trial conducted in subjects with one wound type to subjects with another wound type. Therefore, separate clinical trials should be considered for each type of wound indication sought. However, it also maintains that if a scientific rationale and clinical data support clinical activity of a product in more than one wound type, it may be possible for studies performed in one wound type to support another in establishing substantial evidence of efficacy and safety. 2) Standard of care: The agency does not require adherence to any specific guidelines; the basic principle being that standard care regimens in wound treatment product trials should optimize condition for healing and be prospectively defined in the protocol. The rational for the standard of care chosen should be included in the protocol, and the study plan should be sufficient detail for consistent and uniform application across study centers. 3) Efficacy endpoints: a) improved wound healing- Complete wound closure is defined as skin re-epithelialization without draining or dressing requirements confirmed at two consecutive study visits 2 weeks apart. In the simplest case, a treatment effect would be established if a clinically and statistically significant greater proportion of subjects in the treatment group achieved complete wound closure compared to the control arm. Partial wound healing in early phase clinical trials, if prospectively defined, may indicate relevant biological activity and help guide subsequent trial design. An indication of accelerated wound closure should reflect clinically meaningful reduction in time to healing using a time-to-event analysis, the event being complete closure.b) Improved wound care- wound	

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			management may provide important patient benefit without improving the incidence or timing of wound closure relative to standard care. c) Temporary dressings including interactive temporary dressings, are intended to provide support at care until definitive closure can be accomplished. Temporary dressing is expected to function as a barrier, much like human skin.	
Silverman, MD Ron Chief Medical Officer	KCI	Page ES6	Page ES6: Methods of Review Paragraph 2 Current: The most common reasons for exclusion of submitted materials were: ? not commercially available in the U.S. ? narrative reviews ? case studies (fewer than five patients) ? publications that duplicated an already included study Comments: Exclusion of the following does not meet the 4-point criteria listed above. We respectfully request that the following 2 clinical studies be included as evidence to support the use of Graftjacket in chronic wounds. Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics 2004 January 1;27(1 Suppl):s145-s149. Winters CL, Brigido SA, Liden BA, Simmons M, Hartman JF, Wright ML. A multicenter study involving the use of a human acellular dermal regenerative tissue matrix for the treatment of diabetic lower extremity wounds. Adv Skin Wound Care 2008 August 1;21(8):375-81.	The most common reasons for exclusion listed in the final report are: • Study was not a randomized controlled trial. • Product is not commercially available in the United States. • Study was a narrative review. • Publication duplicated an already included study. These are not the full list of criteria. The full list is contained under the section heading Inclusion Criteria which describes the 11 criteria used in this report. Brigido et al. (2004) did not meet the inclusion criteria since “no outcomes of interest were reported because study lasted only 4 weeks.” Winters et al.(2008) was excluded since this study was “not an RCT.”
Silverman, MD Ron Chief Medical Officer	KCI	Page ES7:	Page ES7: Evidence of Skin Substitutes Paragraph 3 Current: Our examination of the information in Table 2 indicates that skin substitute products using human fibroblasts and keratinocytes (derived from neonatal foreskins)	We have removed Epicel from the report since it is not indicated for chronic wounds. Burns were not one of the wound types we were asked to address. This report is not a critique of the FDA 2006 Guidance. The Guidance informed our assessment of risk of bias.

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			receive the FDA product code MGR (dressing, wound and burn, interactive) and use the term ?treatment? in the indications for use on chronic wounds (see Apligraf/Graftskin and Dermagraft). Besides providing a biologic wound covering these products also contain human cells capable of producing human growth factors and cytokines that stimulate angiogenesis, tissue expansion, and re-epithelialization.5 Thus these products have the potential to be interactive with the wound bed and assist in the wound healing process. Epicel, a cultured epidermal autograft obtained from the patient's own keratinocytes, is in a separate FDA product code OCE (cultured epidermal autograft). Proposed Language: Our examination of the information in Table 2 indicates that the terminology is inconsistent with the FDA 2006 Guidance document defining treatment of wounds and management of wounds. As an example, the skin substitute products using human fibroblasts and keratinocytes (derived from neonatal foreskins) receive the FDA product code MGR (dressing, wound and burn, interactive) and use the term 'treatment' in the indications for use on chronic wounds (see Apligraf/Graftskin and Dermagraft). Besides providing a biologic wound covering these products also contain human cells capable of producing human growth factors and cytokines that stimulate angiogenesis, tissue expansion, and re-epithelialization. Thus these products have the potential to be interactive with the wound bed and assist in the wound healing process. Epicel, a cultured epidermal autograft obtained from the patient's own keratinocytes, is in a separate FDA product code OCE (cultured epidermal autograft). Comments: There is inconsistency with the terminology throughout the document. In this Table, the terminology used is	For this report it was not within our purview to create a formal definition for a skin substitute product or dressing. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. We used the products listed under CMS HCPCS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those 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. We do not believe that the statement "products have the potential to be interactive" is stating a conclusion.

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			from the FDA product descriptors, treatment of wound vs. management of wounds yet within the FDA 2006 Guidance document the terminology differs. 1) Based on the FDA 2006 Guidance; Efficacy endpoints: a) improved wound healing- Complete wound closure is defined as skin re-epithelialization without draining or dressing requirements confirmed at two consecutive study visits 2 weeks apart. In the simplest case, a treatment effect would be established if a clinically and statistically significant greater proportion of subjects in the treatment group achieved complete wound closure compared to the control arm. Partial wound healing in early phase clinical trials, if prospectively defined, may indicate relevant biological activity and help guide subsequent trial design. An indication of accelerated wound closure should reflect clinically meaningful reduction in time to healing using a time to- event analysis, the event being complete closure. b) Improved wound care- wound management may provide important patient benefit without improving the incidence or timing of wound closure relative to standard care. We respectfully request that the following statement be removed. Thus these products have the potential to be interactive with the wound bed and assist in the wound healing process. This statement draws a conclusion. If conclusion is drawn for this class of products, then it should be drawn for all classes listed. Additionally, we point out the challenges facing this report in attempting to segment products into distinct categories because as stated in the paragraph above, Epicel is in a separate FDA product code which again demonstrates inability to segment products into simplistic categories rather than the function, which they provide a chronic wound as proven by the clinical studies.	

