



Evidence-based Practice Center Technical Brief Protocol

Project Title: Skin Substitutes for Treating Chronic Wounds

Initial publication date: November 27, 2018

Amendment Dates: July 24, 2019, October 3, 2019

(Amendments Details—see Section VII)

I. Background and Objectives for the Technical Brief

Chronic Wounds

Wounds are disruptions of the skin's structural and functional integrity. Wounds normally transition through four distinct phases—hemostasis, inflammation, cellular migration and proliferation, and remodeling—until the wound structure and function are restored. Chronic wounds have failed to pass through the normal healing process in an orderly and timely manner and often remain in the inflammation phase. Patients with chronic wounds are burdened with loss of function, wound recurrence, and significant morbidity. Chronic wounds include pressure ulcers, diabetic foot ulcers, and venous leg ulcers. These wounds may need specific interventions to restart the healing process. Complete healing of chronic wounds is marked by reepithelization of epidermis and repair of the dermis. Successful healing of chronic wounds depends on critical factors, such as proper blood flow and nutrition to ensure tissue growth, infection control, maintenance of a moist environment, and removal of dead tissue to allow space for new cells and tissue to fill in the wound void.¹

Treatments for Chronic Wounds

Proper wound care starts with patient and wound assessment. Medical comorbidities (diabetes, kidney disease, coronary artery disease, peripheral artery disease, and other conditions) must be addressed. Wound related conditions such as infection, or vascular problems are also addressed.¹

A large number of dressings are available to treat chronic wounds. Wound dressings include nonadherent dressings that allow wound exudate to pass through into a secondary dressing while helping to maintain a moist wound environment, hydrocolloid dressings that absorb exudate and maintain a moist wound environment, foam dressings also absorb exudate and maintain a moist wound environment, alginate dressings made from natural polysaccharides derived from brown seaweed form a gel on contact with exudate, hydrofiber dressings made of sodium carboxymethylcellulose fibers absorb large amounts of exudate while forming a gel, and hydrogel sheets that provide moisture to dry wounds.²

A standard of care regimen featuring weekly to monthly wound assessments, infection control, debridement, and dressings that maintain a moist wound environment has been recommended by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine.³ Despite standard care and moisture retaining wound dressings, many chronic wounds do not heal. For diabetic foot ulcers, failure to show more than 50% wound area reduction in 4 weeks, indicates the need for adjunctive wound therapy.³ Adjunctive therapy may include negative pressure therapy, hyperbaric oxygen therapy, or

biologics such as bioengineered cellular therapies, extracellular matrix products, and amniotic membrane products.

Potential Role for Skin Substitutes

The skin substitutes included in the earlier evidence report are a broad collection of various combinations of cellular and acellular components, both human and animal derived, intended to stimulate the host to regenerate lost tissue and replace the wound with functional skin.² Cellular therapies, also called bioengineered cellular therapies provide skin cells (fibroblasts, keratinocytes or both) to create a source of growth factors, cytokines, and enzymes that promote tissue regeneration.⁴ Natural and synthetic material, such as collagen and polyglactin, respectively, may be used to create the extracellular matrix for tissue ingrowth. Acellular products provide an extracellular matrix devoid of cells and composed of a collagen substrate or other material into which cells can migrate and initiate tissue regeneration. Beyond being merely a scaffold, the extracellular matrix may also have an active role in stimulating tissue growth.¹ The broad category of skin substitutes may have the potential to stimulate chronic wound healing and reduce the medical burden these wounds create.

Objectives

This Technical Brief will describe the various products commercially available in the United States that may be considered skin substitutes, examine systems used to classify skin substitutes, identify and assess randomized controlled trials evaluating skin substitutes published since the 2012 AHRQ report *Skin Substitutes for Treating Chronic Wounds*, and suggest the best practices that should be part of any future studies evaluating skin substitutes.

