Technology Assessment Program

Skin Substitutes for Treating Chronic Wounds

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Technology Assessment Program - Technical Brief

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Skin Substitutes for Treating Chronic Wounds

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Key Messages

Purpose of Review

To describe skin substitute products commercially available in the United States used to treat chronic wounds, examine systems used to classify skin substitutes, identify and assess randomized controlled trials (RCTs), and suggest best practices for future studies.

Key Messages

- We identified 76 commercially available skin substitutes to treat chronic wounds. The majority of these do not contain cells and are derived from human placental membrane (the placenta's inner layer), animal tissue, or donated human dermis.
- Included studies (22 RCTs and 3 systematic reviews) and ongoing clinical trials found during our search examine approximately 25 (33%) of these skin substitutes.
- Available published studies rarely reported whether wounds recurred after initial healing. Studies rarely reported outcomes important to patients, such as return of function and pain relief.
- Future studies may be improved by using a 4-week run-in period before study enrollment and at least a 12-week study period. They should also report whether wounds recur during 6-month followup.

Disclaimer

A skin substitute's commercial availability is not a reflection of its legal status. Manufacturers self-determine whether their human cells, tissues, or cellular or tissue-based product (HCT/P) can be marketed without FDA preapproval and often misunderstand or mischaracterize the criteria they must meet for the product to be regulated solely for communicable disease risk. See 21 CFR 1271.10(a). For more information, see "FDA Announces Comprehensive Regenerative Medicine Policy Framework." We note that FDA does not refer to any product or class of products as "skin substitutes," and we are not proposing an official definition or classification system. The report includes many products cleared by the FDA as wound dressings via the 510(k) pathway which are not intended to treat wounds but only to cover wounds so that the natural healing process can take place.

This report is based on research conducted by the ECRI Institute-Penn Medicine Evidence-Based Practice Center (ECRI-Penn EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2015-00005-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients.)

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Medicare and Medicaid Services (CMS) requested this report from the Evidence-based Practice Center (EPC) Program at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following EPC: ECRI Institute-Penn Medicine Evidence-based Practice Center (Contract Number: HHSA290201500005I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov

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Key Informants

In designing the study questions, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows:

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Peer Reviewers

Before publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers 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 with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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In addition to these Peer Reviewers, drafts of the document were reviewed by individuals at several agencies within the Department of Health and Human Services."

Skin Substitutes for Treating Chronic Wounds

Structured Abstract

Background. Normal healthy skin provides a protective barrier against microbes, water loss, and ultraviolet light damage; helps with thermoregulation; and provides tactile sensations. Wounds are disruptions of the skin's structural and functional integrity and normally transition through distinct phases of healing until the skin's structure and function are restored. Chronic wounds have failed to pass through the normal healing process. Patients with chronic wounds, such as diabetic foot ulcers and venous leg ulcers, experience loss of function, pain, wound recurrence, and significant morbidity. Care for chronic wounds involves removing necrotic tissue, applying dressings that maintain a moist wound environment, treating wound infections, and restoring blood flow to the wound site. If these procedures fail to restore the healing process, additional therapies may be considered.

Purpose. This Technical Brief describes the various products commercially available in the United States that may be considered skin substitutes, examines systems used to classify skin substitutes, identifies and assesses the clinical literature evaluating skin substitutes published since the 2012 AHRQ report *Skin Substitutes for Treating Chronic Wounds*, and suggests the best practices that may be part of any future studies evaluating skin substitutes.

Methods. We performed a systematic search of the published literature (EMBASE, MEDLINE, PubMed, CINAHL) and grey literature since 2012. We received scientific packets from manufacturers during AHRQ's call for Supplemental Evidence and Data for Systematic Reviews (SEADS) from March 25 to April 29, 2019. We searched for systematic reviews/meta-analyses, randomized controlled trials (RCTs), and prospective nonrandomized comparative studies examining commercially available skin substitutes in individuals with diabetic foot ulcers, venous leg ulcers, pressure ulcers, and arterial leg ulcers. We extracted data on clinical outcomes, such as complete wound healing, healing rate, and recurrence. We compared study eligibility criteria and outcomes measured between included studies and ongoing clinical trials registered in ClinicalTrials.gov to identify trends in the field. We interviewed Key Informants with expertise in chronic wound care to help identify classification systems to categorize the skin substitutes, guide study eligibility criteria, describe limitations in the current field, and recommend best practices for designing future studies.

Findings. We identified 76 commercially available skin substitutes and categorized them based on the Davison-Kotler classification system. Sixty-eight (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Twenty-one ongoing clinical trials (all RCTs) examined an additional nine skin substitutes with similar classifications. Studies rarely reported clinical outcomes, such as amputation, wound recurrence at least 2 weeks after treatment ended, or patient-related outcomes, such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and -reported studies providing more clinically relevant data in this field are this Technical Brief's clearest implications.

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Background

Normal Skin

Normal healthy skin has several distinct functions. It protects underlying tissues from abrasions, entry of microbes, unwanted water loss, and ultraviolet light damage. Tactile sensations of touch, pressure, and vibration; thermal sensations of heat and cold; and pain sensations all originate in the skin's nervous system. The body's thermoregulation relies on the skin's ability to sweat and control blood flow to the skin to increase or decrease heat loss. The skin's functions are performed by three distinct tissue layers: a thin outer layer of cells called the epidermis, a thicker middle layer of connective tissue called the dermis, and an inner, subcutaneous layer. The outer layers of the epidermis are composed of flattened, cornified, dead keratinocytes that form a barrier to water loss and microbe entry. These cells are derived from keratinocytes in the basal layer, which lies above the dermis, and are responsible for skin reepithelization. The epidermis does not contain nerves or blood vessels and obtains water and nutrients through diffusion from the dermis. The dermis is composed mostly of collagen fibers and some elastic fibers both produced by fibroblasts and, along with water and large proteoglycan molecules, makes up the extracellular matrix (ECM). This skin layer provides mechanical strength and a substrate for water and nutrient diffusion; it contains blood vessels, nerves, sweat glands, hair follicles, and cells involved in immune function, growth, and repair. The subcutaneous layer is composed of adipocytes that form a thick layer of adipose tissue.[1,2]

Chronic Wounds

Wounds are disruptions of the skin's structural and functional integrity. Wounds normally transition through four distinct phases—hemostasis, inflammation, proliferation, and remodeling—until the skin's structure and function are restored. Chronic wounds have failed to pass through the normal healing process in an orderly and timely manner and often remain in the inflammation phase.[3,4] A wound may be considered chronic if it has not entered the proliferation phase after 4 weeks of therapy.[4] Repeated tissue injury, microorganisms, and ECM fragments attract inflammatory immune cells and prolong the inflammatory phase. Elevated matrix metalloproteases (MMP) in chronic wounds may break down growth factors and other agents responsible for stimulating native fibroblasts to produce granulation tissue in the wound bed, a key step in wound healing. MMPs include collagenase and gelatinase. In addition, the fibroblasts in chronic wounds appear senescent and unresponsive to growth factor signals. The increased MMP levels result in ECM breakdown that prevents the wound from moving into the proliferative phase. Chronic wounds may also have deficient and defective mesenchymal stem cells (MSCs). MSCs synthesize growth factors and cytokines that affect the proliferation and remodeling phases of wound repair. Recruiting MSC into a wound may be an essential part of the wound healing process.[3]

Patients with chronic wounds experience loss of function, wound recurrence, and significant morbidity, and care of these patients is a major challenge in the United States.[3] The majority of chronic wounds are pressure ulcers, diabetic foot ulcers, and venous leg ulcers, all of which may need specific interventions to restart the healing process. Complete healing of chronic wounds is marked by epidermis reepithelization and dermis repair. 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 the wound void.[3]

According to the International Diabetes Federation Diabetes Atlas 8th edition, about 30.2 million people had diabetes in the United States in 2017.[5] Annually, between 1 to 4 percent of individuals with diabetes will develop a foot ulcer. Among Medicare Parts A and B fee-for-service beneficiaries with diabetes, the annual incidence of diabetic foot ulcer is about 6 percent and of lower-extremity amputation about 0.5 percent. In the United States, the lifetime incidence of foot ulcers has been estimated at between 19 percent and 34 percent of those with diabetes.[6] Recurrence of diabetic foot ulcers is high: about 40 percent of patients at 1 year and almost 60 percent within 3 years.[6] Diabetic foot ulcers are particularly burdensome and associated with markedly increased morbidity and mortality.[7] These wounds are associated with a high risk of limb amputation, with about 20 percent of moderate to severe diabetic foot ulcer infections leading to amputation.[6] Mortality after amputation exceeds 70 percent at 5 years.[6]

Active or healed venous leg ulcers occur in about 1 percent of the general population;[8,9] however, the prevalence, functional impact, and financial burden are greater in the elderly. Using data from the General Practice Research Database, Margolis et al. (2002) estimated the annual prevalence of venous leg ulcers among the elderly (aged 65 years or older) was 1.69 (95% CI, 1.65, 1.74), and the overall incidence rate was 0.76 (95% CI, 0.71, 0.83) per 100 person-years for men and 1.42 (95% CI, 1.35, 1.48) for women.[10] Individuals with venous leg ulcers have a reduced quality of life due to pain, which in turn affects sleep and overall well-being. They also experience impaired physical function and reduced mobility, which often lead to loss of work and isolation. Rice et al. (2014) investigated the financial burden of venous leg ulcers in the United States using two insurance claims databases, a random sample of Medicare beneficiaries aged 65 or older, and a privately insured population aged 18 to 65.[11] The average annual incidence rate of venous leg ulcers was 2.2 percent in Medicare patients and 0.5 percent in those with private insurance. Patients with venous leg ulcers used more medical resources and had more days missed from work, resulting in higher work-loss costs compared with patients who did not have venous leg ulcers. Using these data, the estimated annual U.S. payer burden is $14.9 billion.[11]

The incidence of pressure ulcers is increasing due to an aging population with decreased mobility and increases in morbidity associated with obesity and cardiovascular disease.[12] Each year, more than 2.5 million people in the United States develop pressure ulcers.[13] Two percent to 28 percent of nursing home residents have pressure ulcers.[14] Special wound care is needed in 35 percent of nursing home residents with stage 2 or higher pressure ulcers. Once developed, pressure ulcers typically need a lengthy course of treatment, with an annual cost in the United States near $11 billion, based on data from the Healthcare Cost and Utilization Project for adult hospital stays in 2006.[15]

An analysis of the Medicare 5 percent Limited Data Set for calendar year 2014 reported on the cost of care for chronic wounds, including diabetic foot ulcers, venous leg ulcers, and pressure ulcers.[16] In this dataset, the prevalence of infected diabetic foot ulcers was 3.4 percent, infected venous leg ulcers was 2.3 percent, and pressure ulcers was 1.8 percent. Including noninfected and infected wound costs, the estimated cost of care for diabetic foot ulcers ranged from $6.2 billion to $18.7 billion, for venous leg ulcers the range was $0.7 billion to $1.5 billion, and for pressure ulcers the range was $3.9 billion to $22 billion. The low-range estimate counted only Medicare provider payments when a wound was the claim's primary diagnosis. The high-

range estimate counted Medicare provider payments when a wound was either the primary or secondary diagnosis.

Current Treatments for Chronic Wounds

Standard of Care

Usual care or standard care for established chronic wounds incorporates common principles, as follows, that apply to managing all wound types:[3]

- Remove necrotic tissue through debridement (typically sharp debridement).
- Maintain moisture balance by selecting the proper wound dressing to control exudate.
- Take measures to prevent or treat wound infections.
- Correct ischemia in the wound area.
- For venous leg ulcers, apply some form of compression.
- For diabetic foot ulcers, apply some form of offloading.

However, the methods for achieving each of these wound management principles varies among clinical practice guidelines and clinical studies.[1] Therefore, in this document standard of care refers to the usual or standard care established by individual wound care facilities for the treatment of their patients rather than a standard approach that should be used for all wounds. Using saline wet-to-dry gauze on any chronic wound is no longer considered part of standard wound care.[17] We excluded any studies that used saline wet-to-dry gauze.

Four weeks of standard of care without achieving a 50 percent reduction in wound size may signal the need for a change or additional therapies.[3] An RCT in patients with diabetic foot ulcers demonstrated that a 50 percent reduction in wound area at 4 weeks was a strong predictor of wound healing by 12 weeks when standard of care was used.[18] Only 9 percent of patients who did not meet the 50 percent reduction at 4-weeks threshold healed by 12 weeks. The positive predictive value was 58 percent, and the negative predictive value was 91 percent. For venous leg ulcers, Kantor and Margolis (2000) also showed that percent change in wound area after 4 weeks is predictive of complete wound healing by 24 weeks.[19] The positive predictive value was 68 percent, and the negative predictive value was 75 percent.

Skin Substitutes

If chronic wounds fail to respond to standard of care, skin substitutes may be used as an adjunct to established chronic wound care methods to increase the likelihood of complete healing.[20] We do not propose a definition for skin substitutes (see our product inclusion criteria on page 9), but several investigators have proposed definitions and outlined what skin substitutes should accomplish. According to Ferreira et al.,[21] "skin substitutes are a heterogeneous group of biological and/or synthetic elements that enable the temporary or permanent occlusion of wounds. Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient's skin." Ferreira et al. also noted that skin substitutes should have functional and structural characteristics that closely match those of autologous skin. According to Nathoo et al., "The ideal skin substitute should be durable, completely autologous, endothelialized and contain adnexal structures and adult stem cells."[20] Other authors have stated that commercially manufactured skin substitutes should protect the integument from water loss and infection; provide a stable, biodegradable scaffold to promote the synthesis of new dermal tissue; allow host or other cells to proliferate within the scaffold that

will act as functional dermal cells rather than scar tissue; and resist tearing forces while being easy to handle.[22-24] Eweida and Marei have suggested that growth factors and ECM components of the skin substitute may promote cell proliferation, reduce wound degradation caused by MMPs within the wound, and promote wound vascularization.[25] The skin substitute properties these authors have noted may enhance a skin substitute's wound healing potential beyond that of standard of care.

Guiding Questions

1. What products are commercially available in the United States that may be considered skin substitutes?
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, general health (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal), and prior and concurrent wound treatments
    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 dropouts
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 reepithelialization without drainage or dressing requirements versus failure to heal)
    b. Time to complete wound closure

c. Wound recurrence (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?

Methods

1. Data Collection

a. Discussions with Key Informants (KIs)

We selected KIs with expertise in chronic wound care, including wound assessment technologies, wound care research, tissue engineering, and dermatology. We interviewed either individually or collectively six KIs located in the United States and the United Kingdom. We asked KIs about the advantages and disadvantages of currently regulated skin substitutes and if any products should not be classified as skin substitutes. We asked in what unique situations should skin substitutes not be applied and what basic treatments should be used for standard of care for chronic wounds of interest to the report. We asked how they would define "failure to heal," how to measure the clinical effectiveness of skin substitutes, and what outcomes are important to patients. We also asked how studies can be designed to minimize confounding factors such as ancillary treatments and patient adherence that pose a challenge to interpreting research. We did not ask KIs for input on reimbursement, which is outside the scope of this report. We did not ask KIs to comment on specific skin substitute products to avoid biasing our assessment.

We used KI input to confirm the selection of the classification system used to organize skin substitutes, refine the systematic literature search, provide information about ongoing research, discuss evidence limitations, and recommend approaches to help fill these evidence gaps. KI input helped inform Guiding Questions 2, 3, 4, and 6.

b. Grey Literature Search

ECRI followed the draft grey literature protocol developed by the EPC Librarian Working Group. This includes review organizations, clinical trial registries, regulatory agencies, and Google. We also included secondary sources, such as Epistemonikos, TRIP, and the Cochrane Library, in the search. Since this project's scope included evaluating the classification of skin substitutes as well as evidence, ECRI's searches included the classifications used by FDA, Health Canada, and other controlled vocabularies to index biomedical literature. Date limits and platforms for these sources are listed in Appendix A. For this technical

brief, grey literature was most helpful for addressing Guiding Questions 1, 2, 5, and 6.

c. Published Literature Search

Evidence from the published literature search helped inform Guiding Questions 3, 4, and 6. For this project, ECRI searched the bibliographic databases listed in Appendix A, including EMBASE, MEDLINE, PubMed, and CINAHL. Searches were initially limited to RCTs, systematic reviews, and meta-analyses published since 2012, the publication date of the evidence report *Skin Substitutes for Treating Chronic Wo*unds.[1] Literature searches were expanded to include additional study designs (e.g., prospective nonrandomized comparative studies) after preliminary searches did not identify sufficient evidence for pressure ulcers and arterial leg ulcers. Updated searches did not identify any nonrandomized comparative studies for pressure ulcers and arterial leg ulcers. Literature searches were updated during the peer-review process before finalizing the review.