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Silverman, MD Ron Chief Medical Officer	KCI	Page ES8	Page ES8: Paragraph 1 Current: We did identify one exception to the above classification scheme for Class II devices. EndoForm Dermal Template derived from ovine forestomach, and included in FDA product code KGN, is an exception to the use of the term 'management' of wounds and instead uses the term 'treatment' in the indications for use (see Table 8). The wording of the indications for use of EndoForm is almost identical to the wording used for Integra, MatriStem, Oasis, Primatrix, and Hyalomatrix PA but 'treatment' is substituted for 'management.' The reason for this difference is unclear. Proposed Language: New paragraph Another exception to the rule includes HCT/P's. The FDA defines Homologous use as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. 21 C.F.R. 1271.3(c). Therefore, acellular derived products can be utilized in wound repair or tissue replacement, provided that these claims can be supported by valid scientific evidence. Comments: To be regulated solely under section 361 of the PHSA and 21 C.F.R. Part 1271, the HCT/P must meet the following criteria: (1) it is minimally manipulated; (2) it is intended for homologous use;, (3) it is not combined with another article; and (4) it does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function. FDA defines Homologous use as ?the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. 21	Our statement about EndoForm is only in the context of Class II devices. The differences between HCT/Ps and Class II devices are described elsewhere in the report.

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			C.F.R. 1271.3(c). Therefore, claims of wound "repair" and tissue "replacement" can be permissible claims for skin substitute products regulated as HCT/P?s, provided that such claims are supported by valid scientific evidence.	
Silverman, MD Ron Chief Medical Officer	KCI	Page ES8: Table 1	Page ES8: Table 1 Current Product: Graftjacket Manufacturer: Wright Medical Technology Correction: Product: Graftjacket Manufacturer: LifeCell Corporation, licensed to Wright Medical and licensed to KCI	This change has been made in the document.
Silverman, MD Ron Chief Medical Officer	KCI	Page ES14:	Page ES14: Evidence for Skin Substitutes, Key Question 2, Paragraph 3 Current: Of the 14 RCTs all but one was considered to have a high risk of bias primarily because the studies did not report whether the wound assessor was blinded to patient treatment. Proposed Language: Of the 14 RCTs all but one was considered to have a high risk of bias primarily because the studies did not report whether the wound assessor was blinded to patient treatment. However, it is difficult to blind the investigator to skin substitutes due to the nature of the matrix. Bias can be limited, though, by sound protocol design and procedures other than blinding. RCTs without blinding are referred to as "unblinded".10 Wood et al concluded that the results of unblinded RCTs tended to be biased toward beneficial effects only if the RCTs' outcomes were subjective as opposed to objective.10 In addition, randomization is often used to mitigate the potential for bias. Comments: Per the 2006 FDA Guidance document " in general, blinding of subjects and investigators to the assigned	After reviewing several comments and giving further thought to this issue, we recognized that assessor blinding is not critical for determining the outcome of complete wound healing. While we consider assessor blinding a method for reducing potential for bias, we realized that it should not be given so much weight in this assessment given our focus on complete wound healing. We also decided that a "No" or "not reported" answer to the question "Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?" was the most critical for considering a study to be at high risk-of-bias. These modifications to the assessment tool have resulted in all included studies being considered at low or moderate potential for bias, except for a single study that was considered to have an unclear risk of bias due to poor reporting of methods.

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			treatment reduces bias and should be employed when feasible. Often the standard of care only arm cannot be blinded. In other cases, especially for trials of some medical devices, it is impractical or unethical to implement a control treatment that mimics the test product for the purposes of blinding. Due to the nature of this matrix (ie, Graftjacket? RTM) it would be impossible to blind the evaluator or investigator. A sham matrix would never be placed into the wound. The very presence of the matrix cannot be hidden. Although blinding is acceptable for trials with placebo pills or injections of saline, blinding is not feasible in any Graftjacket RTM studies. Graftjacket RTM is an implantable human acellular matrix that is used for the repair or replacement of damaged or inadequate integumental tissue. As such, a sham matrix into the wound would not be the appropriate control for this study because: 1) a human matrix control for Graftjacket? RTM does not exist and 2) the study compares GJ to standard of care to measure effectiveness of the matrix. This was a single site study where blinding of staff would be technically difficult since the number of clinical care individuals involved in a study are normally limited. Again, the presence of Graftjacket? RTM on subjects wound would be visibly obvious to all staff associated with the study. Bias can be limited by sound protocol design and procedures other than blinding. RCTs without blinding are referred to as "unblinded".10 Wood et al concluded that the results of unblinded RCTs tended to be biased toward beneficial effects only if the RCTs' outcomes were subjective as opposed to objective.10 Reyzelman et al had clearly defined endpoints, complete healing (100% re-epithelialization without drainage) and mean time to healing. Therefore, the outcomes were clearly objective and suggestive of non-bias. In addition, randomization is often used to mitigate the potential for	

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			bias. Proper protocol design normally follows guidelines suggested by the publication, CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomized trials.11 Although Reyzelman et al do not state exactly how they randomized subjects, they did incorporate and execute randomization in their study.	