II. Guiding Questions

1. *What skin substitutes currently used to treat chronic wounds are being regulated by the U.S. Food and Drug Administration (FDA) under the following pathways: PMA, 510(k), PHS 361[21 CFR 1270 and 1271]?*
2. *What classification systems have been developed to categorize skin substitutes?*
 - a. What are important skin substitute parameters and active components currently being used when classifying skin substitutes?
3. *What are the study design characteristics (such as those listed below) in each included investigation for each chronic wound type?*
 - a. Comparator to skin substitute
 - b. Inclusion/exclusion criteria of patients including at least age, gender, and general health requirements (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal)
 - c. Inclusion/exclusion criteria of wounds including at least wound type, wound size/depth/duration/severity, vascular status, infection status, and prior treatment requirements (e.g., no treatment with growth factors or negative pressure wound therapy)
 - d. Patient characteristics of enrollees including at least age, gender, and general health (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal)

- e. Wound characteristics of enrollees including at least wound type, wound size/depth/duration/severity, vascular status, and infection status
 - f. Basic study design and conduct information including at least method of patient enrollment, care setting, and use of run-in period
 - g. Definition of wound characteristics: definition of “failure to heal”, and definition of a successfully healed wound
 - h. Method of applying skin substitutes including provider, frequency of application, definition of standard of care, and handling of infections
 - i. Measurement and assessment methods including method of assessment(s); frequency and time points for assessment(s); and blinding of assessors
 - j. Statistical methods including power calculations, intent-to-treat analysis for studies designed to test superiority, and handling of drop-outs
4. *What are the outcomes of treatment strategies including skin substitutes alone and/or in addition to other wound care modalities compared to other wound care modalities in patients with different types of chronic wounds, for patient oriented outcomes such as the following? Consider at least:*
- a. Number/percentage of completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing requirements versus failure to heal)
 - b. Time to complete wound closure
 - c. Wound reoccurrence (include time when initial wound healing was measured, and followup to assess durability of healed wounds)
 - d. Wound infection
 - e. Need for amputation
 - f. Need for hospitalization (frequency and duration)
 - g. Return to baseline activities of daily living and function
 - h. Pain reduction
 - i. Exudate and odor reduction
 - j. Adverse effects (besides those above)
5. *What skin substitutes are currently being investigated in ongoing trials?*
6. *What best practices in study design could be used to produce high quality evidence on skin substitutes?*

III. Methods

1. Data Collection

a. Discussions with Key Informants

The KIs will have expertise in one or more of the following areas: chronic wound care including wound assessment technologies, wound care research, tissue engineering,

dermatology, and reconstructive surgery. We will ask for KI input to refine the systematic literature search, identify grey literature resources, provide information about ongoing research, discuss evidence limitations, and recommend approaches to help fill these evidence gaps. KI input will be helpful for informing Guiding Questions 3, 4, and 6. Table 1 presents potential questions that we will ask the KIs.

Table 1. Potential KI Questions

KI Group	Potential Questions
Clinical Experts	<ol style="list-style-type: none"> 1. Is there any accepted definition of skin substitutes? 2. What products would you not consider acceptable skin substitutes? 3. What are the current advantages and disadvantages of currently regulated skin substitutes (by classification)? 4. Are there situations in which a clinician should not use a skin substitute when treating chronic wounds? 5. How do you think that the clinical effectiveness of skin substitutes should be measured? 6. Are there some basic treatments that should constitute standard of care for specific ulcer types (e.g., pressure off-loading or debridement for diabetic foot ulcers, compression bandages for venous ulcers)? 7. Are there some products described as “standard of care” that should not be defined that way (e.g., wet-to-dry dressing)? 8. Are there any wound care modalities that are not reasonable comparators for skin substitutes? 9. What are important patient-oriented outcomes that current research should report? 10. At what short-term and long-term follow-up time points should studies be measuring outcomes? 11. What confounding factors (e.g., ancillary treatments, patient comorbidities, patient compliance, patient activity) pose a challenge to interpreting research on skin substitutes, and how can studies be designed to minimize these factors? 12. What patient inclusion or exclusion criteria should be standardized in clinical research on skin substitutes? 13. What are the criteria that define the need for a skin substitute? 14. What are the criteria that indicate a skin substitute should be “switched” to another product or discontinued altogether? What are the criteria that determined a skin substitute was successful in healing a wound?
Payers	<ol style="list-style-type: none"> 1. What important patient-oriented outcomes would be helpful for making coverage decisions? 2. What study variables (e.g. patient age, comorbidities, ancillary therapies, type of treatment center) would be helpful for decision-making?
Patient Advocates	<ol style="list-style-type: none"> 1. What outcomes are important to patients?

b. Grey Literature Search

ECRI will follow the draft grey literature protocol developed by the EPC Librarian Working Group. This includes review organizations, clinical trial registries, regulatory agencies, and Google. Secondary sources such as Epistemonikos, TRIP and the Cochrane Library will also be included in the search. Since the scope of this project includes evaluating classification of skin substitutes as well as evidence, ECRI’s searches will include the classifications used by the U.S. FDA, Health Canada, and other controlled vocabularies used to index biomedical literature. Date limits and platforms for these sources are listed in Table 2. For this technical brief, grey literature will be most helpful for addressing Guiding Questions 1, 2, 5, and 6.