We performed literature screening by a single reviewer using the database Distiller SR (Evidence Partners, Ottawa, Canada). We initially screened the results for relevancy based on predetermined eligibility criteria (see Table 1) and requested full text for relevant abstracts.

d. Supplemental Evidence and Data for Systematic Reviews (SEADS)

Evidence from AHRQ's invitation for SEADS also helped inform Guiding Questions 3, 4, 5, and 6. On March 25, 2019, the AHRQ Technology Assessment (TA) Program called for scientific information packets with study-specific information relevant to the report's guiding questions to have full access to relevant research from industry stakeholders, professional societies, and other interested researchers. The SEADS portal was open for 4 weeks, ending on April 29, 2019. Due to the government shutdown in January 2019, the SEADS for this report was not announced in the Federal Register and emails were not sent to stakeholders. Changes made to the current report in accordance with the SEAD were not in the posted draft report. Therefore AHRQ provided an opportunity to comment on the disposition of SEADS comments.

SEADS submissions were screened for relevancy based on predetermined eligibility criteria (see Table 1). We included studies and ongoing clinical trials if they addressed a guiding question, presented data on patients with chronic wounds being treated with a skin substitute commercially available in the United States, and provided details on standard of care administered to all enrolled individuals. The principal investigator resolved questions regarding inclusion. Questions regarding adequate standard of care were discussed with the KIs.

Table 1. 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*	Other skin substitutes not available in the United States

PICOTs and Other Criterion	Inclusion Criteria	Exclusion Criteria
Comparator	Other skin substitute product Standard of care (as established by individual wound care facilities) 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). We excluded any studies that used saline wet-to-dry gauze.
Ancillary treatments	Studies administering similar standard of care as established by individual wound care facilities	Studies not administering similar standard of care or not describing standard of care
Study design	Systematic review of RCTs or individual RCTs. If <5 RCTs are identified for each wound type, prospective nonrandomized 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 for which insufficient evidence (<5 RCTs) has been identified
Study enrollment	Minimum of 5 patients per arm for RCTs and prospective nonrandomized comparative studies	<5 patients per study arm for RCTs and prospective nonrandomized 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

RCT=randomized controlled trial

* We used the products listed under the Centers for Medicare & Medicaid Services (CMS) codes Q4101 to Q4204[27] as a starting point and looked for similar products to generate a list of products. We included only products primarily marketed for chronic wounds and commercially available in the United States. Some of the products that CMS listed were not included because they are not yet commercially available in the United States. Several of the animal collagen-based products are designed more for exudate absorption and maintaining a moist wound environment than interaction with the wound healing process. We did not include Colla-Pad, CollaSorb, and Collexa for this reason. The other Collagen Wound Dressings included in our report are promoted as having an interaction with the healing process. We did not include or exclude products based on their CMS coding alone.

e. Risk-of-Bias Assessment

Risk of bias for systematic reviews was based on the review author's risk-of-bias assessment. Risk of bias for individual studies was conducted in duplicate using risk-of-bias criteria based on Viswanathan et al. 2018[26] and emphasizing criteria important to chronic wound care management. We used a 10-item risk-of-bias tool consisting of questions that address various areas of study design and conduct that influence the potential for bias in individual studies. We modified the questions to reflect important study design and conduct issues in wound care (e.g., wound recurrence reported). We made our assessments based on complete wound healing as the primary outcome of interest.

Each question was answered as "Yes" or "No." A "Yes" answer means the study reported using this aspect of study design or conduct. A "No" answer means the study reported that this aspect of study design or conduct was not used or was not reported. The questions are phrased so that a "Yes" answer reflects a lower risk of bias and a "No" reflects a higher risk of bias.

Industry funding of clinical research may affect whether negative data are published and lead to publication bias in which only positive data are published. Viswanathan et al. 2018[26] do not recommend using industry funding in a risk-of-bias tool but instead recommend commenting on the potential impact of industry funding and publications bias. In the Summary and Implications section, we

consider the possibility of publication bias due to industry funding by examining the publication status of 15 ongoing clinical trials from the 2012 report *Skin Substitutes for Treating Chronic Wounds*.[1]

Risk-of-Bias Questions

Selection Bias

Question 1. Did the study use appropriate randomization methods?
Question 2. Was there concealment of treatment-group allocation?
Question 3. Were the numbers of comorbidities similar (no more than a 15% difference) at the start of treatment between groups?
Question 4. Were the mean wound sizes at the start of treatment similar (no more than a 15% difference) between groups?
Question 5. Were the mean wound durations at the start of treatment similar (no more than a 15% difference) between groups?
Question 6. Was the method of measuring wound condition at enrollment reported?

Detection Bias

Question 7. Was the wound assessor blinded to the patient's treatment group?

Reporting Bias

Question 8. Did the study report wound recurrence as an outcome, and was it assessed at least 2 weeks after treatment ended?

Attrition Bias

Question 9. Did 85 percent or more of enrolled patients provide data at the time point of interest?
Question 10. Was there a 15 percent or less difference in completion rates in the study arms?

We categorized the risk of bias for complete wound healing in each study as "Low," "Medium," or "High" using the following method:

- Low potential for risk: No more than three "No" answers.
- Moderate potential for risk: four to seven "No" answers.
- High potential for risk: 8 to 10 "No" answers.

2. Data Organization and Presentation

a. Information Management

For Guiding Question 1, we categorized skin substitutes identified in the grey literature. We extracted information on product descriptions to determine distinguishing features of these products. For Guiding Question 2, we selected the Davison-Kotler classification system[22] as the basis for organizing the skin substitutes identified in Guiding Question 1. We used only the sections of the system appropriate for skin substitutes for chronic wounds since the original system also includes products solely intended for burns.

Results from the screening of clinical evidence from the published literature helped inform Guiding Questions 3, 4, and 6. Information on patient characteristics, wound treatments, and outcomes assessed are stratified by wound type. When available, results stratified by baseline wound size and duration are

presented. Studies are grouped by the Davison-Kotler classification (e.g., acellular dermal substitute), and a summary sentence for each included investigation was provided. Ongoing clinical trials sourced from the grey literature and included in the SEADS submission helped inform Guiding question 5. KI input on best practices helped inform Guiding Questions 6.

b. Data Presentation

A list of skin substitutes and ongoing trials, as well as data abstracted from clinical studies, are presented in evidence tables. Distinguishing features of skin substitute classifications and a summary of published evidence are displayed graphically in evidence maps.

Findings

Guiding Question 1: What products are commercially available in the United States that may be considered skin substitutes?

Key Points

- Our searches identified 76 skin substitute products that are sold in the United States (see Table 2).

For this report, we have not created a definition for a skin substitute product. Instead, we used the products listed under the Centers for Medicare & Medicaid Services (CMS) codes Q4101 to Q4204[27] as a starting point and looked for similar products to generate a list of products. We included only products primarily marketed for chronic wounds and commercially available in the United States. Some of the products that CMS listed were not included because they are not yet commercially available in the United States. We note that FDA does not refer to any product or class of products as "skin substitutes," and we are not proposing an official definition or classification system. The report includes many products cleared by the FDA as wound dressings via the 510(k) pathway which are not intended to treat wounds but only to cover wounds so that the natural healing process can take place.

Disclaimer: A skin substitute's commercial availability is not a reflection of its legal status. Manufacturers self-determine whether their human cells, tissues, or cellular or tissue-based product (HCT/P) can be marketed without FDA preapproval and often misunderstand or mischaracterize the criteria they must meet for the product to be regulated solely for communicable disease risk. See 21 CFR 1271.10(a). For more information, see "FDA Announces Comprehensive Regenerative Medicine Policy Framework."

Appendix D provides detailed product information.

Table 2. Products commercially available in the United States that may be considered skin substitutes

Product	Manufacturer	Manufacturer's Product Description[a]
Affinity® Human Amniotic Allograft	Organogenesis, Inc., Canton, MA, USA	Affinity is a fresh amniotic membrane aseptically processed and hypothermically preserved.
AlloPatch®	Musculoskeletal Transplant Foundation (dba MTF Biologics), Edison, NJ, USA	AlloPatch is an aseptically processed human reticular dermal tissue for use as a chronic or acute wound covering.

Product	Manufacturer	Manufacturer's Product Description[a]
AlloPatch® Pliable	Musculoskeletal Transplant Foundation (dba MTF Biologics)	AlloPatch Pliable is human reticular dermal tissue.
AlloSkin™ AC Acellular Dermal Matrix	AlloSource, Centennial, CO, USA	AlloSkin AC is a meshed dermis-only human skin graft.
AlloSkin™ RT	AlloSource	AlloSkin RT is a meshed human dermal graft.
AlloWrap®	AlloSource	AlloWrap is a human placental membrane.
AltiPlast®	Aziyo Biologics, Silver Spring, MD, USA	AltiPlast is a cryopreserved placental matrix derived from human amniotic and chorionic membranes.
AltiPly®	Aziyo Biologics	Lyophilized placental membrane.
AmnioBand® Allograft Placental Matrix	MTF Biologics	AmnioBand is an aseptically processed human allograft placental matrix composed of amnion and chorion for use as an acute or chronic wound covering.
Amnioexcel®	Integra LifeSciences Corp. acquired Derma Sciences, Plainsboro, NJ, USA	Amnioexcel is dehydrated human amnion-derived tissue allograft with intact extracellular matrix.
AmnioFill® Human Placental Tissue Allograft	MiMedx Group, Inc., Marietta, GA, USA	AmnioFill is a nonviable cellular tissue matrix allograft derived from human placental tissue.
AmnioFix® Amnion/Chorion Membrane Allograft	MiMedx Group	AmnioFix is an allograft composed of dehydrated human amnion/chorion membrane.
Amniomatrix® Human Amniotic Suspension Allograft	Integra LifeSciences acquired Derma Sciences	Amniomatrix is a cryopreserved suspension allograft derived from the amniotic membrane and components of the amniotic fluid.
Apligraf	Organogenesis, Inc., Canton, MA, USA	Apligraf is a living, bilayered skin substitute. The lower dermal layer combines bovine type 1 collagen and human fibroblasts (dermal cells). The upper epidermal layer is formed by human keratinocytes (epidermal cells).
Architect® stabilized collagen matrix	Harbor MedTech, Inc., Irvine, CA, USA	Architect is made from decellularized equine pericardial tissue.
Artacent® Wound	Tides Medical, Lafayette, LA, USA	Wound-specific, dual-layer amniotic tissue graft designed for enhanced efficacy and ease of use. Intended for chronic wounds.
Bio-ConneKt® Wound Matrix	MLM Biologics, Inc., Alachua, FL, USA	The bio-ConneKt Wound Matrix is composed of reconstituted type I collagen derived from equine tendon.
BioDFactor Viable Tissue Matrix	Integra LifeSciences, originally BioD, LLC	BioDFactor Viable Tissue Matrix is a flowable tissue allograft derived from morselized amniotic tissue and components of the amniotic fluid.
BioDFence®	Integra LifeSciences, originally BioD, LLC	BioDFence G3 and BioDDryFlex are membrane allografts derived from the human placental tissues.
Biovance® Amniotic Membrane Allograft	Alliqua Biomedical, Langhorne, PA, USA	Biovance is a decellularized, dehydrated human placental membrane with a preserved natural epithelial basement membrane and an intact extracellular matrix structure.
Cellesta™ Amniotic Membrane	Ventris Medical, Newport Beach, CA, USA	Cellesta Amniotic Membrane is a placental allograft product. The single-layered allografts are affixed to a poly mesh backing and can be sutured, glued, or laid over the desired tissue.
CollaWound collagen sponge	Collamatrix Co., Ltd., Miaoli County, Taiwan	CollaWound wound dressing is composed of cross-linked porous collagen matrix.
Coll-e-derm™	Parametrics Medical, Leander, TX, USA	Coll-e-derm is a human derived dermal allograft.
Cygnus® Amnion Patch Allografts	Vivex Biomedical, Atlanta, GA, USA	Cygnus is derived from human placental membrane.

Product	Manufacturer	Manufacturer's Product Description[a]
Cytal® wound matrix	Acell, Inc., Columbia, MD, USA	Cytal is composed of porcine urinary bladder matrix with an intact epithelial basement membrane.
DermACELL® Human Acellular Dermal Matrix. DermACELL AWM is intended for chronic wounds.	LifeNet Health, Virginia Beach, VA, USA	DermACELL is a human acellular dermal matrix.
Dermagraft	Organogenesis	Dermagraft is a cryopreserved human fibroblast derived dermal substitute, composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold.
Dermapure®	Tissue Regenix Group, San Antonio, TX, USA	DermaPure is a decellurized human dermis product.
DermaSpan™ Acellular Dermal Matrix	Zimmer Biomet. (manufactured by Biomet Orthopedics, Warsaw, IN, USA)	DermaSpan Acellular Dermal Matrix is derived from allograft human skin.
Dermavest® and Plurivest® Human Placental Connective Tissue Matrix	Aedicell, Inc., Honeoye Falls, NY, USA	Dermavest Human Placental Tissue Matrix is composed of human placental tissue.
Endoform™ dermal template	Hollister Wound Care, Libertyville, IL, USA	Endoform Dermal Template contains a naturally derived ovine collagen ECM that is terminally sterilized.
EpiCord®	MiMedx	EpiCord is a dehydrated, nonviable cellular umbilical cord allograft.
Epifix®	MiMedx	Epifix is a dehydrated human amnion/chorion membrane allograft.
Excellagen®	Taxus Cardium Pharmaceuticals Group, San Diego, CA, USA	Excellagen is collagen gel composed of formulated, 2.6% (26 mg/mL) fibrillar bovine dermal collagen (type 1) that is topically applied directly to the wound surface.
EZ Derm®	Mölnlycke Health Care, Norcross, GA, USA	EZ Derm is a porcine xenograft for partial skin loss injuries or as temporary cover.
FlōGraft® Amniotic Fluid-Derived Allograft	Applied Biologics, Scottsdale, AZ, USA	FlōGraft is chorion-free allograft composed of amnion and amniotic fluid derived from prescreened, live, healthy donors.
FlowerAmnioPatch™ and FlowerAmnioFlo™	Flower Orthopedics, Horsham, PA, USA	FlowerAmnioPatch is a dual-layer amniotic membrane allograft. FlowerAmnioFlo is a flowable amnion tissue allograft.
FlowerDerm™	Flower Orthopedics	FlowerDerm is a meshed dermis-only decellularized human skin graft.
GammaGraft™	Promethean LifeSciences, Inc., Pittsburgh, PA, USA	GammaGraft is an irradiated human skin allograft.
Geistlich Derma-Gide™	Geistlich Pharma North America Inc., Princeton, NJ, USA	Derma-Gide is a porcine, porous, resorbable, 3D matrix designed specifically for the management of wounds.
Genesis Amniotic Membrane	Genesis Biologics, Anaheim, CA, USA	Genesis Amniotic Membrane is derived from human placental membrane.
Grafix®	Osiris Therapeutics, Inc., Columbia, MD, USA	Grafix is a cryopreserved cellular placental membrane.
GrafixPL Prime	Osiris Therapeutics	GrafixPL Prime is a lyopreserved cellular placental amniotic membrane.
GraftJacket™ RTM	Wright Medical Group N.V., Memphis, TN, USA	GraftJacket Matrix is a human dermal collagen matrix
Helicoll™	EnColl Corp., Fremont, CA, USA	Helicoll is an acellular collagen matrix derived from bovine sources.
hMatrix® ADM	Bacterin International, Inc., Belgrade, MT, USA	hMatrix ADM is an allograft derived from donated human skin.