Silverman, MD Ron Chief Medical Officer	KCI	Page ES14:	Page ES14: Evidence for Skin Substitutes, Key Question 2, Paragraph 3 Current: The patients examined in these studies were of generally good health and under good glycemic control. Proposed Language: The patients examined in these studies were of generally good health and under good glycemic control as required by the inclusion and exclusion criteria. Comments: Per Medicare's definition, a chronic wound is one that has been present for 30 days. Chronic wound patients typically have one or more co-morbid conditions (diabetes, smoker, poor glycemic control, obesity, etc) that inhibit wound healing. These co-morbid conditions should be addressed as part of a good wound healing treatment plan. When conducting RCTs, most inclusion/exclusion criteria will insist that before randomization can occur, each patient is screened for specific co-morbid conditions to reduce unknown causality of results and to fair comparison between study and control groups. While RCTs are the highest form of evidence, in many cases, this patient population does not mimic real world conditions.	We agree with the reviewer's comments about RCTs and real world conditions and have commented on this is the report. The paragraph mentioned by the reviewer has been modified for other reasons and we did not use the reviewer's proposed language. Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Introduction/ Background	Page 1& 2: Background, Chronic Wounds, Paragraph 2 Current: These wounds usually do not close without interventions, and are sometimes resistant to healing interventions. Diabetic foot ulcers, pressure ulcers or bed sores, vascular ulcers, and complications of surgically created sternal wounds commonly become chronic wounds because their etiologies impede healing and they persist without proper medical care. For the purposes of this review, we consider chronic wounds to be those wounds present for more than 30 days. Proposed Language: These wounds usually do not close without interventions, and are sometimes resistant to healing interventions. Diabetic foot ulcers, pressure ulcers or bed sores, vascular ulcers, and complications of surgically created sternal wounds commonly become chronic wounds because their etiologies impede healing and they persist without proper medical care. Furthermore, patient comorbidities, such as COPD, diabetes, obesity, poor vascularization, smoking, etc, often prevent wounds from healing14, 15 and should be considered when selecting therapy options. For the purposes of this review, we consider chronic wounds to be those wounds present for more than 30 days. Comments: The statement above implies that wounds do not heal due to their etiology and persist without proper medical care. Most wounds are often difficult to heal because of the multiple co-morbidities, such as COPD, diabetes, obesity, poor vascularization etc, that plague many chronic wound care patients. The additional burden of a patient's condition, beyond the etiology, increases the duration of the healing process, which supports the need for advanced technologies.	We have added text elsewhere in the report to reflect the influence of comorbidities on wound healing. We did not change this paragraph as proposed by the reviewer.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Page 2	Page 2: Diabetic Foot Ulcers, Paragraph 3 Current: The management of diabetic foot ulcers requires appropriate therapeutic footwear, a wound dressing that provides a moist environment, debridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present, and evaluation and correction of peripheral arterial insufficiency. Proposed Language: The management of diabetic foot ulcers requires a wound dressing that provides a moist wound environment, debridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present, evaluation and correction of peripheral arterial insufficiency and off loading (eg, therapeutic footwear) to reduce repetitive related damage to the foot. Comments: The use of a wound dressing providing a moist wound environment is a broad statement. In this context, there are many published peer reviewed articles identifying these types of dressings from moistened gauze, hydrocolloids, hydrogels, NPWT and skin substitutes. This statement references a dressing that provides a moist wound environment? yet in other terminology, the committee references documents by FDA identifying advanced skin substitutes as dressings by FDA codes of MGR,KGN, FRO, MGP. Reporting such variance in definitions of dressings validates the inconsistencies and to broad segmentation of products within the document.	We did not change this paragraph. We acknowledge that this is a broad statement, but the purpose of this document is not to propose any specific method of treatment.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Page 4	Page 4: Venous Leg Ulcers Paragraph 3 Current: A systematic review from 2009 examined the evidence for compression treatment of venous leg ulcers. According to the authors venous ulcers heal more rapidly with compression than without and multi-component systems achieve better healing outcomes than single-component compression. Proposed Reference for Statement: A systematic review from 2009 examined the evidence for compression treatment of venous leg ulcers. According to the authors venous ulcers heal more rapidly with compression than without and multi-component systems achieve better healing outcomes than single-component compression.16 Comments: A reference is needed for this statement so we have included the following reference: O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. Cochrane Database Syst Rev 2009 January 21;(1):CD000265.	We discussed the O'Meara review in the report. The following sentences were added to the general description of care for venous leg ulcers: "A systematic review from 2009 examined the evidence for compression treatment of venous leg ulcers. According to the authors, venous ulcers heal more rapidly with compression than without and multi-component systems achieve better healing outcomes than single-component compression."