Table 2. Grey Literature Sources

Name	Date Limits	Platform/Provider
Cochrane Library	2012–2018	Wiley
U.S. Food and Drug Administration		www.fda.gov
Health Technology Assessment Information Services (HTAIS)	2012–2018	ECRI Institute
Healthcare Product Comparison System (HCPCS)	2012–2018	ECRI Institute
Health Devices Alerts	2012–2018	ECRI Institute
Clinicaltrials.gov	Ongoing trials	www.clinicaltrials.gov
National Institute for Health and Clinical Effectiveness		National Health Service (UK)
Epistemonikos		https://www.epistemonikos.org/
Trip		https://www.tripdatabase.com/

c. Published Literature Search

Evidence from the published literature search will help inform Guiding Questions 3, 4 and 6. For this project, ECRI will search the bibliographic databases listed in Table 3.

Table 3. Bibliographic Databases

Name	Date Limits	Platform/Provider
EMBASE (Excerpta Medica)	2012–2018	Embase.com
MEDLINE	2012–2018	Embase.com
PubMed (In process and Publisher subsets)	2012–2018	PubMed.gov
CINAHL	2012–2018	EBSCO

Searches will be limited to randomized controlled trials, systematic reviews, and meta-analyses published since 2012, the publications date of the evidence report “Skin Substitutes for Treating Chronic Wounds.”² Literature searches will be updated during the Peer Review process, before finalization of the review. Literature searches may also be expanded to include additional study designs (e.g., prospective non-randomized comparison studies) if preliminary searches identify insufficient evidence (<5 randomized controlled trials for any wound type).

Table 4 displays our proposed strategy in Embase.com syntax. We will translate the strategies for the Wiley, EBSCO, and PubMed platforms. Since searching is an iterative process, there may be differences between this initial proposed strategy and that included in the final version of this report.

Table 4. Sample Search Strategy

Set #	Concept	Strategy
S1	Skin Substitutes	'acellular dermal matrix'/exp OR 'artificial skin'/exp OR 'biological dressing'/exp OR 'engineered cartilage graft'/exp OR 'engineered skin autograft'/exp OR 'tissue engineering'/exp OR 'tissue scaffold'/exp
S2		((acellular OR artificial* OR bioengineer* OR biosynthetic* OR engineer* OR equivalen* OR regenerat* OR replac* OR synthetic* OR substitut* OR templat*) NEAR/2 (epidermal OR epidermis OR dermis OR dermal OR skin OR tissue*)):ab,ti OR ((matrices OR matrix) NEAR/2 (acellular OR extracellular OR decellular* OR dermal OR skin OR tissue* OR wound*)):ab,ti OR (scaffold* NEAR/2 (dermal OR engineer* OR repair* OR tissue* OR skin)):ab,ti