Product	Manufacturer	Manufacturer's Product Description[a]
Hyalomatrix® tissue reconstruction matrix	Anika Therapeutics, Bedford, MA, USA	Hyalomatrix is a nonwoven pad composed of a wound contact layer made of a derivative of hyaluronic acid in fibrous form with an outer layer composed of a semipermeable silicone membrane.
Integra® Bilayer Matrix Wound Dressing	Integra LifeSciences	Integra Bilayer Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone layer).
Integra® BioFix® Amniotic Membrane Allograft	Integra LifeSciences	Integra BioFix and Integra BioFix Plus are human tissue allografts derived from allogeneic dehydrated and decellularized amniotic membrane.
Integra® BioFix® Flow Placental Tissue Matrix Allograft	Integra LifeSciences	Integra BioFix Flow is derived from decellularized particulate human placental connective tissue matrix.
Integra Dermal Regeneration Template and Integra Omnigraft Regeneration Template	Integra LifeSciences	Integra Dermal Regeneration Template has 2 layers: a thin outer layer of silicone and a thick inner matrix layer of pure bovine collagen and glycosaminoglycan.
Integra® Flowable Wound Matrix	Integra LifeSciences	Integra Flowable Wound Matrix is composed of granulated cross-linked bovine tendon collagen and glycosaminoglycan.
Integra® Matrix Wound Dressing; originally Avagen wound dressing.	Integra LifeSciences	Integra Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan.
InteguPly®	Aziyo Biologics	InteguPly is human acellular dermis.
Interfyl™ Human Connective Tissue Matrix	Alliqua Biomedical, Langhorne, PA, USA	Interfyl is connective tissue matrix filler derived from human placenta.
Matrix HD® Allograft	RTI Surgical, Alachua, FL, USA	Matrix HD allograft is an acellular human dermis allograft.
MicroMatrix®	Acell	MicroMatrix is composed of a porcine-derived extracellular urinary bladder matrix.
Miroderm®	Miromatrix Medical, Inc., Eden Prairie, MN, USA	Miroderm is a noncross-linked acellular wound matrix derived from porcine liver
Neox® Wound Allografts	Amniox Medical, Inc., Miami, FL, USA	Neox Wound Matrix is preserved human umbilical cord and amniotic membrane.
NuShield®	Organogenesis, Inc.	NuShield is a dehydrated placental allograft.
Ologen™ Collagen Matrix	Aeon Astron Europe B.V.	Ologen Collagen Matrix is made of cross-linked lyophilized porcine type I atelocollagen (≥90%) and glycosaminoglycans (≤10%).
Omega3 Wound (originally Merigen wound dressing)	Kerecis, Arlington, VA, USA	Kerecis MariGen Wound Dressing is processed fish dermal matrix composed of fish collagen and is supplied as a sterile intact or meshed sheet.
Oasis® Wound Matrix	Smith & Nephew, Inc., Fort Worth, TX, USA	Oasis Matrix products are naturally derived scaffolds of ECM, composed of porcine small intestinal submucosa.
PalinGen® Membrane and Hydromembrane	Amnio Technology LLC, Phoenix, AZ, USA	PalinGen Membrane and Hydromembrane are human allografts processed from healthy placental tissue.
PriMatrix® Dermal Repair Scaffold	Integra LifeSciences	PriMatrix Dermal Repair Scaffold is derived from fetal bovine dermis.
Puracol® and Puracol® Plus Collagen Wound Dressings	Medline Industries, Northfield, IL, USA	Composed of 100% bovine collagen.
PuraPly® Antimicrobial (PuraPly AM) Wound Matrix (formally called FortaDerm)	Organogenesis, Inc.	PuraPly Antimicrobial Wound Matrix consists of a collagen sheet coated with 0.1% polyhex-methylenebiguanide hydrochloride.
Restorigin™ Amniotic Tissue Patches	Parametrics Medical, Leander, TX, USA	Restorigin Amniotic Tissue Patches is derived from human placenta.

Product	Manufacturer	Manufacturer's Product Description[a]
Restrata™	Acera Surgical, Inc., St. Louis, MO, USA	Restrata is a fully synthetic electrospun wound dressing composed of randomly oriented nanofibers
Revita®	StimLabs, LLC, Roswell, GA, USA	Revita is an intact human placental membrane allograft.
SkinTE™	PolarityTE, Salt Lake City, UT, USA	SkinTE is an entirely autologous product derived from a sample of the patient's skin.
Talymed®	Marine Polymer Technologies, Inc., Burlington, MA, USA	Talymed advanced matrix is composed of shortened fibers of poly-N-acetyl glucosamine isolated from microalgae.
TheraForm™ Standard/Sheet Absorbable Collagen Membrane	Sewon Cellontech Co., Seoul, Korea	TheraForm is a sterile, pliable, porous scaffold made of biocollagen
TheraSkin®	LifeNet Health (procurement and processing) Solsys Medical, Newport News, VA, USA (distribution)	TheraSkin is a human, living, split-thickness allograft.
WoundEx® Membrane and WoundEx Flow	Skye Biologics, Inc., El Segundo, CA, USA	WoundEx Membrane is a dehydrated amniotic membrane. WoundEx Flow is a flowable human placental connective tissue matrix.
Xwrap® Amniotic Membrane-Derived Allograft	Applied Biologics, Scottsdale, AZ, USA	Xwrap is a chorion-free amniotic membrane wrap, cover, or patch.

[a] The U.S. Government has not evaluated the product descriptions in this column.

Guiding Question 1 Overview

Our searches identified 76 products commercially available in the United States that may be considered skin substitutes.

Guiding Question 2: What classification systems have been developed to categorize skin substitutes? What are important skin substitute parameters and active components currently being used when classifying skin substitutes?

Key Points

- Some classification systems were based on the skin layers to be replaced and the source of material used in the product (human versus animal or synthetic) but did not distinguish between cellular and acellular products.
- Davison-Kotler et al.[22] proposed a system organized according to cellularity, layering, replaced region, material used, and permanence (see Figure 1). The authors consider cellularity the most important discriminator among skin substitutes since the presence of cells increases the rejection risk and manufacturing complexity. In this system, skin substitute products are divided first into acellular and cellular groups.
- Acellular dermal substitutes made from natural biological materials are the most common commercially available skin substitute product for treating or managing chronic wounds. This category includes decellularized donated human dermis (14 products identified, see Table 4), human placental membranes (28 products identified, see Table 5), and animal tissue (21 products identified, see Table 6). Fewer products are made from synthetic materials (2 products identified, see Table 7) or a combination of natural and synthetic

materials (2 products identified, see Table 8). A few skin substitute products are acellular replacements for both the epidermis and dermis (1 product identified, see Table 9).

- We identified only eight products that contain cells and would be classified in the cellular grouping (see Table 10, Table 11, Table 12, and Table 13).

The earliest classification systems used to categorize skin substitutes were based on the skin layers to be replaced. For example, in 2001, Balasubramani et al.[28] proposed a classification system with three categories or classes based on the skin's layers. Class I consisted of cultured epidermal equivalent only. Class II included dermal components from processed skin or fabricated with collagen and other ECM proteins. Class III included products with distinct epidermal and dermal components. This system does not distinguish between cellular and acellular products or the source of material used in the product (human vs. animal or synthetic).

Kumar proposed a three-category system in 2008 based on whether the skin substitute was temporary or durable.[29] Class I included temporary impervious dressing material, Class II included single-layer durable skin substitutes, and Class III included composite skin substitutes that replaced both dermal and epidermal layers.

Ferreria et al. proposed a more comprehensive classification system in 2011 based on three criteria: the skin layer to be replaced, the durability in the wound bed, and the origin of the grafting material.[21] Skin layer was divided into epidermal (E), dermal (D), and dermal/epidermal composites (C). Durability was divided into temporary (T) and permanent (P). Origin of grafting material was divided into biological (b), which includes human and animal, biosynthetic (bs), and synthetic (s).

In 2014, Nathoo et al. categorized skin substitutes based on their origin: xenografts (ECM material derived from an animal source), synthetic bilayers (collagen matrix with a layer of silicone), acellular allografts (decellularized donated human dermis), allogeneic living epidermal substitutes (neonatal keratinocytes are used to generate a living epidermis), allogeneic dermal substitutes (cell-based dermal substitute derived from newborn foreskin), composite allografts (collagen scaffold with cultured fibroblasts and a layer of human keratinocytes), and autologous cultured skin grafts (cultured autologous epithelial substitute).[20]

ASTM International published a "Standard Guide for Classification of Cellular and/or Tissue-Based Products (CTPs) for Skin Wounds" in 2016,[30] which stated, "CTPs are defined primarily by their composition and comprise cells and/or the extracellular components of tissue. CTPs may contain cells (viable or nonviable), tissues, proteins, and other materials for which there is a rationale for benefit beyond that achievable with conventional wound coverings. CTPs may additionally include synthetic components." The guide also has a classification system for CTPs based on four composition categories: biosynthetic, biosynthetic and animal based, non-living tissue based, and living cells biological. The nonliving tissue based category is further divided by source (human or animal), and the living cells biological category is divided by processing (minimal, cultured, and cultured and animal). Living cells are presumed to be human.

In 2018, Davison-Kotler et al. proposed a new skin substitute classification system that built on the older systems and corrected their shortcomings, particularly some confusing and nonintuitive categories (in some systems acellular and cellular products could be placed in the same category).[22] Davison-Kotler et al.'s new system organized skin substitutes according to cellularity, layering, replaced region, materials used, and permanence. The authors considered cellularity the most important discriminator among skin substitutes since the presence of cells increases the rejection risk and increases manufacturing complexity. Layering is either single or bilayer, with bilayer generally replacing both dermis and epidermis. Replaced region refers to

whether the product is intended to replace dermis, epidermis, or both. The product's composition determines which layers it is designed to replace. Materials used to produce the skin substitute are either natural (sourced from human or animal), synthetic, or both. Permanence is described as biodegradable (temporary) and nonbiodegradable (permanent). These parameters are used in a factorial design to produce a classification system that can be used for any new or old skin substitute. Figure 1 displays the classification pathway for acellular products. The pathway for cellular products is identical.

We have organized the 76 skin substitute products by Davison-Kotler et al.'s classification principles[22] and present them in this section. We used Acellular/Cellular, followed by Dermal and Epidermal/Dermal, and Source material (natural human, natural animal, and synthetic) in our organization scheme. We did not consider permanence because all the skin substitute products are biodegradable/temporary and contain no permanent nonbiodegradable components. For detailed information on each product, see Appendix D in Table D-1 to Table D-10.

Table 3 presents the ASTM International classification system along with their numbering system and category description, and the corresponding Davison-Kotler et al.'s classification for comparison.

Table 3. Comparison of ASTM International classification system for cellular and/or tissue-based products and Davison-Kotler classification system for skin substitutes

ASTM International Classification	Davison-Kotler et al. Classifications
6.1.1 Biosynthetic (partly synthesized or produced by living cells and partly chemically synthesized)	Acellular dermal replacement from synthetic materials (Table 7)
6.1.2 Biosynthetic and animal based	Acellular dermal replacement from synthetic and animal sources (Table 8)
6.1.3 Non-living Tissue based (acellular: free of intact cells and not carrying out any metabolic reactions. A scaffold made from biomaterials or made by extracting killed cells from tissue would be acellular)	Acellular
6.1.3.1 Human	Dermal replacement from donated human dermis (Table 4), Dermal replacement from human placental membrane (Table 5), Dermal replacement from human placental membrane for epidermis and dermis (Table 9)
6.1.3.2 Animal	Dermal replacement from animal tissue source (Table 6)
6.1.4 Living cells biological (synthesized or produced by living cells)	Cellular
6.1.4.1 Minimally processed	Dermal replacement from placental membrane (Table 10), or human skin (Table 12)
6.1.4.2 Cultured (cells propagated by cell culture)	Dermagraft (Table 11)
6.1.4.3 Cultured and Animal	Apligraf (Table 13)

Acellular Skin Substitutes

Acellular dermal substitutes made from natural biological materials are the most common commercially available skin substitute products for treating or managing chronic wounds.[3] This category includes decellularized donated human dermis (Table 4), human placental membranes (Table 5.), and animal tissue (Table 6.). Fewer products are made from synthetic materials (Table 7) or a combination of natural and synthetic materials (Table 8). A few skin substitute products are acellular replacements for both the epidermis and dermis (Table 9). Natural sources have the advantage of having a scaffold that is similar in composition and organization to native dermis.[24] While composed mostly of collagen, these natural materials contain glycosaminoglycans, proteoglycans, and glycoproteins to produce a scaffold similar to native

dermal tissue. Amniotic membranes contain large amounts of cytokines and growth factors, which may enhance chronic wound healing.

The major disadvantage of natural products is the rejection risk if cell remnants are not removed during processing.[24] Processing must be sufficient to remove immunogenic components without destroying the ECM's native structure. Different processing methods lead to different means of preserving the tissues. Some products must be stored frozen and then thawed before use, while other products can be stored at room temperature. Shelf life also varies across products. Tissues obtained from human donors also have the risk of infectious disease transmission; therefore, industry standards developed by FDA[31] and the American Association of Tissue Banks are used to minimize and eliminate this risk.[32]

The human dermis is composed mostly of collagen fibers along with elastic fibers secreted by fibroblasts. Together with water and large proteoglycan molecules, these proteins make up the ECM. Human dermal skin substitutes provide a structurally intact, natural, three-dimensional ECM.[23,24] The natural structure provides the right pore size for host cell recruitment, vascularization, and the formation of a new dermis. The ECM also contains bioactive compounds, including collagen and various growth factors.[25] Dermal substitutes are prone to degradation by MMP secreted by fibroblasts in the wounds. Some dermal substitutes are chemically cross-linked to decrease degradation, but this may have detrimental effects on wound healing. Harsh processing will not only remove cell remnants, but also damage or destroy the extracellular structure. Sterilization with ethylene oxide or gamma-irradiation may induce structural changes as well. Various manufacturers of acellular dermal skin substitutes compete based on their proprietary processing technique and maintenance of the ECM.[33] Products derived from donated human dermis are presented in Table 4.

Table 4. Acellular/dermal replacement from donated human dermis

Product	Manufacturer
AlloPatch®	Musculoskeletal Transplant Foundation (dba MTF Biologics) Edison, NJ, USA
AlloPatch Pliable	
Alloskin™ AC Acellular Dermal Matrix	AlloSource, Centennial, CO, USA
AlloSkin RT	AlloSource
Coll-e-derm™	Parametrics Medical, Leander, TX, USA
DermACELL® Human Acellular Dermal Matrix and DermACELL AWM	LifeNet Health, Virginia Beach, VA, USA
Dermapure®	Tissue Regenix Group, San Antonio, TX, USA
DermaSpan™ Acellular Dermal Matrix	Zimmer Biomet (manufactured by Biomet Orthopedics, Warsaw, IN, USA)
FlowerDerm™	Flower Orthopedics, Horsham, PA, USA
GammaGraft™	Promethean LifeSciences, Inc., Pittsburgh, PA, USA
GraftJacket™ RTM	Wright Medical Group N.V., Memphis, TN, USA
hMatrix® ADM	Bacterin International, Inc., Belgrade, MT, USA
InteguPly®	Aziyo Biologics, Silver Spring, MD, USA
Matrix HD® Allograft	RTI Surgical, Alachua, FL, USA

Commercially available human placental membranes are now being used for management of chronic wounds. An earlier AHRQ evidence report on skin substitutes did not consider amniotic membrane products.[1] The amnion/chorion membranes or separate amnion are obtained from the placenta of screened donors after caesarean delivery. The membranes have an ECM rich in collagen as well as growth factors.[2] Rejection is not a risk with placental tissue. Antibacterial and pain-reduction properties have also been reported. Processing these tissues is necessary to remove bloodborne pathogens and stabilize the membranes for storage and off-the-shelf use. Harsh processing as with donated human dermis may damage the biological activity of placental

membranes.[34] Placental membranes are now available in dehydrated or cryopreserved states for application to chronic wounds.[3] Products derived from human placental membrane are presented in Table 5.