Silverman, MD Ron Chief Medical Officer	KCI	Page 5	Page 5: Skin Substitutes Paragraph 2 Current: The ideal skin substitute should adhere to the wound bed and provide the physiological and mechanical function of normal skin while not being rejected by the host. This ideal situation is not likely to be provided by any current skin substitute. However, for chronic wounds, a skin substitute should be able to provide a temporary biologic dressing that stimulates the host to regenerate lost tissue and replace the wound with functional skin. A skin substitute may stimulate regrowth by maintaining a moist wound environment, by providing structural support of cell invasion and tissue regeneration, and by providing tissue growth factors. Proposed Language:	The paragraph mentioning an "ideal" skin substitute has been rewritten. The term "ideal skin substitute" has been removed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			A critical factor in wound healing is to accommodate the needs of the compromised wound environment. Therefore, it is important to have a modality (skin substitute) adhere to the wound bed and provide the physiological and mechanical function necessary to bring the wound to closure while not being rejected by the host. Each product provides a different component to aid in bringing the wound to closure. Bioengineered tissues may offer dermal or epidermal cells; however, they typically require multiple applications. Human acellular matrices offer natural biological components that provide like structure and function of the native extracellular matrix that is being replaced.4 Comments: An effective acellular matrix would be one that closely approximates the structure and function of the native extracellular matrix it is replacing.4 As an example, Graftjacket? RTM provides an intact, acellular matrix to the wound. The steps used to process the material are non-damaging, and therefore, Graftjacket? RTM can support cellular repopulation and revascularization by host tissue with a minimal inflammation and rejection response.5, 6	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Page 5	Page 5: Skin Substitutes Paragraph 3 Current: Skin substitutes can be divided into two broad categories: biomaterials and cellular. Biomaterial skin substitutes do not contain cells (acellular) and are derived from natural or synthetic sources. Proposed Language: Skin substitutes can range from various origins and contribute different components to the healing of chronic wounds. Some of the products do not contain cells (acellular) and are derived from natural (human or animal) or synthetic sources. Natural sources include human cadaver skin processed to remove the cellular components and retain the structural proteins of the dermis, and collagen simulating normal function or from animal sources, such as bovine and porcine sources. Synthetic sources include various degradable polymers such as polylactide. Lastly, some skin substitutes may have a combined source to include human origin with synthetic factors as supportive mesh structure.Human and animal acellular products attempt to simulate the necessary structure of an extracellular matrix. Addition of the acellular matrix to the wound provides a scaffold for normal cell migration into the wound, providing structural support and sites for binding of growth factors.4 Providing such a necessary structure is also aligned with the need for only one application. Cellular products, on the other hand, typically contain epidermal and or dermal cells cultured on a synthetic or biologic mesh or lattice.9 Cellular matrices act as delivery vehicles for growth factors and some ECM components to the wound.	This paragraph has been modified in response to the comments from several reviewers. The report now contains the following paragraph: "Dieckmann et al. have suggested that skin substitutes can be divided into two broad categories: biomaterial and cellular. Biomaterial skin substitutes do not contain cells (acellular) and are derived from natural or synthetic sources. Natural sources include human cadaveric skin processed to remove the cellular components and retain the structural proteins of the dermis and collagen matrix obtained from bovine and porcine sources. Synthetic sources include degradable polymers such as polylactide and polyglycolide. Whether natural or synthetic, the biomaterial provides an extracellular matrix that allows for infiltration of surrounding cells. Cellular skin substitutes are distinguished by their origin: xenogeneic (from nonhuman species), autologous (from the patient), and allogenic (from another human). Keratinocytes and fibroblasts obtained from these sources are cultured in vitro to produce the cellular material used to make the substitute. However, the classification of skin substitutes into either biomaterial or cellular is not completely accurate since the two are combined into several wound care products (see Table 7)."
Silverman, MD Ron Chief Medical Officer	KCI	Page 9	Page 9: Human cells, tissues, and cellular and tissue-based products Paragraph 1 Current: HCT/P establishments are not required to demonstrate	The FDA reviewer has provided input that has been used to address HCT/P products and their regulatory pathways.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			the safety or efficacy of their products and the FDA does not evaluate the safety or efficacy of these products. Proposed Language: HCT/P?s are regulated under section 361 of the Public Health Service Act (PHSA) and 21 CFR Part 1271. HCT/Ps are not subject to premarket regulation by FDA. However, the applicable regulations include requirements for procurement, processing, storage and distribution of human tissue and are intended, among other things, to ensure the safety of U.S. HCT/P?s. Manufacturers of HCT/Ps are required to register their establishments, list their products, and are subject to periodic FDA inspection in much the same manner as manufacturers of other medical products. Further, manufacturers are required to report adverse events involving the possible transmission of infectious diseases to the FDA. Comments: The statement “HCT/P establishments are not required to demonstrate the safety or efficacy of their products and the FDA does not evaluate the safety or efficacy of these products” is inaccurate. HCT/P’s are regulated under section 361 of the Public Health Service Act (PHSA) and 21 CFR Part 1271. These regulations include requirements for procurement, processing, storage and distribution of human tissue and are intended, among other things, to ensure the safety of U.S. HCT/P?s. Manufacturers of HCT/Ps are required to register their establishments and list their products in much the same manner as manufacturers of other medical products. Further, manufacturers are required to report adverse events involving the possible transmission of infectious diseases to the FDA.	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Methods	Page 15: Study Design #4 Current: Studies must be randomized controlled trials (RCT). Comments: This HTA only included RCT evidence. Evidence of effectiveness for wound care products and services is not limited to clinical research. It can be established through a combination of scientific evidence, expert knowledge and patient preference. This approach is consistent with the widely-accepted definition of evidence-based medicine (EBM): ". . . integration of best research evidence with clinical expertise and patient values." The EBM approach is particularly important in chronic wound care.12, 13	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be "skin substitutes" and the regulatory pathways they may take. The second reason for the report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.
Silverman, MD Ron Chief Medical Officer	KCI	Methods	Page 16 Search Strategy Search Strategy appears to be accurate.	We thank the reviewer for his/her comment.
Silverman, MD Ron Chief Medical Officer	KCI	Methods	Page 20: **Strength of Evidence Base** Comments: The report states "An evidence base consisting of studies with a high risk of bias implies a low strength of evidence." While we agree that all products should be evaluated by a non-bias means, what remains is almost always that physicians and hospitals lack capital and tangible resources to conduct such studies without industry assistance. Companies, such as KCI, are committed to the innovation and production of medical products for wound healing but are also required by federal and international laws to evaluate these products for safety and where appropriate per regulation for efficacy. This medical evidence is generated from clinicians experienced with treatment of chronic wounds and often funded by industry partners such as KCI. While only 14 RCTs were considered in this review, we recommend that the evaluation consider additional	The grading of the strength of evidence in this report follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23. Grading the strength of evidence is a judgment about all studies for a given population, intervention, comparison and outcome, considering the risk of bias within individual studies, the consistency of findings across studies, the precision and magnitude of the effect, and the directness of the evidence for the question at hand. We have added tables to the report to add clarity to the presentation of results and strength of evidence. Brigido et al. (2004) did not meet the inclusion criteria since "no outcomes of interest were reported because study lasted only 4 weeks."