Set #	Concept	Strategy
S3		(acellular NEAR/2 allograft*):ab,ti OR ((amniot* OR cadaver*) NEAR/2 (skin* OR tissue*)):ab,ti OR (biologic* NEXT/1 dressing*):ab,ti OR (collagen NEAR/2 (bovine OR porcine)):ab,ti OR (regenerat* NEAR/2 (template* OR matrix)):ab,ti OR 'bilayer* living cell*' OR hadm
S4		(affinity NEAR/2 amniotic) OR allderm OR allomax OR allopatch OR alloskin OR allowrap OR (AMNIO next/1 wound) OR amnioband OR amnioexcel OR amniofix OR amniomatrix OR (aongen NEAR/2 matrix) OR (architect NEAR/2 matrix) OR apligraf OR artacent OR (arthrex NEXT/1 amnion) OR 'atlas wound matrix' OR arthroflex OR 'avagen wound dressing' OR Biobrane OR 'bio-connekt' OR 'biodfence' OR 'biodexcel' OR 'bioDFactor' OR 'biodmatrix' OR 'biomembrane' OR 'bioskin' OR 'biovance amniotic' OR celaderm OR clarix OR 'collagen sponge' OR 'collaguard' OR 'collaSorb' OR 'collawound' OR 'collexa' OR 'conexa reconstructive matrix' OR 'CorMatrix' OR 'Cytal wound matrix' OR 'cygnus' OR cymetra OR dermacell OR dermagraft OR 'dermapure' OR 'dermaspan' OR 'dermavest' OR dressskin OR 'Endoform' OR epicel OR epicord OR epidex OR 'ez-derm' OR 'flex hd' OR floweramnioflo OR floweramniopatch OR flowerderm OR flowerflo OR fortaderm OR gammagraft OR gelapin OR grafix OR grafixPL OR graftjacket OR graftskin OR helicoll OR hyalograft OR hyalomatrix OR hmatrix OR 'hyalomatrix tissue reconstruction matrix' OR integra OR keramatrix OR kerecis OR kollagen OR laserskin OR lyofoam OR lyomousse OR matriderm OR matristem OR 'matrix hd' OR mediskin OR memoderm OR miroderm OR neoPatch OR 'NEOX wound allografts' OR 'nushield placental' OR oasis OR omnigraft OR orcel OR 'PalinGen amniotic' OR permacol OR permaderm OR plurivest OR primatrix OR promatrix OR promogran OR puraply OR 'puros dermis' OR renoskin OR repliform OR repriza OR revita OR revitalon OR stratagraft OR strattice OR suprathel OR 'syspur-derm' OR syspurderm OR talymed OR tensix OR theraskin OR 'tielle non-adhesive' OR Tissuemend OR transcyte OR tranzgraft OR truskin OR 'vitro-skin' OR woundex OR 'UBM hydrated wound dressing' OR 'UBM lyophilized wound dressing' OR 'xcm biologic tissue matrix'
S5	Chronic Wounds	bedsore* OR 'chronic wound'/exp OR decubitus/exp OR 'diabetic foot'/exp OR ((injur* OR wound* OR ulcer*) NEAR/2 (chronic* OR intractab* OR 'non-healing' OR nonhealing OR persisten*)):ab,ti OR ((bed OR foot OR feet OR diabet* OR leg OR legs OR pressure OR venous) NEAR/2 (sore* OR ulcer*)):ab,ti OR (diabet* NEAR/2 (feet or foot)):ab,ti
S6	Combine Concepts	(S1 OR S2 OR S3 OR S4) AND S5
S7	Apply Language and Date Restrictions/ Remove Unwanted Study Designs TOTAL RESULTS	S6 AND ([english]/lim AND [humans]/lim AND [2012-2018]/py) NOT (abstract:nc OR annual:nc OR book/de OR 'case report'/de OR conference:nc OR 'conference abstract':it OR 'conference paper'/de OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR editorial/de OR editorial:it OR erratum/de OR letter:it OR note/de OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/de OR symposium:nc)
S8	Screen for relevancy/omit out-of-scope material TOTAL SELECTED RECORDS	
S9	Limit to Meta-Analyses	S8 AND ('meta analysis'/de OR (meta* NEXT/1 anal*):ti)
S10	Limit to RCTs	S8 AND ('randomized controlled trial'/de OR random*:ti)
S11	Limit to Systematic Reviews	S8 AND ('systematic review'/de OR systematic*:ti)

Set #	Concept	Strategy
S12	TOTAL HIGH-LEVEL STUDIES	S9 OR S10 OR S11 (Some abstracts are classified with more than one study design, ie. systematic review <i>and</i> meta-analyses)

Literature screening will be performed using the database Distiller SR (Evidence Partners, Ottawa, Canada). Literature search results will initially be screened for relevancy. Relevant abstracts will then be screened by a single reviewer based on eligibility criteria listed in Table 5. Studies that appear to fit the scope of the brief will be retrieved in full and screened again. Studies will be included if they address a guiding question; present data on patients with chronic wounds being treated with a skin substitute commercially available in the U.S.; and administer similar standard of care to all individuals enrolled in the study. Questions regarding inclusion will be resolved by the principal investigator. This process will be repeated if additional evidence is identified in updated literature searches.