Table 5. Acellular/dermal replacement from human placental membrane

Product	Manufacturer
AlloWrap®	AlloSource, Centennial, CO, USA
AltiPlast®	Aziyo Biologics, Silver Spring, MD, USA
AmnioBand®	Musculoskeletal Transplant Foundation (dba MTF Biologics), Edison, NJ, USA
Amnioexcel®	Integra LifeSciences Corp. acquired Derma Sciences, Plainsboro, NJ, USA
AmnioFill® Human Placental Tissue Allograft	MiMedx Group, Inc., Marietta, GA, USA
AmnioFix® Amnion/Chorion Membrane Allograft	MiMedx Group
Amniomatrix® Human Amniotic Suspension Allograft	Integra LifeSciences acquired Derma Sciences
Artacent® Wound	Tides Medical, Lafayette, LA, USA
BioDFactor® Viable Tissue Matrix	Integra LifeSciences, originally BioD, LLC
Biodfence®	Integra LifeSciences, originally BioD
Biovance® Amniotic Membrane Allograft	Alliqua Biomedical, Langhorne, PA, USA
Cellesta Amniotic Membrane	Ventris Medical, Newport Beach, CA, USA
Cygnus® Amnion Patch Allografts	Vivex Biomedical, Atlanta, GA, USA
Dermavest® and Plurivest® Human Placental Connective Tissue Matrix	Aedicell, Inc., Honeoye Falls, NY, USA
EpiCord®	MiMedx, Marietta, GA, USA
Epifix®	MiMedx
FlowerAmnioPatch™ and FlowerAmnioFlo™	Flower Orthopedics, Horsham, PA, USA
Genesis Amniotic Membrane	Genesis Biologics, Anaheim, CA
Integra® BioFix® Amniotic Membrane Allograft	Integra LifeSciences
Integra® BioFix® Flow Placental Tissue Matrix Allograft	Integra LifeSciences
Interfyl™ Human Connective Tissue Matrix	Alliqua Biomedical
Neox® Wound Allografts	Amniox Medical, Inc., Miami, FL, USA
NuShield®	Organogenesis, Inc., Canton, MA, USA
PalinGen® Membrane & Hydromembrane	Amnio Technology LLC, Phoenix, AZ, USA
Restorigin™ Amniotic Tissue Patches	Parametrics Medical, Leander, TX, USA
Revita®	StimLabs, LLC, Roswell, GA, USA
WoundEx® Membrane and WoundEx Flow	Skye Biologics, Inc., El Segundo, CA, USA
Xwrap® Amniotic Membrane-Derived Allograft	Applied Biologics, Scottsdale, AZ, USA

Several skin substitute products are derived from animal sources. Porcine-derived small intestinal submucosa, porcine urinary bladder matrix, bovine dermis, equine pericardium, and sheep tissue are processed for use as skin substitutes because of their type 1 collagen content. Type 1 collagen is the primary collagen found in skin and provides tensile strength and support. It stretches without breaking. Integra bilayer wound matrix (Integra LifeSciences, Plainsboro, NJ, USA) contains cross-linked bovine collagen, glycosaminoglycans, and a synthetic silicone layer. Oasis® wound matrix (Smith & Nephew, Inc., Fort Worth, TX, USA) is derived from porcine small intestinal submucosa. Primatrix® (Integra LifeSciences) uses fetal bovine dermis as a source of type III collagen. Type III collagen forms reticular fibers, which make a fine mesh network in organs, such as the liver. Some patients may have an allergic reaction to animal-sourced products. Products derived from animal tissue are presented in Table 6.

Table 6. Acellular/dermal replacement from animal tissue source

Product	Manufacturer	Source
Architect® stabilized collagen matrix	Harbor MedTech, Inc., Irvine, CA, USA	Decellularized equine pericardial tissue
Bio-ConneKt® Wound Matrix	MLM Biologics, Inc., Alachua, FL, USA	Reconstituted collagen derived from equine tendon
CollaWound collagen sponge	Collamatrix Co., Ltd., Miaoli County, Taiwan	Porcine collagen
Cytal® wound matrix	Acell, Inc., Columbia, MD, USA	Porcine urinary bladder matrix
Endoform™ dermal template	Hollister Wound Care, Libertyville, IL, USA	Ovine collagen
Excellagen®	Taxus Cardium Pharmaceuticals Group, San Diego, CA, USA	Bovine dermal collagen
EZ Derm®	Mölnlycke Health Care, Norcross, GA, USA	Porcine dermis
Geistlich Derma-Gide™	Geistlich Pharma North America Inc., Princeton, NJ., USA	Porcine tissue
Helicoll™	EnColl Corp., Fremont, CA, USA	Bovine collagen
Integra® Matrix Wound Dressing; originally Avagen wound dressing.	Integra LifeSciences Corp., Plainsboro, NJ, USA	Bovine tendon collagen and glycosaminoglycan
Integra Flowable Wound Matrix	Integra LifeSciences Corp.	Granulated cross-linked bovine tendon collagen and glycosaminoglycan
MicroMatrix®	ACell	Porcine urinary bladder matrix
Miroderm®	Miromatrix Medical, Inc., Eden Prairie, MN, USA	Porcine liver
Ologen™ Collagen Matrix	Aeon Astron, Europe B.V.	Porcine type I atelocollagen and glycosaminoglycans
Kerecis ™ Omega3 Wound (originally Merigen wound dressing)	Kerecis, Arlington, VA, USA	Fish dermal matrix composed of fish collagen
Oasis® Wound Matrix	Smith & Nephew, Inc., Fort Worth, TX, USA	Porcine small intestinal submucosa
PriMatrix® Dermal Repair Scaffold	Integra LifeSciences Corp.	Fetal bovine dermis
Puracol® and Puracol® Plus Collagen Wound Dressings	Medline Industries, Northfield, IL, USA	Bovine collagen
PuraPly® Antimicrobial (PuraPly® AM) Wound Matrix (formally called FortaDerm)	Organogenesis, Inc., Canton, MA, USA	Porcine intestinal collagen
Talymed®	Marine Polymer Technologies, Inc., Burlington, MA, USA	Fibers of poly-N-acetyl glucosamine isolated from microalgae
TheraForm™ Standard/Sheet Absorbable Collagen Membrane	Sewon Cellontech Co., Seoul, Korea	Porcine collagen

Some skin substitute products are made from synthetic material that mimics skin properties. Hyalomatrix® tissue reconstruction matrix (Anika Therapeutics, Bedford, MA, USA) is a nonwoven pad composed of a hyaluronic acid derivative in fibrous form with an outer layer composed of a semipermeable silicone. Restrata™ (Acera Surgical, Inc., St. Louis, MO, USA) provides a porous scaffold made of bioabsorbable polyglactin 910 and polydiaxonone. Some products, such as Integra Bilayer Matrix Wound Dressing, are a combination of animal-sourced collagen and synthetic material. Integra Bilayer Matrix Wound Dressing is composed of cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone layer). Products derived from synthetic material are presented in Table 7, and products derived from natural and synthetic sources are presented in Table 8. We identified one acellular product designed to replace both the epidermis and dermis. AltiPly® (Aziyo Biologics, Silver Spring, MD, USA) derived from placental membranes maintains the outer basement membrane and an epithelial layer scaffold to promote reepithelialization (see Table 9).

Table 7. Acellular/dermal replacement from synthetic materials

Product	Manufacturer
Hyalomatrix® tissue reconstruction matrix	Anika Therapeutics, Bedford, MA, USA
Restrata™	Acera Surgical, Inc., St. Louis, MO, USA

Table 8. Acellular/dermal replacement from combined natural and synthetic materials

Product	Manufacturer	Source
Integra® Bilayer Matrix Wound Dressing	Integra LifeSciences Corp., Plainsboro, NJ, USA	Cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone layer).
Integra Dermal Regeneration Template and Integra Omnigraft Regeneration Template	Integra LifeSciences	Cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone layer).

Table 9. Acellular/epidermal and dermal replacement from human placental membrane

Product	Manufacturer
AltiPly®	Aziyo Biologics, Silver Spring, MD, USA

Cellular Skin Substitutes

Our examination of the commercially available skin substitute products found that only eight contain viable cells that the manufacturers believe provide a unique benefit that enhances wound healing. Four amniotic membrane-derived products claim to have viable cells: Affinity® human amniotic allograft, FlōGraft® amniotic fluid-derived allograft, Grafix®, and GrafixPL Prime (Table 10). Dermagraft (Table 11) is a human fibroblast-derived dermal substitute. Fibroblast cells from human foreskin are seeded onto a bioabsorbable polyglactin mesh scaffold. They proliferate and secrete cytokines to form a metabolically active dermal substitute. Dermagraft is used to treat diabetic foot ulcers greater than 6-weeks duration.[3,20] TheraSkin (Table 12) is a cryopreserved human, living, split-thickness allograft that contains fibroblasts and keratinocytes. The tissue is procured within 24-hours postmortem from an organ donor. When procured, the allograft is washed with antibiotics and cryopreserved. According to the manufacturer, living cells survive through procurement, cryopreservation, and thawing.[35] According to the manufacturer, SkinTE™ (Table 12) is an autologous product derived from a sample of the patient's skin. Apligraf (Table 13) is a bioengineered skin substitute with two layers.[3,20] The dermal layer is type I bovine collagen gel seeded with living human neonatal fibroblasts. The epidermis is neonatal keratinocytes. The cells actively secrete growth factors, cytokines, and ECM proteins. Apligraf is used to treat diabetic foot ulcers and venous leg ulcers.

Table 10. Cellular/dermal replacement from human placental membrane

Product	Manufacturer
Affinity® Human Amniotic Allograft	Organogenesis, Inc., Canton, MA, USA
FlōGraft® Amniotic Fluid-Derived Allograft	Applied Biologics, Scottsdale, AZ, USA
Grafix®	Osiris Therapeutics, Inc., Columbia, MD, USA
GrafixPL Prime	Osiris Therapeutics

Table 11. Cellular/dermal replacement from combined natural and synthetic materials

Product	Manufacturer
Dermagraft®	Organogenesis, Inc., Canton, MA, USA

Table 12. Cellular/epidermal and dermal replacement from donated human dermis or autologous skin sample

Product	Manufacturer
SkinTE™	PolarityTE, Salt Lake City, UT, USA
TheraSkin®	LifeNet Health, Virginia Beach, VA, USA (procurement and processing) Solsys Medical, Newport News, VA, USA (distribution)

Table 13. Cellular/epidermal and dermal replacement from combined human and animal sources

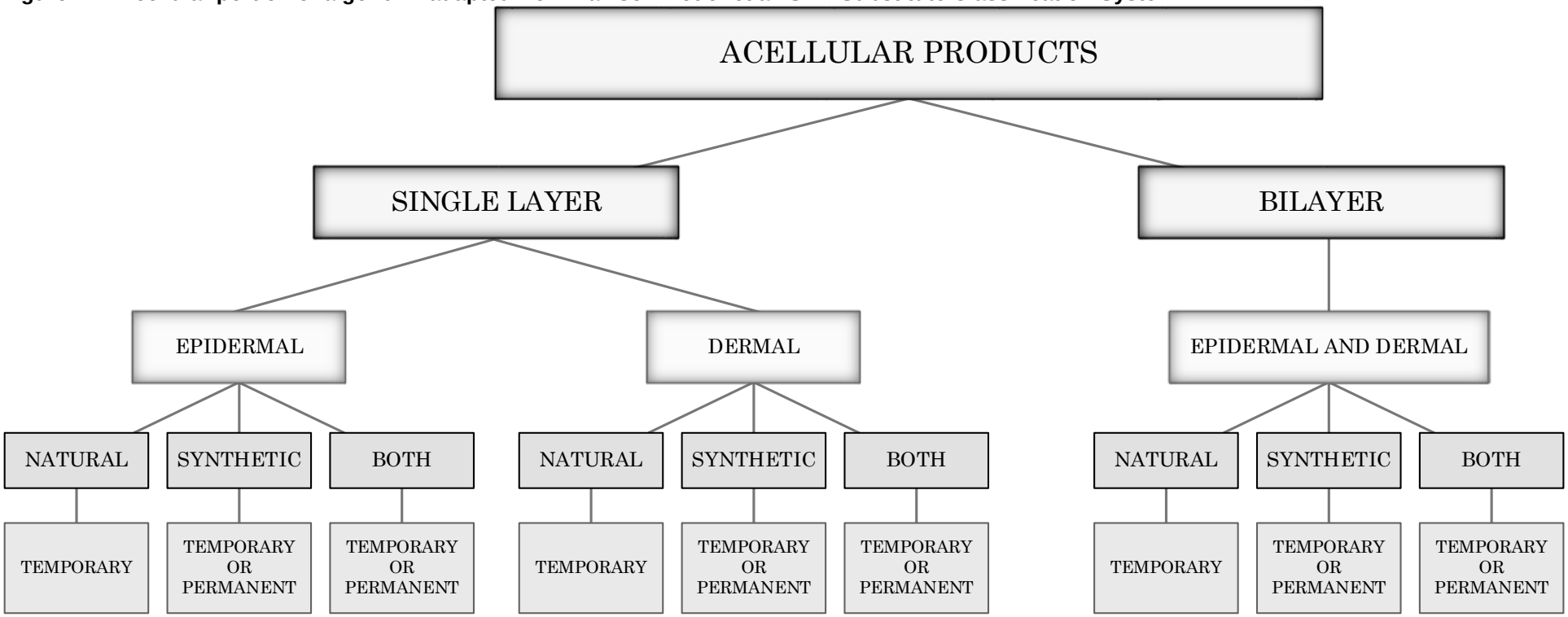
Product	Manufacturer
Apligraf®	Organogenesis, Inc., Canton, MA, USA

Guiding Question 2 Overview

The skin substitute classification system proposed by Davison-Kotler et al.[22] emphasizes cellularity as the primary discriminator to group these products. Products are divided into groups that contain cells (cellular) and those that do not (acellular) followed by the skin being replaced (epidermal, dermal, or both) and the source of the material used to create the product (natural, synthetic, or both). Figure 1 depicts the acellular portion of the Davison-Kotler et al. classification pathway. The cellular pathway is identical. We divided acellular and cellular skin substitute products according to whether they replaced just the dermis or the dermis and epidermis. No skin substitute products replace only the epidermis. We then grouped products according to their source (natural human, natural animal, and synthetic). We split Davison-Kotler's natural source group into natural human and natural animal. Using this modification to the Davison-Kotler et al. classification scheme, we identified donated human dermis (14 products), human placental membranes (28 products), animal tissue sources (21 products), synthetic sources (2 products), and a combination of natural and synthetic materials (2 products) as acellular dermal substitutes. One product was an acellular replacement for both epidermis and dermis.

Only eight products contained cells and would be considered in the cellular pathway of the Davison-Kotler et al. classification. Four amniotic membrane-derived products claim to have viable cells. The other four are Dermagraft (four amniotic membrane-derived products claim to have viable cells), TheraSkin (cryopreserved human, living, split-thickness allograft), SkinTE (derived from an autologous skin sample), and Apligraf (bioengineered skin substitute with neonatal keratinocyte epidermis and a type I bovine collagen dermis).

Figure 1. Acellular portion of algorithm adapted from Davison-Kotler et al. Skin Substitute Classification System*



* The pathway for cellular products is identical.

Adapted from a figure from Davison-Kotler E, Sharma V, Kang NV, et al. A universal classification system of skin substitutes inspired by factorial design. Tissue Eng Part B Rev. 2018.[22]

Guiding Question 3: What are the study design characteristics (such as those listed below) in each included investigation for each chronic wound type?)

- Comparator to skin substitute.
- 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).
- 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).
- Patient characteristics of enrollees including at least age, gender, general health (e.g., status of HbA1c, diabetes, peripheral vascular disease, obesity, smoking, renal), and prior and concurrent wound treatments.
- Wound characteristics of enrollees including at least wound type, wound size/depth/duration/severity, vascular status, and infection status.
- Basic study design and conduct information including at least method of patient enrollment, care setting, and use of run-in period.
- Definition of wound characteristics: definition of "failure to heal" and definition of a successfully healed wound.
- Method of applying skin substitutes including provider, frequency of application, definition of standard of care, and handling of infections.
- Measurement and assessment methods including method of assessment(s), frequency and time points for assessment(s), and blinding of assessors.
- Statistical methods including power calculations, intent-to-treat analysis for studies designed to test superiority, and handling of dropouts.