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			evidence that shows a more real-world use of skin substitutes. RCTs are as stated, controlled studies bringing the best possible patients who have the wound to be studied to the studies as defined by the inclusion and exclusion criteria in the study protocol. However, the AHRQ has recommended that other studies, such as registries, can be considered because they evaluate outcomes ranging from the natural history of disease, to the safety of drugs or devices, and to real-world effectiveness of therapies.17 Evidence of effectiveness for wound care products and services is not limited to clinical research. It can be established through a combination of scientific evidence, expert knowledge and patient preference. This approach is consistent with the widely-accepted definition of evidence-based medicine (EBM): ". . . integration of best research evidence with clinical expertise and patient values." The EBM approach is particularly important in chronic wound care.12, 13 Therefore, we respectfully request that the **following two studies be included** within your review to support the use of Graftjacket?for chronic wounds. **Brigido** SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics 2004 January 1;27(1 Suppl):s145-s149. **Winters** CL, Brigido SA, Liden BA, Simmons M, Hartman JF, Wright ML. A multicenter study involving the use of a human acellular dermal regenerative tissue matrix for the treatment of diabetic lower extremity wounds. Adv Skin Wound Care 2008 August 1;21(8):375-81.	Winters et al.(2008) was excluded since this study was "not an RCT."
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 1	Page 22 Results Paragraph 2 "We did identify one exception to the above classification scheme for Class II devices. EndoForm Dermal Template derived from ovine forestomach, and included in FDA product code KGN, is an exception to	Our statement about EndoForm is only in the context of Class II devices. The differences between HCT/Ps and Class II devices are described elsewhere in the report.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			the use of the term “management” of wounds and instead uses the term “treatment” in the indications for use (see Table 8). The wording of the indications for use of EndoForm is almost identical to the wording used for Integra, MatriStem, Oasis, Primatrix, and Hyalomatrix PA but “treatment” is substituted for “management.” The reason for this difference is unclear. Proposed Language: New paragraph Another exception to the rule includes HCT/P‘s. The FDA defines Homologous use as “the repair, reconstruction, replacement, or supplementation of a recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.? 21 C.F.R. 1271.3(c). Therefore, acellular derived products can be utilized in wound repair or tissue replacement provided that these claims can be supported by valid scientific evidence. Comments: To be regulated solely under section 361 of the PHSA and 21 C.F.R. Part 1271, the HCT/P must meet the following criteria: (1) it is minimally manipulated; (2) it is intended for homologous use; (3) it is not combined with another article; and (4) it does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function. FDA defines Homologous use as “the repair, reconstruction, replacement, or supplementation of a recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.” 21 C.F.R. 1271.3(c). Therefore, claims of wound “repair” and tissue “replacement” can be permissible claims for skin substitute products regulated as HCT/P?s provided that such claims are supported by valid scientific evidence.	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 1	Page 22-23: Human Derived Products Regulated as HCT/P, Graftjacket (Wright Medical Technology, licensed to KCI Medical) Current: Graftjacket (Wright Medical Technology, licensed to KCI Medical) Graftjacket RTM is a processed human dermal membrane designed to provide a framework for wound repair. Donated human tissue is treated to remove the epidermis and cellular components but retain collagen, elastin, and proteoglycans. The internal matrix of the dermis remains intact. The tissue is then cryogenically preserved. The company states that removal of the cellular component reduces rejection, the retention of dermal proteins allows for revascularization and cellular repopulation, and the preserved tissue matrix reduces inflammation. Wright Medical Technology, Inc. (Arlington, TN, U.S.A.) is registered with the FDA as an establishment producing HCT/Ps. Proposed Language: Graftjacket (LifeCell Corporation) Graftjacket RTM is an intact acellular matrix from donor human cadaver tissue that provides a scaffold for the body's repair or replacement of damaged or inadequate integumental tissue, such a diabetic foot ulcers, or for other homologous uses of human integument. Donated human tissue is treated to remove the epidermis and cellular components but retain collagen, elastin, and proteoglycans. The internal matrix of the dermis remains intact. The tissue is then cryogenically preserved. The company states that removal of the cellular component reduces rejection, the retention of dermal proteins allows for revascularization and cellular repopulation, and animal studies show that the preserved tissue matrix reduces the inflammatory response. LifeCell (Branchburg, NJ, U.S.A.) is registered with the FDA as	We have revised the section covering Graftjacket. We created groupings specific for this report only to address the goals of this report. The primary purpose of this report was to examine the regulatory pathways required for a broad range of wound care products that are commonly referred to as "skin substitutes." 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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			an establishment producing HCT/Ps. The Graftjacket?name and use in chronic wounds is licensed to KCI and Wright Medical Technology for a different application within the medical field. Comments: Please note that the report is based on 4 groups. We suggest they be grouped according to FDA established broad categories of Biomaterials and Cellular Products.	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 2	Page 44: Quality of Evidence, Graftjacket?Paragraph 4 Current: Graftjacket Both studies were at a high risk for bias because wound assessor blinding was not reported. Neither study reported information on randomization method or concealment of treatment allocation. Many other questions could also not be addressed with the information presented in the publications (see Table 21). Comments: Bias can be limited by sound protocol design and procedures other than blinding. RCTs without blinding are referred to as "unblinded".10 Wood et al concluded that the results of unblinded RCTs tended to be biased toward beneficial effects only if the RCTs' outcomes were subjective as opposed to objective.10 Reyzelman et al had clearly defined endpoints, complete healing (100% re-epithelialization without drainage) and mean time to healing. Therefore, the outcomes were clearly objective and suggestive of non-bias. In addition, randomization is often used to mitigate the potential for bias. Proper protocol design normally follows guidelines suggested by the publication, ?CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomized trials?.11 Although Reyzelman et al do not state exactly how they randomized subjects, they did incorporate and execute randomization in their study.	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 2	Page 47 Efficacy of Skin Substitutes Current: Graftjacket is processed human dermal membrane used as a skin substitute. Proposed Language: Graftjacket is processed human dermal matrix used as a skin substitute. Comments: The term “membrane” as defined in Stedmans Medical Dictionary includes “a thin sheet or layer of pliable tissue, serving as a covering” which would seem to be appropriate. However, the manufacturer does not claim Graftjacket? RTM as a “membrane”, but rather refers to it as a “matrix”. Therefore, the word “membrane” should be changed to “matrix” to be consistent with the Manufacturer’s trade name for the product, and how the manufacturer describes the product in its labeling.	This change has been made to the document.