Table 5. Inclusion and Exclusion Criteria

PICOTs and Other Criterion	Inclusion Criteria	Exclusion Criteria
Population	Human subjects in whom a chronic wound (pressure ulcer, diabetic foot ulcer, venous leg ulcer, or arterial leg ulcer) lasting more than 30 days without healing has been diagnosed	Animal subjects Humans subjects with acute wounds (lasting fewer than 30 days), surgical wounds, or burns
Intervention	Commercially available skin substitute products regulated by the FDA (Pre-market Approval, 510(k) marketing clearance, and Human cells, tissues, and cellular and tissue-based products)	Non FDA-regulated skin substitutes
Comparator	Other FDA-regulated skin substitute product Standard of care Standard of care plus synthetic dressings, growth factors, skin grafts Other acceptable treatments used as a comparison	Inadequate standard of care (based on clinical practice guidelines, literature searches, and opinion of Key Informants)
Ancillary treatments	Studies administering similar standard of care	Studies not administering similar standard of care or not describing standard of care
Study design	Systematic review of randomized controlled trials (RCTs) or individual RCTs. If < 5 RCTs are identified for each wound type, prospective non-randomized comparative studies enrolling a minimum of 5 patients per arm will be included.	Any study design in which patients are not randomly allocated to treatment except for wound types where insufficient evidence (<5 RCTs) has been identified.
Study enrollment	Minimum of 5 patients per arm for RCTs and prospective non-randomized comparative studies	<5 patients per study arm for RCTs and prospective non-randomized comparative studies
Publication type	Peer-reviewed articles available in full text	Conference abstracts
Outcomes	Reports at least 1 outcome of interest listed under Guiding Question 4	Does not report any outcome of interest listed under Guiding Question 4
Timing	Any	NA
Setting	Any	NA

Study quality assessment for systematic reviews will be based on the author's risk-of-bias assessment. Study quality assessment for individual studies will be conducted in duplicate

using risk-of-bias criteria based on Viswanathan et al. 2018⁵ and emphasizing criteria important to chronic wound care management.

2. Data Organization and Presentation

a. Information Management

For Guiding Questions 1 and 2, we will categorize skin substitutes by FDA regulatory classifications identified in the grey literature, by classification systems identified in the literature, and by systems suggested by clinical experts among the Key Informants. We will extract information on product descriptions to determine distinguishing features of these products. Results from the screening of clinical evidence from the published literature will inform Guiding Questions 3, 4 and 6. Information on patient characteristics, wound treatments, and outcomes assessed will be stratified by wound types. A summary sentence for each included investigation will be provided. Ongoing clinical trials sourced from the grey literature and KI input on best practices will help inform Guiding Question 5 and 6.

b. Data Presentation

A list of FDA-regulated skin substitutes and ongoing trials as well as data abstracted from clinical studies will be presented in evidence tables. Distinguishing features of skin substitute classifications and a summary of published evidence will be displayed graphically in an evidence map.

IV. References

1. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle)*. 2015 Sep 1;4(9):560-82. Also available: <http://dx.doi.org/10.1089/wound.2015.0635>. PMID: 26339534.
2. Snyder DL, Sullivan N, Schoelles KM. Skin substitutes for treating chronic wounds. Final report. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2012 Dec 18. 203 p. (Technology assessment report; Also available: http://www.ahrq.gov/research/findings/ta/skinsubs/HCPRO610_skinsubst-final.pdf.
3. Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, Driver VR, Frykberg R, Carman TL, Marston W, Mills JL Sr, Murad MH. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg*. 2016 Feb;63(2 Suppl):3S-21S. Also available: <http://dx.doi.org/10.1016/j.jvs.2015.10.003>. PMID: 26804367.
4. Savoji H, Godau B, Hassani MS, Akbari M. Skin tissue substitutes and biomaterial risk assessment and testing. *Front Bioeng Biotechnol*. 2018 Jul 26;6:86. Also available: <http://dx.doi.org/10.3389/fbioe.2018.00086>. PMID: 30094235.
5. Viswanathan M, Patnode CD, Berkman ND, Bass EB, Chang S, Hartling L, Murad MH, Treadwell JR, Kane RL. Recommendations for assessing the risk of bias in systematic reviews of health-care interventions. *J Clin Epidemiol*. 2018 May;97:26-34. Epub 2017 Dec 14. Also available: <http://dx.doi.org/10.1016/j.jclinepi.2017.12.004>. PMID: 29248724.

V. Definition of Terms

Not applicable.