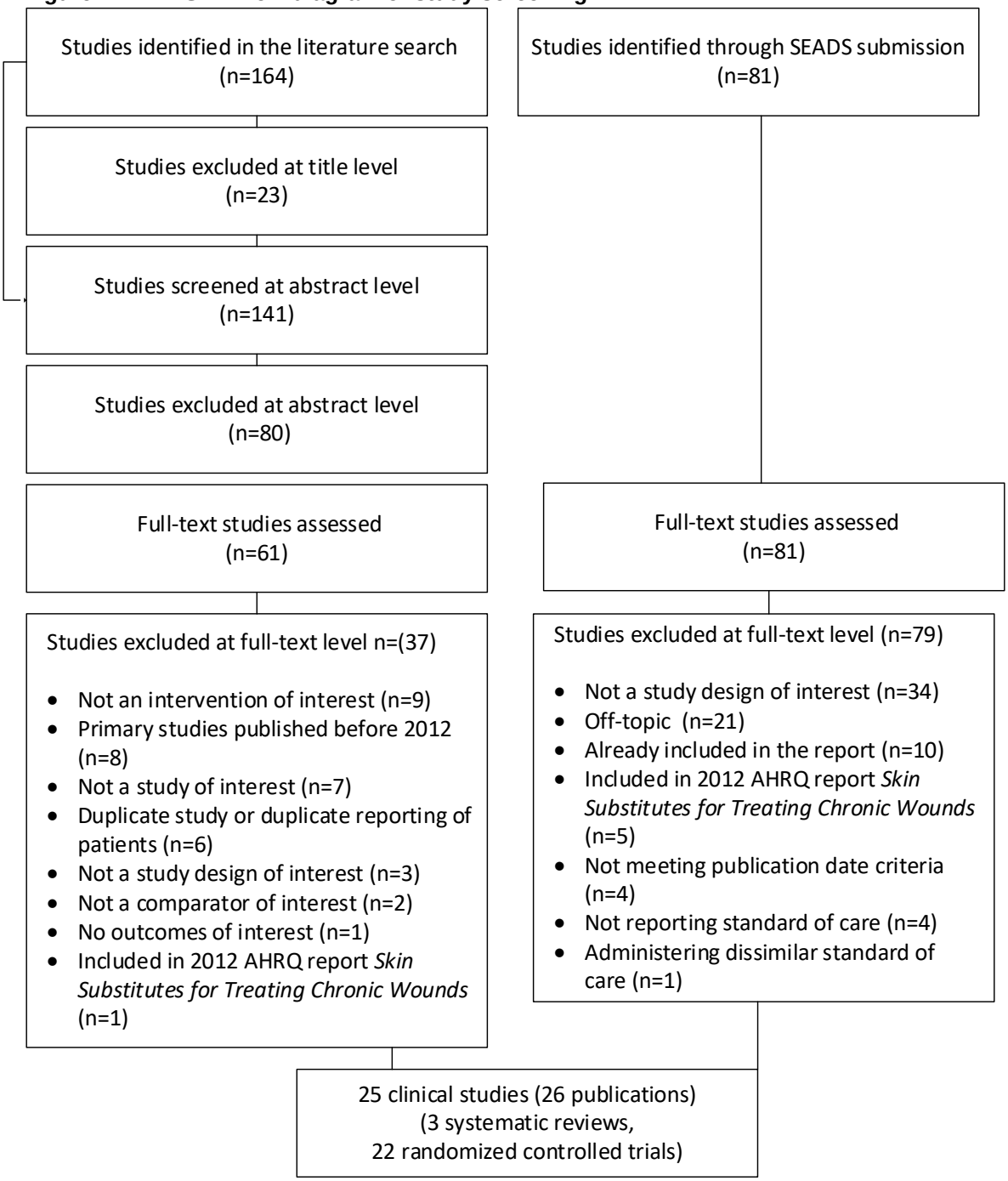
Our search of the published literature identified 164 potentially relevant studies. We excluded 23 articles at title screening as irrelevant to skin substitutes or chronic wound healing. Of the 141 remaining articles, we excluded 80 articles at the abstract level for reasons including not addressing a guiding question, not a study design of interest (e.g., retrospective comparative), and study protocol. Of the 61 remaining articles, we excluded 37 studies at the full-text level. Studies were excluded for including products that are not available in the United States and duplicate studies or duplicate reporting of patients. See Appendix B for a list of studies organized by reason for exclusion.

We received scientific packets from nine manufacturers during the SEADS submission period (March 25 to April 29, 2019). Submitters included ACELL, Inc., Kerecis Limited, LifeNet Health, MiMedx, Organogenesis, Osiris Therapeutics, Inc., PolyMedics Innovations GmbH, SolSys Medical LLC, and Smith & Nephew. Of the 103 submissions, 81 were clinical studies. Two studies (Serena 2019,[36] Bianchi 2019[37]) met protocol inclusion criteria (see Table 1) and were included, while 79 studies did not meet inclusion criteria and were excluded. Reasons for exclusion (see Table 1) included not a study design of interest (34 studies), not a topic of interest (21 studies), already included in the report (10 studies), not meeting publication date criteria (9 studies), not reporting standard of care (4 studies), and administering dissimilar standard of care (1 study). Irrelevant study designs included case series (17 studies); case reports (7 studies); retrospective comparison studies based on registries that did not report methodolgy

related to patient selection, patient care across wound care centers, including standard of care, handling of missing data, or qualifications of wound care centers (6 studies); not peer-reviewed publications (3 studies); and single arm, open-label extension of a RCT (1 study). Of 9 studies not meeting publication date criteria, 5 studies were included in the 2012 AHRQ report *Skin Substitutes for Treating Chronic Wounds*, and 4 studies were published from 2006 to 2011.

See Figure 2 for a PRISMA flow diagram of our study screening.

Figure 2. PRISMA flow diagram of study screening



Key Points

- Of the 76 commercially available skin substitutes, three systematic reviews and 22 RCTs (23 publications) examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers.
- Three systematic reviews examined the use of amniotic membranes and acellular dermal matrices (ADMs) in diabetic foot ulcers. Thirteen primary studies examined nine distinct skin substitutes. Most studies enrolled fewer than 25 patients per arm and measured outcomes up to 16 weeks.
- Twenty-two RCTs examined 16 distinct skin substitutes (7 skin substitutes not examined in the systematic reviews) in diabetic foot ulcers (15 studies), pressure ulcers (1 study), and venous leg ulcers (6 studies). Comparators were standard of care (16 studies) and another skin substitute (6 studies).
- Of the 16 distinct skin substitutes examined in 22 RCTs, seven skin substitutes were examined in more than one study. One skin substitute (EpiFix[38-42]) was examined in five studies. One skin substitute (Dermagraft[43-46]) was examined in four studies. Five skin substitutes (Grafix/GrafixPrime,[44,47] MatriStem Wound Matrix/MatriStem Micromatrix,[46,48] Apligraf,[35,41] TheraSkin,[35,45] DermACELL[49,50] were examined in two studies each.
- Eligibility criteria in 22 RCTs were most commonly reported as a noninfected debrided wound of at least 4-weeks duration, with a wound size of 1 cm^2 to 25 cm^2. Conditions such as uncontrolled diabetes (HbA1c >12%), morbid obesity, peripheral vascular disease, severe malnutrition, severe liver disease, and severe renal disease were excluded.
- Most studies enrolled fewer than 60 patients per arm. Twenty (90%) studies were manufacturer-funded (one study did not report funding,[41] and one study reported no funding[35]). Most studies were conducted in U.S. wound care centers.
- Fourteen (64%) RCTs reported participants' race. Thirteen studies (59%) enrolled ≥70 percent white/Caucasian patients, while one study enrolled 55 percent white and 45 percent black patients.[45] Eight (36%) studies reported enrolling Hispanic/Latino individuals.
- Our risk-of-bias analysis indicated that 50 percent and 59 percent of included studies had more than a 15 percent difference between study arms in baseline mean wound size (range up to 53.5 cm^2) and baseline mean wound duration (range up to 479 weeks), respectively.
- Successful wound closure was mostly described as 100 percent reepithelialization without drainage or dressing.

We identified three systematic reviews[51-53] and 22 RCTs[35,36,38-50,54-60] that addressed Guiding Question 3. Diabetic foot ulcers were examined in all three reviews and 15 RCTs,[36,39,41,42,44-48,50,54-56,59,60] pressure ulcers were examined in one RCT,[58] while venous leg ulcers were examined in six RCTs (7 publications).[35,37,38,40,43,49,57] We did not identify any relevant studies examining skin substitutes in arterial leg ulcers. We also did not identify any studies examining skin substitutes classified under the modified Davison-Kotler system[22] as acellular epidermal, acellular epidermal and dermal, and cellular epidermal. We present below study design characteristics of all included studies.

Systematic Reviews

Findings from 2012 Technology Assessment

In the 2012 AHRQ report *Skin Substitutes for Treating Chronic Wounds*, we identified 57 skin substitute products available in the United States that were used to manage or treat chronic wounds. Skin substitutes were organized into four groups: human-derived products, human/animal-derived products, animal-derived products, and synthetic products. At the time, no placenta-based skin substitute products were being marketed for chronic wound care. Three years after our report was published, Brantley and Verla reported 16 commercially available placental membrane products for treating chronic wounds.[61] They also noted that "Most commercial placental membranes do not have randomized, controlled clinical data, and existing data are limited to case studies presented in companies' marketing materials and/or website."

In the 2012 report, we identified 18 RCTs examining only seven of the skin substitute products. Apligraf was examined in three studies, TheraSkin in one study, Dermagraft in five studies, Graftjacket in three studies, Hyalograft 3D in two studies, Oasis Wound Matrix in five studies, and Talymed poly-N-acetyl glucosamine in one study (an Apligraf versus TheraSkin study and an Oasis Wound Matrix versus Dermagraft study have been double-counted). Twelve of the studies examined diabetic foot ulcers, and six studies examined vascular leg ulcers. None of the RCTs had a high risk of bias, but no studies reported blinding of the person assessing wound healing. All studies defined healing as full wound epithelialization with no drainage. Based on this outcome, most studies reported significantly more healed wounds in the patients treated with skin substitutes than standard of care when measured between 8 and 20 weeks, but the reported results varied widely across studies (see Table 14). The two studies comparing different skin substitutes reported no significant differences in wound healing rate.

Our 2012 evaluation of the clinical literature indicated that studies comparing the efficacy of skin substitutes to that of alternative wound care approaches were few, applied mainly to generally healthy patients, and examined only a small portion of the skin substitute products available in the United States at that time. In the report, we suggested that additional studies of skin substitutes for chronic wound care would be helpful to provide treatment data for many of the other skin substitute products, to allow better comparisons between wound care products, and to provide better information on wound recurrence when using skin substitute products.

Table 14. RCTs included in 2012 AHRQ report *Skin Substitutes for Treating Chronic Wounds*: Results for complete wound healing[1]

Study	Wound Type	Skin Substitute	Comparison	Number of Patients in Study	Difference in Rate of Wounds Healed (Skin Substitute–Comparator)	p-Value[a]	Relative Risk for Complete Wound Healing (95% CI) for Skin Substitute vs. Comparator[a]
DiDomenico et al. 2011[62]	DFU	Apligraf	TheraSkin	28	Healed at 12 weeks 41%-67%=-26%	NS (p=0.21)	0.66 (0.33 to 1.30)
Landsman et al. 2008[63]	DFU	Oasis Wound Matrix	Dermagraft	26	Healed at 12 weeks 77%-85%=-8%	NS (p=0.62)	0.91 (0.62 to 1.33)
Reyzelman et al. 2009[64]	DFU	GraftJacket acellular matrix	Moist wound therapy with alginates, foams, hydrocolloids, or hydrogels	85	Healed at 12 weeks 70%-46%=24%	0.03	1.51 (1.02 to 2.22)
Brigido 2006[65]	DFU	GraftJacket acellular matrix	Weekly debridement, Curasol wound hydrogel and gauze dressing	28	Healed at 12 weeks 57%-7%=50%	0.001	8.00 (1.15 to 55.80)
Niezgoda et al. 2005[66]	DFU	Oasis Wound Matrix	Regranex Gel (contains platelet-derived growth factor)	98	Healed at 12 weeks 49%-28%=21%	NS (p=0.06)	1.75 (0.94 to 3.26)
Edmonds 2009[67]	DFU	Apligraf	Nonadherent dressing	72	Healed at 12 weeks 52%-26%=26%	0.03	1.96 (1.05 to 3.66)
Marston et al. 2003[68]	DFU	Dermagraft	Saline-moistened gauze	245	Healed at 12 weeks 30%-18%=12%	0.03	1.64 (1.03 to 2.62)
Naughton et al. 1997[69]	DFU	Dermagraft	Saline-moistened gauze	109	Healed at 12 weeks 39%-32%=7%	NS (p=0.28)	1.21 (0.86 to 1.72)
Gentzkow et al. 1996[70]	DFU	Dermagraft	Saline-moistened gauze	50	Healed at 12 weeks[b] 30%-8%=22%	0.04	1.93 (0.49 to 7.59)
Veves et al. 2001[71]	DFU	Graftskin	Saline-moistened gauze	208	Healed at 12 weeks 56%-38%=18%	0.01	1.50 (1.11 to 2.04)
Uccioli et al. 2011[72]	DFU	Hyalograft 3D autograft/LasersSkin	Nonadherent paraffin gauze	160	Healed at 12 weeks 24%-21%=3%	NS (p=0.64)	1.15 (0.64 to 2.04)
Caravaggi et al. 2003[73]	DFU	Hyalograft 3D autograft/Lasers Skin	Nonadherent paraffin gauze	79	Healed at 11 weeks 65%-50%=15%	NS (p=0.17)	1.30 (0.88 to 1.93)
Falanga et al. 1998[74]	Leg, Venous	Apligraf and elastic compression bandage	Compression therapy with a Unna boot and elastic compression bandage	275	Healed at 12 weeks[c] 53%-22%=31%	<0.001[a]	2.38 (1.67 to 3.39)

Study	Wound Type	Skin Substitute	Comparison	Number of Patients in Study	Difference in Rate of Wounds Healed (Skin Substitute–Comparator)	p-Value[a]	Relative Risk for Complete Wound Healing (95% CI) for Skin Substitute vs. Comparator[a]
Krishnamoorthy et al. 2003[75]	Leg, Venous	Dermagraft plus multilayered compression bandage therapy (Profore™)	Multilayered compression therapy	52	Healed at 12 weeks 28%-15%=13%[c]	NS (p=0.30)[c]	1.83 (0.47 to 7.21)[c]
Romanelli et al. 2010[76]	Leg, Mixed	Oasis Wound Matrix	Petrolatum-impregnated gauze	48	Healed at 8 weeks[d] 80%-65%=15%	NS (p=0.25)[d]	1.23 (0.86 to 1.75)
Romanelli et al. 2007[77]	Leg, Mixed	Oasis Wound Matrix	Hyaloskin (contains hyaluronan)	54	Healed at 16 weeks 83%-46%=37%	0.001	1.91 (1.16 to 3.14)
Mostow et al. 2005[78]	Leg, Venous	Oasis Wound Matrix with compression	Compression alone	120	Healed at 12 weeks 55%-34%=21%	0.022	1.59 (1.04 to 2.42)
Kelechi et al. 2012[79]	Leg, Venous	Talymed poly-N-acetyl glucosamine (pGlcNAc) with compression	Nonadherent absorptive primary dressing with compression	82	Healed at 20 weeks[e] 66%-45%=21%	NS (p=0.10)	1.47 (0.88 to 2.46)[e]

DFU=diabetic foot ulcer; HYAFF=Benzyl esters of hyaluronic acid; VLU=venous leg ulcer; NS=not statistically significant

[a] Calculated by ECRI Institute; p values are for Risk Difference.

[b] Calculated for all three active groups combined vs. control. A dose-response was noted with more frequent application of Dermagraft associated with higher percentage of patients with complete wound healing.