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 2	Page 44: Section-Quality of the Evidence Base Current: “Twelve of the studies were funded by the manufacturer and two studies did not report funding? Comments: Often, clinical research studies are expensive and can provide a burden on government funded institutions. However, manufacturers serve both as inventors and marketers of these products. Industry investments in clinical studies are necessary to confirm that that products designed are safe and effective for the consumer and often act to generate evidence required by the FDA to market these products.	We have removed the question regarding funding from our risk of bias assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 2	Page 46: Section-Efficacy of Skin Substitutes Comments This HTA only included RCT evidence. Evidence of effectiveness for wound care products and services is not limited to clinical research. It can be established through a combination of scientific evidence, expert knowledge and patient preference. This approach is consistent with the widely-accepted definition of evidence-based medicine (EBM): ". . . integration of best research evidence with clinical expertise and patient values." The EBM approach is particularly important in chronic wound care.12, 13	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be “skin substitutes” and the regulatory pathways they may take. The second reason for the report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 2	Page 48: Strength of Evidence Paragraph 1 Current: Also mentioned above was the narrow eligibility criteria that eliminated patients in poor health. Commonly mentioned reasons for exclusion included the following: infected wounds; use of medications that could impede wound healing; clinically significant medical conditions that could impair wound healing; renal, hepatic, neurologic, or immunologic diseases; significant peripheral vascular disease; malnutrition and uncontrolled diabetes. This restricts the available evidence to a generally healthy patient group. Comments: This HTA only included RCT evidence. Evidence of effectiveness for wound care products and services is not limited to clinical research. It can be established through a combination of scientific evidence, expert knowledge and patient preference. This approach is consistent with the widely-accepted definition of evidence-based medicine (EBM): ". . . integration of best research evidence with clinical expertise and patient values." The EBM approach is particularly important in chronic wound care.12, 13 Chronic wound patients typically have one or more co-morbid conditions (diabetes, smoker, poor glycemic control, obesity, etc) that inhibit wound healing. These co-morbid conditions should be addressed as part of a good wound healing treatment plan. When conducting RCTs, most inclusion/exclusion criteria will insist that before randomization can occur, each patient is screened for specific co-morbid conditions to allow for good wound healing. While RCTs are the highest form of evidence, in many cases this patient population does not mimic real world conditions.	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies. . We do not disagree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 2	Page 48: Strength of Evidence Paragraph 1 Current Publication bias, the failure to publish studies that do not support the efficacy of a new product, may be a possible explanation for the absence of published pressure ulcer studies. Studies may have been conducted but because of poor results compared to usual care, like the Payne et al. study, the study may have been terminated and the results never published. Comments: This HTA only included RCT evidence. Evidence of effectiveness for wound care products and services is not limited to clinical research. It can be established through a combination of scientific evidence, expert knowledge and patient preference. This approach is consistent with the widely-accepted definition of evidence-based medicine (EBM): ". . . integration of best research evidence with clinical expertise and patient values." The EBM approach is particularly important in chronic wound care.12, 13	We agree that publication bias could be the explanation for absence of relevant RCTs for the treatment of pressure ulcers. We examined ClinicalTrials.gov for completed but unpublished trials, but did not identify any, nor did we identify any ongoing trials involving patients with pressure ulcers.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Resutls: Key Question 2	Page 49: Strength of Evidence Paragraph 2 Current: Taking all these issue of applicability into consideration, overall applicability of the evidence base is limited to a small number of skin substitutes used to treat diabetic foot ulcers and venous leg ulcers, and to patients in generally good health. Comments: This HTA only included RCT evidence. Evidence of effectiveness for wound care products and services is not limited to clinical research. It can be established through a combination of scientific evidence, expert knowledge and patient preference. This approach is consistent with the widely-accepted definition of evidence-based medicine (EBM): ". . . integration of best research evidence with clinical expertise and patient values." The EBM approach is particularly important in chronic wound care.12, 13 For example, registries are alternative studies that are organized to collect real-world data for scientific, clinical and policy purposes. Registries are valuable complements to RCTs since registries do not have the restrictive inclusion and exclusion of RCTs as well as do not prohibit the clinician specific treatments.17 In some instances, registries provide sufficient evidence where RCTs are not able to conducted (ie, open-abdomen or cardiac surgery).	Our report found that very few of the “skin substitute” products have been examined through RCTs. Our statement is still correct that the evidence base collected for this report has limited applicability. We do not disagree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Table 2. Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Discussion/ Conclusion	Page 50: Only generally healthy patients were enrolled in studies and patients with infected wounds, who used medications that could impede wound healing, had clinically significant medical conditions, significant peripheral vascular disease, malnutrition, and uncontrolled diabetes were excluded. Comments: Per Medicare?s definition, a chronic wound is one that has been present for 30 days. Chronic wound patients typically have one or more co-morbid conditions (diabetes, smoker, poor glycemic control, obesity, etc) that inhibit wound healing. These co-morbid conditions should be addressed as part of a good wound healing treatment plan. When conducting RCTs, most inclusion/exclusion criteria will insist that before randomization can occur, each patient is screened for specific co-morbid conditions to allow for good wound healing. While RCTs are the highest form of evidence, in many cases this patient population does not mimic real world conditions.	Applicability of evidence is limited when patients similar to those seen in practice (who are appropriate candidates for the intervention) are excluded from clinical studies. The paragraph mentioned by the reviewer has been modified.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Discussion Conclusion	Page 51: While these results are consistent (all studies reported a better healing rate when treated with a skin substitute) and suggest that skin substitutes could be used in the treatment of diabetic foot ulcers and venous leg ulcers, the comparisons were made to relatively simple usual care approaches such as saline-moistened gauze. Only four of the studies used a more advanced wound dressing product. Comparisons with other advanced wound care products in terms of efficacy and cost are needed to determine where and when skin substitutes should be used. Comments: In the evolution of wound care technologies, we caution use of any wound treatment other than advanced moist wound healing products when evaluating the control group in the RCTs.	Key Question 2 has been clarified as follows: "For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures:…"