VI. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
July 24, 2019	Section II Guiding Questions	1. What skin substitutes currently used to treat chronic wounds are being regulated by the U.S. Food and Drug Administration (FDA) under the following pathways: PMA, 510(k), PHS 361[21 CFR 1270 and 1271]?	1. What products are commercially available in the United States that may be considered skin substitutes?	FDA requested that the question be changed to remove any reference to FDA regulatory procedures.
July 24, 2019	Section III Methods Table 5 Inclusion and Exclusion Criteria row for Intervention	Commercially available skin substitute products regulated by the FDA (Premarket Approval, 510(k) marketing clearance, and Human cells, tissues, and cellular and tissue-based products). Non FDA-regulated skin substitutes	Commercially available skin substitute products Other skin substitutes not available in the United States	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes.
July 24, 2019	Section III Methods Table 5 Inclusion and Exclusion Criteria row for Comparator	Other FDA-regulated skin substitute product Standard of care Standard of care plus synthetic dressings, growth factors, skin grafts Other acceptable treatments used as a comparison	Other skin substitute product Standard of care Standard of care plus synthetic dressings, growth factors, skin grafts Other acceptable treatments used as a comparison	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes.
July 24, 2019	Section III Methods 2. Data Organization a. Information Management	For Guiding Questions 1 and 2, we will categorize skin substitutes by FDA regulatory classifications identified in the grey literature, by classification systems identified in the literature, and by systems suggested by clinical experts among the Key Informants.	For Guiding Questions 1 and 2, we will categorize skin substitutes by classification systems identified in the literature, and by systems suggested by clinical experts among the Key Informants.	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes.

Date	Section	Original Protocol	Revised Protocol	Rationale
July 24, 2019	Section III Methods 2. Data Organization a. Data Presentation	A list of FDA-regulated skin substitutes and ongoing trials as well as data abstracted from clinical studies will be presented in evidence tables.	A list of skin substitutes and ongoing trials as well as data abstracted from clinical studies will be presented in evidence tables.	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes.
Oct 03, 2019	Section II Guiding Questions	1. What skin substitutes currently used to treat chronic wounds are being regulated by the U.S. Food and Drug Administration (FDA) under the following pathways: PMA, 510(k), PHS 361[21 CFR 1270 and 1271]?	1. What products are commercially available in the United States that may be considered skin substitutes?	FDA requested that the question be changed to remove any reference to FDA regulatory procedures. The fact that a skin substitute is commercially available is not a reflection of its legal status.
Oct 03, 2019	Section III Methods Table 5 Inclusion and Exclusion Criteria row for Intervention	Commercially available skin substitute products regulated by the FDA (Premarket Approval, 510(k) marketing clearance, and Human cells, tissues, and cellular and tissue-based products). Non FDA-regulated skin substitutes	Commercially available skin substitute products Other skin substitutes not available in the United States	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes. The fact that a skin substitute is commercially available is not a reflection of its legal status.
Oct 03, 2019	Section III Methods Table 5 Inclusion and Exclusion Criteria row for Comparator	Other FDA-regulated skin substitute product Standard of care Standard of care plus synthetic dressings, growth factors, skin grafts Other acceptable treatments used as a comparison	Other skin substitute product Standard of care Standard of care plus synthetic dressings, growth factors, skin grafts Other acceptable treatments used as a comparison	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes. The fact that a skin substitute is commercially available is not a reflection of its legal status.

Date	Section	Original Protocol	Revised Protocol	Rationale
Oct 03, 2019	Section III Methods 2. Data Organization a. Information Management	For Guiding Questions 1 and 2, we will categorize skin substitutes by FDA regulatory classifications identified in the grey literature, by classification systems identified in the literature, and by systems suggested by clinical experts among the Key Informants.	For Guiding Questions 1 and 2, we will categorize skin substitutes by classification systems identified in the literature, and by systems suggested by clinical experts among the Key Informants.	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes. The fact that a skin substitute is commercially available is not a reflection of its legal status.
Oct 03, 2019	Section III Methods 2. Data Organization a. Data Presentation	A list of FDA-regulated skin substitutes and ongoing trials as well as data abstracted from clinical studies will be presented in evidence tables.	A list of skin substitutes and ongoing trials as well as data abstracted from clinical studies will be presented in evidence tables.	FDA requested that we remove any reference to FDA regulatory procedures that may pertain to skin substitutes. The fact that a skin substitute is commercially available is not a reflection of its legal status.

VII. Key Informants

Within the Technical Brief process, Key Informants serve as a resource to offer insight into the clinical context of the technology/intervention, how it works, how it is currently used or might be used, and which features may be important from a patient or policy standpoint. They may include clinical experts, patients, manufacturers, researchers, payers, or individuals with other perspectives, depending on the technology/intervention in question. Differing viewpoints are expected, and all statements are crosschecked against available literature and statements from other Key Informants. Information gained from Key Informant interviews is identified as such in the report. Key Informants do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals invited to serve as Key Informants who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific

literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

IX. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

X. Role of the Funder

This project was funded under Contract No. HHSA 290 2015 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.