[c] Complete healing at 12 weeks calculated from Figure 1 C in Brigido (2006) and from Table 2 and Figure 5 in Falanga (1998).

[d] The publication states that the p-value for this comparison was "P<0.05"; however, we calculate a risk difference of 0.15 (-0.10 to 0.40), p=0.25, a nonsignificant result. The authors state they used "analysis of variance for multiple comparisons" but do not discuss variables by which the data might have been adjusted.

[e] All 3 Talymed groups combined vs. placebo; for groups receiving Talymed every other week to every third week vs. control, the difference was significant at the p=0.016 level, and the relative risk was 1.69 (1.01 to 2.83).

Systematic Reviews Published After 2012

Three systematic reviews examined use of skin substitutes in diabetic foot ulcers.[51-53] Two reviews examined amniotic membranes,[51,53] while one examined ADM.[52] Nine studies examined acellular dermal substitutes versus standard of care, one study examined a cellular dermal substitute versus standard of care, one study examined two acellular dermal substitutes, and two studies examined an acellular dermal substitute versus a cellular epidermal and dermal substitute. Skin substitutes examined in these reviews included AlloPatch Pliable, AmnioBand®, AmnioExcel®, Apligraf®, DermACELL®, EpiFix®, Grafix®, GraftJacket®, and Integra® Dermal Regeneration Template. See Table 15 for additional details on the primary studies included in these reviews.

Paggiaro et al. 2018[51] included six RCTs of amniotic membranes used to treat diabetic foot ulcers published from 2013 to 2017 and conducted in the United States. One RCT each evaluated Grafix, AmnioBand, EpiFix, and AmnioExcel. One study examined weekly versus biweekly EpiFix, while one three-arm RCT examined EpiFix, Apligraf, and standard of care. Enrollment ranged from 25 to 100 patients; 66 percent of studies enrolled fewer than 25 patients per arm. Followup was 6 weeks and 12 weeks. Standard of care was described as alginate or collagen alginate.

Haugh et al. 2017[53] meta-analyzed studies comparing commercially available amniotic tissue products with standard wound care in RCTs. Five RCTs analyzed results from 259 patients after excluding 52 patients also treated with a bioengineered skin substitute (Apligraf). Four studies analyzed dehydrated amniotic products (EpiFix and AmnioExcel), while one study analyzed a cryopreserved amniotic product (Grafix). Standard of care described in three studies included debridement and moist wound therapy or nonadherent dressings. Two studies used offloading, and only one study included infection surveillance or compression dressings. Enrollment and followup were similar to those in the Paggiaro et al. 2018 review.[51]

Guo et al. 2017[52] included six RCTs published from 2004 to 2015 that compared ADM with standard of care in 632 patients with diabetic foot ulcers. ADMs were human-derived in five studies and animal-derived in one study. One study each evaluated AlloPatch Pliable and Integra Dermal Regeneration Template. Three studies examined GraftJacket, while one study examined GraftJacket and DermACELL. Standard of care was described as including sharp debridement, glucose control, infection control, offloading, and daily dressing change. Dressings were described as alginate, advanced moist therapy, 0.9 percent sodium chloride/gel/foam/gauze, alginate/hydrocolloids/ hydrogel/foam, and wound gel with gauze dressings (2 studies). Enrollment ranged from 28 to 307 patients; 50 percent of studies enrolled fewer than 25 patients per arm. Followup ranged from 4 weeks to 16 weeks. Additional information on study design characteristics is provided in Table C-1 in Appendix C.

Table 15. Primary studies included in systematic reviews

Randomized Controlled Trial	Skin Substitutes Examined	Category	Systematic Review Paggiaro et al. 2018[51]	Systematic Review Guo et al. 2017[52]	Systematic Review Haugh et al. 2017[53]
DiDomenico et al. 2016	AmnioBand® vs. SOC	Acellular dermal	X		
Snyder et al. 2016	AmnioExcel® vs. SOC	Acellular dermal	X		X

Randomized Controlled Trial	Skin Substitutes Examined	Category	Systematic Review Paggiaro et al. 2018[51]	Systematic Review Guo et al. 2017[52]	Systematic Review Haugh et al. 2017[53]
Walters et al. 2016	DermACELL® vs. GraftJacket® Regenerative Tissue Matrix vs. SOC	Acellular dermal vs. Acellular dermal		X	
Zelen et al. 2016	EpiFix® vs. Apligraf vs. SOC	Acellular dermal vs. Cellular epidermal and dermal	X		X
Zelen et al. 2016	AlloPatch Pliable vs. SOC	Acellular dermal		X	
Lavery et al. 2014	Grafix vs. SOC	Cellular dermal	X		X
Driver et al. 2015	Integra® Dermal Regeneration Template vs. SOC	Acellular dermal		X	
Zelen et al. 2015	EpiFix vs. Apligraf vs. SOC	Acellular dermal vs. Cellular epidermal and dermal			X
Zelen et al. 2014	EpiFix (biweekly vs. weekly)	Acellular dermal	X		
Zelen et al. 2013	EpiFix vs. SOC	Acellular dermal	X		X
Reyzelman et al. 2009	GraftJacket® vs. SOC	Acellular dermal		X	
Brigido et al. 2006	GraftJacket vs. SOC	Acellular dermal		X	
Brigido et al. 2004	GraftJacket vs. SOC	Acellular dermal		X	

SOC=standard of care

Primary Studies

Study design characteristics for the 22 primary studies were grouped by the modified Davison-Kotler classification system. Patient enrollment criteria, patient characteristics, and basic study design characteristics are summarized in Table C-3 to Table C-17 in Appendix C. Details on wound closure assessments, definitions of failure to heal, and details on all wound treatments (including standard of care) are described in Table C-18 to Table C-20 in Appendix C. Standard of care in these studies included sharp debridement, glucose control, compression bandages for venous leg ulcers, pressure redistribution support surfaces for pressure ulcers, infection control, offloading, and daily dressing changes with a moisture-retentive dressing such as an alginate or hydrocolloid. Further information on the skin substitutes is presented in Appendix D.

Of the 22 RCTs, 16 studies compared standard of care with 13 unique skin substitutes (see Table 16) plus similar standard of care.[36,38-40,42,43,47-49,54-60] Thirteen studies examined acellular dermal substitutes, including Allopatch® Acellular Dermal Matrix, AmnioBand, AmnioExcel, DermACELL, EpiCord, EpiFix (studies), Hyalomatrix Wound Matrix, Integra Dermal Regeneration Template, MatriStem Wound Matrix and Oasis Wound Matrix.[38-40,42,48,49,54-60] Three studies examined cellular dermal substitutes (Affinity, Dermagraft, Grafix).[36,43,47]

Table 16. Skin substitutes compared with standard of care in 16 RCTs

Skin Substitute	Category	Study	Study Comparator(s)	Wound Type
Affinity®	Cellular dermal	Serena et al. 2019[36]	SOC	DFU
Allopatch®	Acellular dermal	Zelen et al. 2018[54]	SOC	DFU
AmnioBand® Allograft Placental Matrix	Acellular dermal	DiDomenico et al. 2018[60]	SOC	DFU
AmnioExcel®	Acellular dermal	Snyder et al. 2016[55]	SOC	DFU
DermACELL®	Acellular dermal	Cazzell 2019[49]	SOC	VLU
Dermagraft®	Cellular dermal	Harding et al. 2013[43]	SOC	VLU
EpiCord®	Acellular dermal	Tettelbach et al. 2019[59]	SOC	DFU

Skin Substitute	Category	Study	Study Comparator(s)	Wound Type
EpiFix®	Acellular dermal	Tettelbach et al. 2019[42]	SOC	DFU
EpiFix®	Acellular dermal	Bianchi et al. 2018[37,38]	SOC	VLU
EpiFix	Acellular dermal	Zelen et al. 2013[39]	SOC	DFU
EpiFix	Acellular dermal	Serena et al. 2014[40]	SOC	VLU
Grafix®	Cellular dermal	Lavery et al. 2014[47]	SOC	DFU
Hyalomatrix® Wound Matrix	Acellular dermal	Alvarez et al. 2017[57]	SOC	VLU
Integra® Dermal Regeneration Template	Acellular dermal	Driver et al. 2015[56]	SOC	DFU
MatriStem® Wound Matrix*	Acellular dermal	Alvarez et al. 2017[48]	SOC	DFU
Oasis® Wound Matrix	Acellular dermal	Brown-Etris et al. 2019[58]	SOC	PU

DFU=diabetic foot ulcer; PU=pressure ulcer; SOC=standard of care; VLU=venous leg ulcer
* Now marketed as Cytal® Wound Matrix

The remaining six RCTs compared one skin substitute with another skin substitute.[35,41,44-46,50] We examined three additional unique skin substitutes (Apligraf, GraftJacket Regenerative Tissue Matrix, and TheraSkin).

One three-arm study compared standard of care with two acellular dermal substitutes (DermACELL, GraftJacket).[50] One study compared an acellular dermal substitute (MatriStem Wound Matrix and MatriStem Micromatrix, GrafixPrime) with a cellular dermal substitute (Dermagraft).[46] One study compared an acellular dermal substitute with a cellular epidermal and dermal substitute (EpiFix vs. Apligraf).[41] One study compared two cellular dermal substitutes (GrafixPrime vs. Dermagraft).[44] One study compared a cellular dermal substitute with a cellular epidermal and dermal substitute (Dermagraft vs. TheraSkin).[45] Lastly, one study compared two cellular epidermal and dermal substitutes (Apligraf vs. TheraSkin).[35] See Table 17 for a list of head-to-head comparative studies.

Table 17. Skin substitutes examined in 6 head-to-head comparative studies

Skin Substitutes	Category	Study	Wound Type
GrafixPrime® vs. Dermagraft®	Cellular dermal vs. Cellular dermal	Ananian et al. 2018[44]	DFU
Apligraf® vs. Theraskin®	Cellular epidermal and dermal vs. Cellular epidermal and dermal	Towler et al. 2018[35]	VLU
DermACELL® vs. GraftJacket® Regenerative Tissue Matrix* vs. SOC	Acellular dermal vs. Acellular dermal	Cazzell et al. 2017[50]	DFU
Dermagraft vs. Theraskin	Cellular dermal vs. Cellular epidermal and dermal	Sanders et al. 2014[45]	DFU
MatriStem® Micromatrix and MatriStem Wound Matrix** vs. Dermagraft	Acellular dermal vs. Cellular dermal	Frykberg et al. 2016[46]	DFU
EpiFix vs. Apligraf	Acellular dermal vs. Cellular epidermal and dermal	Zelen et al. 2016[41]	DFU

DFU=diabetic foot ulcer; SOC=standard of care; VLU=venous leg ulcer
* Now GraftJacket RTM
** Now marketed as Cytal® Wound Matrix

Acellular Dermal Substitutes versus Standard of Care

Thirteen studies compared standard of care with acellular dermal substitutes, including Allopatch, AmnioBand, AmnioExcel, DermACELL**,** EpiCord, EpiFix (4 studies), Hyalomatrix Wound Matrix, Integra Dermal Regeneration Template, MatriStem Wound Matrix, and Oasis Wound Matrix.[38-40,42,48,49,54-60] Patient enrollment criteria, patient characteristics, and basic study design characteristics are summarized in Table C-3 to Table C-5 in Appendix C.

Eligible patients in these studies were required to have adequate circulation to the wound (9 studies) and no infection (12 studies). Age eligibility was ≥18 years (10 studies), 18 to 85

years (1 study), and 21 to 80 years (1 study). HbA1c was required to be less than 12 percent (8 studies) and less than 10 percent (1 study) in studies reporting. Eligible diabetic foot ulcers were classified as Wagner 1 or 2[55,56] or Grade I-A Texas[48] (based on the University of Texas Wound Classification System[48]) (for more information on these classification systems, see the article by Clayton and Elasy[80]). Pressure ulcers were classified as Stage III and Stage IV[58] (see the article by the National Pressure Ulcer Advisory Panel[81]). Venous leg ulcers were classified as CEAP 6[49] based on the Clinical-Etiology-Anatomy-Pathophysiology ulcer classification system (see article by Eklof et al. 2004[82]). Ten different criteria were used for wound surface requirements. The most commonly reported was >1 cm^2 to <25 cm^2. Minimum wound duration was 4 weeks (8 studies) and 8 weeks (2 studies) in studies reporting.

Studies excluded patients with New York Heart Association Class III and IV chronic heart failure,[40] active or unstable Charcot foot,[49,55,56,58] and wounds that decreased by more than 20 percent or 30 percent in area during the screening period.[42,54-56,59,60] One study did not report inclusion/exclusion criteria.[57]

Enrollment in each study arm was fewer than 70 patients in 11 studies. Mean age was 60 years in both arms (range, 54 to 78 years). The percent of males ranged from 45 to 81 in the acellular dermal arm and 37 to 92 in the standard-of-care arm. Eight studies reported enrolling ≥75 percent white/Caucasian patients.[38,42,54-56,58-60] Five studies did not report race.[39,40,48,49,57] Six studies reported enrolling Hispanic/Latino individuals.[38,42,55,56,59,60]

Mean wound size ranged from 2.1 cm^2 to 48 cm^2 in the acellular dermal arm and 2.7 cm^2 to 53.5 cm^2 in the standard-of-care arm. Seven (54%) studies had more than a 15 percent difference in mean wound size between arms at baseline. Mean wound duration ranged from 6.5 weeks to 94.0 weeks in the acellular dermal arm and 4.8 weeks to 66.0 weeks in the standard-of-care arm. Seven (54%) studies had more than a 15 percent difference in mean wound duration between arms. Severity of diabetic foot ulcers was rated as Grade I-A (University of Texas Wound Classification System),[48] Wagner 1 or 2,[55] and 70 percent to 75 percent Wagner 2[56] in 3 studies. Severity of pressure ulcers and venous leg ulcers was rated as 52 percent to 58 percent Stage III and CEAP 6, respectively.[49,58] Stage III pressure ulcers exhibit full-thickness loss and exposed subcutaneous fat.[12] CEAP 6 venous leg ulcers exhibit skin changes with active ulceration and are the most severe class of venous leg ulcers.[8]

Enrolled patients were described as having type 1 or type 2 diabetes (8 studies), obesity (11 studies), and as tobacco and alcohol users (6 studies). One study enrolled individuals with Charcot foot and partial amputation.[48] Ten (77%) studies had more than a 15 percent difference in number of comorbidities reported at the start of treatment. All studies were conducted in the United States; 61 percent were conducted in outpatient wound care centers. Research institutes, long-term care, and academic and private practices were other care settings. Eight (61%) studies used a 2-week run-in period. Most common study lengths were 12 weeks and 16 weeks. All studies were manufacturer-funded.

Cellular Dermal Substitutes versus Standard of Care

Three studies addressed cellular dermal substitutes versus standard of care. Serena et al. 2019[36] evenly allocated 76 patients with diabetic foot ulcers to Affinity (n=38) or standard of care (n=38). Individuals with wounds 0.50 cm^2 to 25 cm^2 and ulcer duration of 4 weeks were eligible. Diabetic foot ulcers with adequate lower-extremity perfusion and no evidence of unresolved gross soft-tissue infection or osteomyelitis were included. Mean age was 59 years; over 76 percent were men. Average wound size was approximately 3.2 in both arms. Wound

severity was described as Wagner 1 and 2. This study was conducted across 14 U.S. centers (unspecified) and was manufacturer-funded. Lavery et al. 2014[47] randomly allocated patients with diabetic foot ulcers to Grafix (n=50) or standard of care (n=47). Individuals with an ulcer surface of 1 cm^2 to 15 cm^2 and ulcer duration of 4 weeks to 52 weeks were eligible. Diabetic foot ulcers with adequate circulation and no evidence of active infection and no reduction of wound area by ≥30 percent during the 1-week screening period were enrolled. Mean age was 55 years; over 66 percent were males. Mean wound size was less than 4 cm^2, and mean wound duration was fewer than 125 days. This study was conducted at U.S. research centers and was manufacturer-funded.