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Discussion/ Conclusion	Page 50: Current: "Applicability of the evidence base to address important questions about the efficacy of skin substitutes for the treatment of chronic wounds was limited. Very few of the skin substitute products identified in this report have been examined in RCTs. Only generally healthy patients were enrolled in studies and patients with infected wounds, who used medications that could impede wound healing, had clinically significant medical conditions, significant peripheral vascular disease, malnutrition, and uncontrolled diabetes were excluded. Comparisons with other alternatives to usual wound care were also lacking. Overall applicability of the evidence base is limited to a small number of skin substitutes examining diabetic foot ulcers and venous leg ulcers and to patients in generally good health." Comments: Based on FDA requirements, not all products required an RCT to be permitted to be on the market. However, manufacturers or distributors whose products, such as Graftjacket, are not required to have an RCT actually have invested resources to fund RCTs, which demonstrates the manufacturer's due diligence.	No response needed.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Executive Summary Tables	Current Table 1 and Table 6: Graftjacket'is described as "Processed human dermal **membrane**" and **Wright medical as manufacturer.** Proposed Language: Graftjacket'is described as "Processed human dermal **matrix**" and **LifeCell (a KCI company) as manufacturer**. Comments: Regarding use of the term membrane: The term "membrane" as defined in Stedman's Medical Dictionary includes "a thin sheet or layer of pliable tissue, serving as a covering" which would seem to be appropriate. However, the manufacturer does not claim Graftjacket RTM as a "membrane" but rather refers to it as a "matrix". Therefore, the word "membrane" should be changed to "matrix" to be consistent with the manufacturer's trade name for the product, and how the manufacturer describes the product in its labeling. Regarding listing Wright Medical as the manufacturer of Graftjacket RTM: KCI is the exclusive distributor for Graftjacket RTM and Graftjacket Xpress in the wound care field pursuant to a distribution agreement with LifeCell Corporation, and a trademark licensing agreement (for the trade name ?Graftjacket) with Wright Medical Technologies. The attached FDA establishment registration for Graftjacket tissue listing KCI USA, Inc. as the responsible company for storage and distribution of Graftjacket confirms this fact. LifeCell Corporation in Branchburg, NJ continues to be responsible for manufacturing of Graftjacket RTM as evidenced by the attached LifeCell FDA establishment registration.	This change has been made to the document.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Silverman, MD Ron Chief Medical Officer	KCI	Executive Summary Tables	Table 1 and Table 6: This question identifies Alloderm as “Acellular human dermis product” and Graftjacket as “Processed human dermal membrane” Comments: Regarding use of the term membrane: The term “membrane” as defined in Stedman’s Medical Dictionary includes “a thin sheet or layer of pliable tissue, serving as a covering? which would seem to be appropriate. However, the manufacturer does not claim Graftjacket Regenerative Tissue Matrix as a “membrane” but rather refers to it as a “matrix”. Therefore, the word “membrane” should be changed to “matrix” to be consistent with the manufacturer’s trade name for the product, and how the manufacturer describes the product in its labeling.	Revisions to the description of Graftjacket as “processed human dermal matrix” have been made.
Silverman, MD Ron Chief Medical Officer	KCI	References	Page 52 Current: Footnote 9: “Center for Biologics Evaluation and Research (CBER). Guidance for industry: chronic cutaneous ulcer and burn wounds developing products for treatment. Rockville (MD): U.S. Food and Drug Administration, Center for Drug Evaluation and Research; 2006 Jun. 22 p. Also available: http://www.fda.gov/cder/guidance/index.htm#clinical%20medicine.? Comment: **The link is broken.**	The link to this document has been fixed
Silverman, MD Ron Chief Medical Officer	KCI	General	The following fifteen references have been used to support our comments. (1) Derwin KA, Baker AR, Spragg RK, Leigh DR, Iannotti JP. Commercial extracellular matrix scaffolds for rotator cuff tendon repair. Biomechanical, biochemical, and cellular properties. J Bone Joint Surg Am 2006 December 1;88(12):2665-72. (2) Reyzelman A, Crews RT, Moore JC et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised,	No response needed

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			multicentre study. Int Wound J 2009 June 1;6(3):196-208. (3) Werdin F, Tennenhaus M, Schaller HE, Rennekampff HO. Evidence-based management strategies for treatment of chronic wounds. Eplasty 2009 June 4;9:e19. (4) Harding K, Kirsner R, Lee D, Mulder G, Serena T. International Consensus: Acellular matrices for the treatment of wounds. Wounds Int 2010 January 1;1-13. (5) Xu H, Wan H, Sandor M et al. Host response to human acellular dermal matrix transplantation in a primate model of abdominal wall repair. Tissue Eng Part A 2008 December 1;14(12):2009-19. (6) Sandor M, Xu H, Connor J et al. Host response to implanted porcine-derived biologic materials in a primate model of abdominal wall repair. Tissue Eng Part A 2008 December 1;14(12):2021-31. (7) Pruitt BA, Jr. The evolutionary development of biologic dressings and skin substitutes. J Burn Care Rehabil 1997 January 1;18(1 Pt 2):S2-S5. (8) Luterman A, Kraft E, Bookless S. Biologic dressings: an appraisal of current practices. J Burn Care Res 1980 September 1;1(1):18-22. (9) Clark RA, Ghosh K, Tonnesen MG. Tissue engineering for cutaneous wounds. J Invest Dermatol 2007 May 1;127(5):1018-29. (10) Wood L, Egger M, Gluud LL et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. Br Med J 2008 March 15;336(7644):601-5. (11) Moher D, Hopewell S, Schulz KF et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Br Med J 2008 March 23;340:c869. (12) Sackett DL, Rosenberg WM, Gray JA, Haynes RB,	

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996 January 13;312(7023):71-2. (13) Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-Based Medicine: How to Practice and Teach EBM. 2nd ed. Philadelphia, PA: Churchill Livingstone; 2000. (14) Abbas SM, Hill AG. Smoking is a major risk factor for wound dehiscence after midline abdominal incision; case-control study. ANZ J Surg 2009 April 1;79(4):247-50. (15) Riou JP, Cohen JR, Johnson H, Jr. Factors influencing wound dehiscence. Am J Surg 1992 March 1;163(3):324-30.	