Harding et al. 2013[43] randomly allocated patients with venous leg ulcers to Dermagraft plus four-layer compression therapy (n=186) or four-layer compression therapy (n=180). Patients were required to have sufficient circulation to the study leg to make wound healing possible. Ulcers that reduced in size (cm^2) by less than 50 percent while under compression therapy during the study's 2-week screening period were eligible. Patients with morbid obesity, severe peripheral vascular disease/renal disease, or uncontrolled diabetes were excluded. Mean age was approximately 68 years; 46 percent were male. Both studies reported enrolling ≥70 percent white/Caucasian patients. Black, Asian, American Indian, and Alaska Native races were also enrolled. Median wound size was over 7 cm^2 (range 2.3 to 28.2) with median wound duration 45 to 50 weeks (range 8.9 to 470.4). The study was conducted in 25 hospital and community-based venous leg ulcer clinics in the United Kingdom (19 centers), Canada (1 center), and United States (1 center) and had a 2-week screening period. This study was manufacturer-funded. See additional information on patient enrollment criteria, patient characteristics, and basic study design characteristics in Table C-6 to Table C-8 in Appendix C.

Acellular Dermal Substitutes versus Acellular Dermal Substitutes

One 3-arm study addressing acellular dermal substitutes versus acellular dermal substitutes (Cazzell et al. 2017)[50] randomly allocated patients to DermACELL (n=71), GraftJacket (n=28), or standard of care (n=69). Patients were required to have adequate circulation to the affected area and a noninfected single-target diabetic foot ulcer with a Wagner Ulcer Classification of 1 or 2. Patients with peripheral vascular disease, Charcot's disease, or HbA1c >12 percent within 90 days of screening were excluded. Age was limited to individuals between 20 and 80 years of age. Mean age was mid-50s, and the majority were males. Race was not reported. Mean wound duration was 35 to 40 weeks but ranged as high as 479 weeks. Wound severity was mostly Grade 2 Wagner. Besides having type 1 and type 2 diabetes mellitus, some individuals were also current smokers. The study was conducted in 13 outpatient wound care centers in 9 U.S. states and had a 30-day run-in period. This study was manufacturer-funded. See Table C-9 to Table C-11 in Appendix C.

Acellular Dermal Substitutes versus Cellular Dermal Substitutes and Cellular Epidermal and Dermal Substitutes

Two studies compared acellular dermal substitutes with a cellular dermal substitute[46] or a cellular epidermal and dermal substitute[41] in diabetic foot ulcers. Individuals in these studies were required to have clean, noninfected wounds with adequate circulation and HbA1c below 12 percent. Individuals with index ulcers that improved over 20 percent to 30 percent during the run-in period were excluded from both studies. One study excluded severely malnourished patients.

Studies randomly allocated fewer than 34 patients to each study arm. Males accounted for more than 70 percent in 1 study and less than 20 percent in another study. Studies reported enrolling more than 80 percent white/Caucasian; 37 percent[46] were Hispanics in one study. Mean wound size was less than 4.4 cm^2 in either arm, and one study had more than a 15 percent difference in mean wound size.[46] One study reported overall wound duration as 263 days (range, 30 to 1095).[46] Wound severity was mostly Grade A1 Texas in one study.[46] Comorbidities included diabetes, obesity, smoking use, and heart disease, including chronic heart failure.

Studies were conducted in wound care centers, Veterans Affairs medical facilities, research clinics, private practices, and hospital-based outpatient clinics in the United States. Run-in periods were 2 weeks and 4 weeks. Study lengths were 12 weeks and 6 months. One study reported manufacturer funding, while one study did not report funding.[41] See Table C-12 to Table C-14 in Appendix C.

Cellular Dermal Substitutes versus Cellular Dermal Substitutes and Cellular Epidermal and Dermal Substitutes

Two studies compared a cellular dermal substitute with a cellular dermal substitute[44] or a cellular epidermal and dermal substitute in diabetic foot ulcers.[45] Eligible patients had noninfected ulcers, with HbA1c <12 percent, and wounds greater than 30-days duration in one study.[45] Ulcers extending through the dermis with no exposed muscle, tendon, bone, or joint capsule of 4 weeks to 52 weeks in duration were eligible in another study.[44] Age eligibility in one study was 18 to 80 years[44] (See Table C-15 to Table C-17).

Thirty-eight patients was the maximum enrollment in any study arm. Studies reported enrolling 45 percent black patients[45] and 58 percent Hispanics.[44] Both studies had more than a 15 percent difference in mean wound size and mean wound duration between arms. Comorbidities included diabetes, peripheral arterial disease, smoking use, and neuropathy. Run-in periods were 1 week and 30 days. Studies were conducted in wound care centers, wound care clinics, and medical centers. Both studies were manufacturer-funded.

Cellular Epidermal and Dermal Substitutes versus Cellular Epidermal and Dermal Substitutes

One study compared two cellular epidermal and dermal substitutes in venous leg ulcers.[35] Eligible patients had wounds greater than 30-days duration and area less than 40 cm^2. Individuals with end-stage renal disease, severe malnutrition, or severe liver disease were excluded. Fifteen patients was the maximum enrollment in any study arm. Mean age was early 60s, with mostly males enrolled. Race was not reported. Mean wound size was 6.3 cm^2 in the intervention arm and 4.9 cm^2 in the standard-of-care arm. Mean wound duration was not reported. Comorbidities included diabetes, obesity, peripheral vascular disease, smoking use, lymphedema, and neuropathy. This 20-week study used a 30-day run-in period, was conducted in a U.S. wound care center, and reported “no funding.” For additional details, see Table C-15 to Table C-17 in Appendix C.

Successfully Healed Wound

Studies defined a successfully healed wound as 100 percent reepithelialization without drainage or dressing required (9 studies),[41,42,46,48,50,54-56,60] 100 percent reepithelialization without drainage (7 studies),[35,38,40,43,45,47,49] and 100 percent reepithelialization (4 studies).[39,44,58,59] One study defined wound closure as an ulcer achieving an area between 0 and 0.1 cm^2,[36] while

another study did not define a healed wound.[57] Two studies reassessed healing two weeks after initial wound healing,[47,50] which agrees with FDA guidance of confirming complete wound healing at two consecutive study visits 2 weeks apart.[83] KIs agreed that a completely healed wound must include no drainage or require dressing and 100 percent reepithelialization. See Table C-18 for details on assessing wound closure and primary outcomes.

Failure to Heal

Failure to heal during the treatment phase was described as not achieving a reduction in area by at least 40 percent to 50 percent.[38,39,41,54,60] Failure to heal was not defined in 17 (77%) studies. See Table C-19.

Assessor Blinding

Of the 22 primary studies, 11 studies reported blinding of outcome assessors, 1 study reported not blinding outcome assessors,[58] while 10 (45%) studies did not report assessor blinding. See Table C-18.

Standard of Care

Standard of care varied considerably across studies, although debridement was a component of standard of care for 21 (95%) primary studies (1 not reporting). Offloading was an additional component in 14 (93%) studies examining diabetic foot ulcers, while multilayer compression was added to standard of care for all studies examining venous leg ulcers. One study examining pressure ulcers reported use of appropriate pressure redistribution support surfaces.[58] Moist wound therapy was applied using alginate, foam, or hydrogel dressings. Four (23%) studies reported treatments for comorbidities and included infection management[40,54,55] and infection and diabetes management.[60] For details on all wound treatments, see Table C-20 in Appendix C.

Guiding Question 3 Overview

Of the 76 commercially available skin substitutes, three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Of these 16 distinct skin substitutes, seven were examined in more than one study. One skin substitute (EpiFix[38-42]) was examined in five studies. One skin substitute (Dermagraft[43-46]) was examined in four studies. Five skin substitutes (Grafix/GrafixPrime,[44,47] MatriStem Wound Matrix/MatriStem Micromatrix,[46,48] Apligraf,[35,41] Theraskin,[35,45] DermACELL[49,50]) were examined in two studies each.

Standard of care was the most common comparator in the included studies but varied considerably. Few studies reported infection surveillance and diabetic control as key components of standard of care. Six RCTs compared a skin substitute with another skin substitute. Most studies enrolled fewer than 60 patients per arm, were manufacturer-funded, and conducted in U.S. wound care centers. Enrollees were mostly white/Caucasian, required to have adequate circulation to noninfected debrided wounds, and controlled diabetes if enrolled in a study examining diabetic foot ulcers. Successful wound closure was mostly described as 100 percent reepithelialization without drainage or dressing.

Guiding Question 4: What are the outcomes of treatment strategies, including skin substitutes alone and/or in addition to other wound care modalities, compared to other wound care modalities in patients with different types of chronic wounds, for patient-oriented outcomes such as the following? Consider at least:

a. Number/percentage of completely closed/healed wounds (skin closure with complete reepithelialization without drainage or dressing requirements versus failure to heal)
b. Time to complete wound closure
c. Wound recurrence (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)

Key Points

- Acellular dermal substitutes versus standard of care:
    - Three systematic reviews reported more than a 2-fold increased risk for complete healing of diabetic foot ulcers with AlloPatch Pliable, AmnioBand, AmnioExcel, DermACELL, EpiFix, Grafix GraftJacket, and Integra Dermal Regeneration Template versus standard of care. Two reviews also reported a shorter time to heal favoring AlloPatch Pliable, AmnioBand, Grafix, and GraftJacket over standard of care.[51,52] None of the reviews reported an overall risk-of-bias rating for included studies.
    - Ten (77%) RCTs comparing acellular dermal substitutes with standard of care reported statistically significant findings up to 16 weeks favoring the interventions for complete wound closure,[37,38,38,39,42,48,54-56,59,60] and shorter time to heal[37,38,38,39,48,54,55,57,60] in diabetic foot ulcers[39,42,48,54-56,59,60] and venous leg ulcers.[38,57] Three studies rated severity of diabetic foot ulcers as Grade I-A (University of Texas Wound Classification System),[48] Wagner 1 or 2,[55] and mostly Wagner 2.[56] One study rated severity of pressure ulcers as 52 percent to 58 percent Stage III,[58] while another study rated severity of venous leg ulcers as CEAP 6.[49] The most commonly reported enrollment criteria included >1 cm^2 to <25 cm^2 wound surface, >4-weeks duration, ankle brachial index (ABI) 0.7 to ≤1.2, and HbA1c <12 percent. Severe adverse events occurring with acellular dermal substitutes included diabetic foot infections, cellulitis, and osteomyelitis. Six (46%) studies reported less-frequent recurrence with a skin substitute.[42,48,49,56,59,60] One study reported recurrence more frequently with Oasis Wound Matrix than standard of care.[58]

- Cellular dermal substitutes versus standard of care:
    - Study authors reported treatment was significantly favored over standard of care at 12 weeks[36,43,47] and 16 weeks[36] for wounds healed and time to heal, respectively.[47] For venous leg ulcers, significant differences were reported for Dermagraft plus Profore™ four-layer compression over four-layer compression in a subgroup of patients with ulcer duration ≤12 months (percent healed by 12 weeks, 52% vs. 37%; p=0.029). For diabetic foot ulcers, Grafix (probability of complete wound healing, 67.1% vs. 27.1%; Log-Rank, p<0.0001)[47] and Affinity (58% vs. 29%; p=0.01)[36] were significantly favored over standard of care. Authors reported recurrence was lower with Dermagraft at 24 weeks and Grafix at 2-week reassessment. Enrollment criteria included a wound surface <25 cm^2,[36,43,47] wound duration <5 years,[43] and no morbid obesity.[43]
- Acellular dermal substitutes versus acellular dermal substitutes:
    - Results comparing DermACELL versus GraftJacket in diabetic foot ulcers were not provided after a three-arm study intentionally underpowered the GraftJacket arm. Individuals had mostly Wagner Grade 2 ulcers, with ABI ranging from 0.8 to 1.2 and HbA1c <12 percent.[50]
- Acellular dermal substitutes versus cellular dermal substitutes and cellular epidermal and dermal substitutes:
    - Authors reported MatriStem and Dermagraft provided similar benefit for diabetic foot ulcers healed up to 10 weeks, time to closure, change in wound size, and 6-month recurrence. Ulcers were mostly Grade A1 (University of Texas Wound Classification System), and enrollees were required to have wounds ≥4-weeks duration, with an ABI ≥0.7.[46]
    - Authors reported EpiFix provided significant benefit over Apligraf in number of diabetic foot ulcers healed and time to heal at 12 weeks. Individuals had wounds <25 cm^2, a wound duration ≥4 weeks, an ABI between 0.7 and 1.2, and HbA1c <12 percent.[41]
- Cellular dermal substitutes versus cellular dermal substitutes and cellular epidermal and dermal substitutes:
    - Authors reported GrafixPrime provided significant benefit over Dermagraft for diabetic foot wounds ≤5 cm^2 healed at 8 weeks. Enrollees had a wound area <15 cm^2, a wound duration <52 weeks, and an ABI between 0.7 and 1.3.[44]
    - Authors reported statistically significant benefits to Theraskin over Dermagraft in diabetic foot ulcers at 12 weeks included more wounds healed in a shorter time with fewer grafts. No difference in wound healing was reported at 20 weeks. Patients had wounds <10 cm^2, >30-days duration, with HbA1c <12 percent.[45]
- Cellular epidermal and dermal substitutes versus cellular epidermal and dermal substitutes:
    - Authors reported no statistically significant difference between Apligraf and Theraskin for venous leg ulcer healing (at 12 and 20 weeks) and number of grafts per subject. Authors reported recurrence did not occur at 26 weeks. Eligible patients had wounds greater than 30-days duration and area less than 40 cm^2.[35]

We now present an overview of the findings and a risk-of-bias assessment of the three systematic reviews and 22 primary studies included in the report. These studies examined use of

16 distinct skin substitutes (20% of 76 commercially available skin substitutes), including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. We provide details on all the clinical evidence in Appendix C and summarize findings for each primary study in Table 18 and Table 19.

Systematic Reviews

The two systematic reviews on amniotic membranes (Paggiaro et al. 2018[51] and Haugh et al. 2017[53]) reported complete wound healing[51,53] and mean time to complete wound healing[51] in 11 RCTs of diabetic foot ulcers. Four studies were included in both reviews.

Paggiaro et al. 2018[51] reported treatment with amniotic membranes versus standard of care resulted in a significant increase in wound healing (risk ratio 2.77, 95% CI: 1.76 to 4.36) in a significantly shorter time (mean difference -32.28 days, 95% CI: -41.05 to -23.71). Statistical heterogeneity was low to moderate and not further explored given the few studies. The authors noted that use of amniotic membranes resulted in more diabetic foot ulcers healing faster. Haugh et al. 2017[53] reported a similar difference in complete wound healing favoring the intervention (risk ratio 2.75, 95% CI: 2.06 to 3.66; $p<0.001$). Statistical heterogeneity was moderate and not explored further. The authors noted that despite results indicating that treating diabetic foot ulcers with amniotic membrane improves healing rates, further studies are needed to determine whether these products also decrease the incidence of subsequent complications, such as amputations or death.

Findings in Guo et al. 2017[52] indicated a 2.31 and 1.57 significant increased relative risk of complete wound healing at 12 weeks and 16 weeks, respectively, favoring ADM versus standard of care. The systematic review authros reported mean time to complete wound healing was significantly shorter with ADM (mean difference -2.98 weeks, 95% CI: -5.15 to -0.82; $p=0.007$). Statistical heterogeneity was significant for the outcomes complete wound healing at 12 weeks (6 studies) and time to heal (4 studies). For complete wound healing, the authors noted that moderate heterogeneity remained after removing one study measuring the healing rate in the first 4 weeks. For time to heal, one study was noted as having overly influenced the heterogeneity. Risk of adverse events was not significantly different. The authors concluded that "compared with standard of care, acellular dermal matrix may accelerate the healing velocity of uninfected, non-ischemic, full-thickness diabetic foot ulcer… while generating no more complications." For additional data for these reviews, see Table C-1 in Appendix C.