Thomas, MA, MHSA, Sajini President	Global Integrated Reimbursement Services Inc. (GIRS)	General	Comments by GIRS to the Draft AHRQ Technology Assessment entitled Skin Substitutes for Treating Chronic Wounds, dated 12/22/2011) Thanks for the opportunity to comment, our specific comments are below. As we are experiencing difficulty submitting the comments online, please use this version of you get multiple versions of this comment.	We thank the reviewer for these comments.
Thomas, MA, MHSA, Sajini President	Global Integrated Reimbursement Services Inc. (GIRS)	Methods	1) The HTA should not be limited to considering RCTs alone. The evaluation should consider other types of evidence, such as non-randomized controlled clinical trials as well as other types of comparative effectiveness studies (observational and retrospective studies) identifying specific populations and subpopulations that might benefit from skin substitute products, especially as methods for non-randomized trials continue to improve.	The primary purpose of this report was to better understand the types of wound care products that might be broadly considered to be “skin substitutes” and the regulatory pathways they may take. The second reason for the report was to begin to characterize the state of the evidence base on these products for use in patients with chronic wounds. Evidence from RCTs was thought to be most likely to be at lower risk of bias. We agree that additional information may be gleaned from observational studies; however, the scope of this report was more limited.

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Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Thomas, MA, MHSA, Sajini President	Global Integrated Reimbursement Services Inc. (GIRS)	Methods	2)The following RCT was not included among the 14 selected RCTs, and it is not found in Tables 17 and 18: Landsman, A., et al, Living Cells or Collagen Matrix: Which is More Beneficial in the Treatment of Diabetic Foot Ulcers. Wounds 2008; 20:111-6. It should be included, or a statement should be made as to why it was not included.	The Landsman et al., 2008 study is now included in the report.
Thomas, MA, MHSA, Sajini President	Global Integrated Reimbursement Services Inc. (GIRS)	Discussion	3) Usual care for chronic wounds is not standardized, so the criticism that comparisons of skin substitutes were relatively simple standard of care approaches is not warranted.	Statements about simple gauze dressings have been modified or removed.
Thomas, MA, MHSA, Sajini President	Global Integrated Reimbursement Services Inc. (GIRS)	Methods	4)The potential for bias in each study was assessed using a quality assessment instrument developed by ECRI, but this instrument does not appear to be a validated instrument supported by peer-reviewed publications. It is therefore difficult to evaluate its effectiveness in determining bias and its appropriateness for use in the HTA.	The assessment of bias and grading of the strength of evidence follows the approach used by Evidenced-based Practice Centers and is described in: Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23 and Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov/ The assessment tool questions for judging risk of bias used in this report closely follow the recommendations made in these two reports. Additional text describing why these questions are used in a risk of bias assessment has been added to the report.

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Thomas, MA, MHSA, Sajini President	Global Integrated Reimbursement Services Inc. (GIRS)	Methods	5) The determination that the RCTs are at high risk of bias based on a lack of reporting of wound assessor blinding and, therefore, that the evidence base should be considered to have low overall strength excessively discounts the findings of the RCTs, especially as consistency of findings (benefit of skin substitutes over controls) and directness (complete wound healing) were favorable (see Table 13).	We have revised our assessment of the risk of bias of individual studies. Given that our primary outcome of interest is complete wound healing, we decided that blinding was not a critical study design element. However, blinding of outcome assessors is encouraged in studies of wound care, and we believe that it adds to the protection from bias. We also decided that a "No" or "not reported" answer to the question "Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?" was the most critical for considering a study to be at high risk-of-bias. We have also removed the question regarding funding from our risk of bias assessment and replaced it with a question about selective outcome reporting, which is sometimes a concern with manufacturer-sponsored studies. Since complete wound healing was the most important outcome, and since all of the studies included in this report reported complete wound healing, we did not identify evidence for selective outcome reporting.
Thomas, MA, MHSA, Sajini President	Global Integrated Reimbursement Services Inc. (GIRS)	Discussion	6)In the Discussion and Conclusions Section, suggest listing the 5 skin substitutes supported by RCT evidence for diabetic foot ulcers and venous leg ulcers in tabular form with a summary of the studies (which are described in more detail in Appendix C) to better display the available evidence. If you have any questions, please e-mail me at sthomas@girsinc.com. Thank you, Sajini	We thank the reviewer for this suggestion. We have added tables to the report to add clarity to the presentation of results and strength of evidence.

[1] Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.
[2] Affiliation is labeled "NA" for those who did not disclose affiliation.
[3] If listed, page number, line number, or section refers to the draft report.
[4] If listed, page number, line number, or section refers to the final report.