None of the reviews reported an overall risk-of-bias rating for included studies. Two reviews described lack of allocation concealment (selection bias), lack of blinding assessors (detection bias), incomplete outcome data (attrition bias), and other bias (not described) as study limitations.[51,52] These reviews used the Cochrane Handbook for systematic reviews of interventions for their risk-of-bias assessment, while our risk-of-bias assessment tool used for individual studies (see Methods) mostly focused on wound-related outcomes (e.g., reporting of recurrence, similar wound size, and duration in study arms). Haugh et al. 2017[53] assessed risk of bias based on guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology Collaboration[84] but did not report findings. For details of the risk-of-bias assessments, see Table C-2. in Appendix C.

Primary Studies

We briefly summarize below the findings for the 22 RCTs addressing this guiding question. Summaries are categorized by the modified Davison-Kotler classification system[22] as in Guiding Question 3. See Table 18 for an overview of findings and risk-of-bias rating for 16 studies addressing standard of care versus an acellular dermal substitute or cellular dermal substitute. See Table 19 for an overview of findings and risk-of-bias rating for six head-to-head comparisons of acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes.

For further information on the clinical results, see Table C-21 to Table C-30 in Appendix C. For details on all wound treatments (including standard of care), see Table C-20 in Appendix C. Table C-31 summarizes risk-of-bias assessments.

Acellular Dermal Substitutes versus Standard of Care

Of the 13 studies addressing this comparison, six reported statistically significant differences in number of wounds healed and time to heal favoring the intervention over standard of care.[37,38,38,39,48,54,55,60] Latest followup was 6 weeks (2 studies),[39,55] 12 weeks (3 studies),[48,54,60] and 16 weeks (1 study).[37,38,38] Skin substitutes examined in these studies included AlloPatch Pliable,[54] AmnioBand,[60] AmnioExcel,[55] EpiFix (2 studies),[38,39] and MatriStem Wound Matrix.[48] Five studies evaluated effectiveness in diabetic foot ulcers,[39,48,54,55,60] while one study evaluated venous leg ulcers.[37,38,38] Standard of care included debridement and offloading for all studies evaluating diabetic foot ulcers. Standard of care for one study evaluating venous leg ulcers included a standard moist wound dressing and multilayer compression therapy.[37,38] Three studies included infection management[54,55] and infection and diabetes management as standard of care.[60]

The authors of three studies reported statistically significant differences in complete wound closure for diabetic foot ulcers (at 12 weeks[42,56,59] and 16 weeks[56,59]) favoring EpiCord,[59] EpiFix,[42] and Integra Dermal Regeneration Template[56] over standard of care. One study also reported significant findings for pain favoring treatment (Integra Dermal Regeneration Template)[56] over standard of care. In addition to offloading, standard of care included moist wound therapy (0.9% sodium chloride gel plus a secondary dressing),[56] and alginate wound dressing and an absorbent nonadhesive hydropolymer secondary dressing and gauze wrap.[42,59]

Authors of one study reported a significantly shorter time to heal venous leg ulcers with Hyalomatrix® Wound Matrix plus compression.[57] Standard of care included multilayer compression therapy and nonadherent silicone foam dressing but no debridement.[57]

Authors of three studies reported no statistically significant findings. Two studies examining venous leg ulcers reported no statistically significant difference in wound healing at 24 weeks with DermACELL[49] and more frequent closure at 4 weeks with EpiFix plus multilayer compression therapy.[40] Lastly, authors of one study reported no statistically significant difference in healing pressure ulcers at 12 weeks with Oasis Wound Matrix.[58] Standard of care included infection management[40] and multilayer compression therapy in venous ulcers. One study used isotonic saline gel followed by a semi-occlusive absorbent film dressing and appropriate pressure redistribution support surfaces on pressure ulcers.[58]

Authors of six studies reported that recurrence happened less frequently with application of a skin substitute than with standard of care.[42,48,49,56,59,60] Authors of one study reported recurrence more frequently with Oasis Wound Matrix than with standard of care.[58] The most commonly reported enrollment criteria in these studies included >1 cm^2 to <25 cm^2 wound surface, >4-weeks duration, ABI 0.7 to ≤1.2, and HbA1c <12 percent.

Authors of one study reported nine severe adverse events occurred with EpiFix,[37,38] while authors of another study reported 15 adverse events with EpiCord.[59] Authors of one study reported patients receiving AlloPatch Pliable were hospitalized with diabetic foot infections.[54] Authors of one study reported more patients treated with Oasis Wound Matrix had wound worsening and/or desired change in treatment (44% Oasis, 35% standard of care).[58] Authors of two studies reported cellulitis occurring with EpiFix and AmnioExcel,[40,55] while one study reported six target-ulcer infections with EpiFix (6 EpiFix, 5 standard of care).[42] Authors of one study also reported wound infection and osteomyelitis with AmnioExcel.[55] Authors of one study reported similar low adverse event rates.[56] Authors of one study reported only overall adverse events (including cellulitis),[48] while authors of two studies did not report adverse events.[49,57] For additional information on clinical outcomes, see Table C-21 and Table C-22.

See results from a 3-arm study (Cazzell et al. 2017)[50] that includes standard of care in Table C-25 and Table C-26 and the section Acellular Dermal Substitutes versus Acellular Dermal Substitutes below.

Cellular Dermal Substitutes versus Standard of Care

Authors of three studies addressed cellular dermal substitutes versus standard of care. Authors of one study reported statistically significant differences in diabetic foot ulcers healed at 12 weeks (55% vs. 29%; p=0.02) and 16 weeks (58% vs. 29%; p=0.01) and a shorter median time to heal (by 8 weeks) with Affinity.[36] Recurrence was not reported, and no serious adverse events were attributed to treatment. Enrollment criteria included a wound surface 0.50 to 25 cm^2, wound duration ≥4 weeks, and no evidence of soft-tissue infection or osteomyelitis.

Authors of one study reported statistically significant differences in number of diabetic foot ulcers healed and time to heal at 12 weeks favoring Grafix over standard of care.[47] Standard of care included debridement, offloading, and nonadherent dressings. Authors reported recurrence was less frequent with Grafix than with standard of care 2-weeks postclosure (17.8% vs. 30%). Enrollment criteria included a wound surface 1 to 25 cm^2, wound duration 4 to 52 weeks, ABI 0.7 to 1.3, and no HbA1c above 12 percent.

Authors of one 24-week study (Harding et al. 2013)[43] reported no significant differences between Dermagraft plus Profore four-layer compression therapy versus four-layer compression therapy except for venous leg ulcers healed at 12 weeks in a subgroup of patients with ulcer duration ≤12 months. Standard of care included a nonadherent dressing, with deeper ulcers also receiving gauze and heavily exuding ulcers receiving additional absorbent dressings. Authors reported recurrence was lower with Dermagraft at 24 weeks (15% vs. 23%), but venous ulcer pain was slightly higher (5.3% vs. 5.0%). Safety was reported as comparable. Enrollment criteria included a wound surface <25 cm^2, wound duration <5 years, ABI 0.8 to 1.2, and no morbid obesity. For additional information on clinical outcomes, see Table C-23 and Table C-24.

Table 18. Overview of 16 RCTs comparing skin substitutes with standard of care

Skin Substitute	Category	Study	Wound Type	Overview	Risk-of-bias Assessment
Affinity®	Cellular dermal	Serena et al. 2019[36]	DFU	Significant difference favoring Affinity (n=38) over SOC (n=38) for DFUs healed at 12 weeks (55% vs. 29%; p=0.02) and 16 weeks (58% vs. 29%; p=0.01) and a shorter median time to wound closure (11 weeks vs. 19 weeks; 42% faster). No AEs/SAEs were attributed to Affinity.	Low

Skin Substitute	Category	Study	Wound Type	Overview	Risk-of-bias Assessment
Allopatch®	Acellular dermal	Zelen et al. 2018[54]	DFU	Significant differences in DFUs closed (at 6 and 12 weeks) and time to wound closure at 12 weeks favored AlloPatch Pliable (n=40) over SOC (n=40). 8 (10%) patients were hospitalized with diabetic foot infections; 2 (2%) were treated with AlloPatch Pliable.	Moderate
AmnioBand	Acellular dermal	DiDomenico et al. 2018[60]	DFU	Statistically significant differences were reported in wound closure (85% vs. 33%) and time to heal (37 days vs. 67 days) at 12 weeks favoring AmnioBand over SOC. 2 DFUs recurred in the SOC arm at 1-week followup.	Moderate
AmnioExcel®	Acellular dermal	Snyder et al. 2016[55]	DFU	Findings indicated a significant difference in wound closure of DFUs at 6 weeks with AmnioExcel (n=15) over SOC (n=14) (35% AmnioExcel, 0% SOC; p=0.0170) and a significantly shorter time to closure with AmnioExcel (p<0.0001). AmnioExcel-treated AEs included wound infection, osteomyelitis, and cellulitis in 1 patient each.	Moderate
DermACELL	Acellular dermal	Cazzell S. 2019[49]	VLU	No statistically significant difference in venous leg ulcers healed at 24 weeks using DermACELL (n=18) vs. SOC (n=10). Recurrence was reported in 3 wounds (1 DermACELL, 2 SOC) at 12-week followup. Adverse events were not reported.	Low
Dermagraft®	Cellular dermal	Harding et al. 2013[43]	VLU	No significant findings were reported between Dermagraft plus Profore™ compression therapy (n=186) vs. Profore compression therapy (n=180) for time to wound closure and recurrence (at 1 week followup). A subgroup analysis of patients with ulcer duration ≤12 months indicated a statistically significant benefit with Dermagraft plus Profore compression therapy for wounds healed at 12 weeks (p=0.029). Safety was reported as comparable.	Low
EpiCord®	Acellular dermal	Tettelbach et al. 2019[59]	DFU	Statistically significant differences in complete wound healing of DFUs (12 weeks, 16 weeks) favoring EpiCord (n=101) vs. SOC (n=54). Recurrence was reported in 7 DFUs (3 EpiCord, 4 SOC) at 16-week followup. Severe AEs occurred in 25 patients (15 EpiCord, 10 SOC), although none were product-related.	Low
EpiFix®	Acellular dermal	Tettelbach et al. 2019[42]	DFU	Statistically significant differences in DFU healing favored EpiFix vs. SOC (70% vs. 50%, p=0.0338) at 12 weeks. Recurrence was reported in 6 patients (2 EpiFix, 4 SOC) at 16 weeks, while infection occurred in 11 patients (6 EpiFix, 5 SOC). EpiFix-related AEs included cellulitis (n=7) and osteomyelitis (n=3). Wound maceration and positive wound cultures were noted as possible EpiFix-related.	Low

Skin Substitute	Category	Study	Wound Type	Overview	Risk-of-bias Assessment
EpiFix®	Acellular dermal	Bianchi et al. 2018[37,38]	VLU	Significant findings included a benefit to wound closure (at 12 and 16 weeks) and time to heal (log-rank p=0.032) using EpiFix plus compression (n=64) over SOC (n=64). 9 severe adverse events were reported in the EpiFix arm.	Low
EpiFix	Acellular dermal	Zelen et al. 2013[39]	DFU	Findings suggest a biweekly application of EpiFix (n=13) results in significantly more DFU healing at 6 weeks and at a 50% faster healing rate than SOC (n=12). Cellulitis occurred in 2 (16%) patients receiving SOC.	Moderate
EpiFix	Acellular dermal	Serena et al. 2014[40]	VLU	Serena et al. 2014[40] reported more wound closure at 4 weeks with a human amnion/chorion membrane allograft (11.3% EpiFix plus MLCT (n=53) vs. 7.8% MLCT (n=51). 2 cases of cellulitis occurred in the EpiFix plus MLCT arm.	Low
Grafix®	Cellular dermal	Lavery et al. 2014[47]	DFU	DFUs were 6 times more likely to completely heal at 12 weeks with Grafix (n=50) vs. SOC (n=47) (OR 6.037, 95% CI: 2.449 to 14.882). Grafix arm had a significantly higher probability of complete wound healing (67.1% vs. 27.1%; Log-Rank, p<0.0001), faster median time to complete wound closure (42 days vs. 69.5 days; p=0.019) and fewer wound-related infections (18% vs. 36.25; p=0.044). No significant difference was reported for wound recurrence (17.8% vs. 30%; p=0.42) at 2-week followup or hospitalizations related to infections (6% vs. 15%; p=0.15).	Low
Hyalomatrix® Wound Matrix	Acellular dermal	Alvarez et al. 2017[57]	VLU	No statistically significant differences were reported between Hyalomatrix Wound Matrix plus compression (n=9) vs. standard of care (n=7) for wound healing. Time to heal was significantly shorter with Hyalomatrix Wound Matrix plus compression (41 days vs. 104 days; p=0.029). AEs were not reported.	Moderate
Integra® Dermal Regeneration Template	Acellular dermal	Driver et al. 2015[56]	DFU	Significant findings were reported for complete wound closure (at 12 and 16 weeks) and body pain favoring Integra Dermal Regeneration Template (n=154) over SOC (n=153). No statistically significant differences were reported for median time to wound closure (43 days vs. 78 days) and wound recurrence at 28 weeks (19% IDRT vs. 26% SOC; p=0.32). AEs potentially study-related were “similar” (4.5% IDRT vs. 5.2% SOC).	Low

Skin Substitute	Category	Study	Wound Type	Overview	Risk-of-bias Assessment
MatriStem® Wound Matrix*	Acellular dermal	Alvarez et al. 2017[48]	DFU	Significant differences were reported in wounds closed at 12 weeks (91% vs. 33%; p=0.041) and mean days to wound closure (62.4 vs. 92.8) favoring a urinary bladder matrix (n=11) over SOC (n=6). Recurrence was less frequent at 1 year with MatriStem Wound Matrix (10% vs. 50%). Overall AEs included local wound infection (n=6), dermatitis (n=4), and cellulitis (n=1).	Moderate
Oasis® Wound Matrix	Acellular dermal	Brown-Etris et al. 2019[58]	PU	No statistically significant differences in pressure ulcers healed (12 weeks, 6 months) using Oasis Wound Matrix (n=67) vs. SOC (n=63). Recurrence was reported in 2 patients receiving Oasis and no patients receiving SOC at 6-month followup. Subgroup analysis by wound severity, size, and duration at 12 weeks did not result in statistically significant differences. A higher percentage of ulcers healed at 12 weeks with Oasis Wound Matrix that were less severe (49% Stage III, 29% Stage IV), smaller (44%<6 cm^2, 29% ≥6 cm^2), and of shorter duration (50%<6 months, 25% ≥6 months). Oasis Wound Matrix-related AEs included death, dermatitis, and osteomyelitis.	Low

AE=adverse event; CI=confidence interval; DFU=diabetic foot ulcer; IDRT=Integra dermal regeneration template; OR=odds ratio; PU=pressure ulcer; SAE=serious adverse event; SOC=standard of care; VLU=venous leg ulcer
* Now marketed as Cytal® Wound Matrix

Acellular Dermal Substitutes versus Acellular Dermal Substitutes

Authors of one three-arm study comparing two acellular dermal substitutes with standard of care reported a significant difference in diabetic foot ulcers healed at 24 weeks favoring DermACELL over standard of care. The GraftJacket arm was intentionally underpowered since statistical significance was not sought or expected for this study arm. We did not include recurrence rates since data were missing for 48.5 percent of patients in the "per protocol population." Serious treatment-related adverse events were reported as comparable.[50] Individuals had mostly Wagner Grade 2 ulcers, with ABI ranging from 0.8 to 1.2 and HbA1c <12 percent. For additional information on clinical outcomes, see Table C-25 and Table C-26.

Acellular Dermal Substitutes versus Cellular Dermal Substitutes and Cellular Epidermal and Dermal Substitutes

Two studies compared acellular dermal substitutes with a cellular dermal substitute[46] or a cellular epidermal and dermal substitute[41] in diabetic foot ulcers.

Authors of one study reported no statistically significant differences for all outcomes (including wounds healed up to 10 weeks, time to closure, change in wound size) between MatriStem and Dermagraft with similar 6-month recurrence. Ulcers were mostly Grade A1 University of Texas Wound Classification System, and enrollees were required to have wounds ≥4-weeks duration, with an ABI ≥0.7.[46]

Authors reported EpiFix was significantly favored over Apligraf for complete wounds healed and time to heal at 12 weeks. Individuals had wounds <25 cm^2, ≥4-weeks duration, an ABI between 0.7 and 1.2, and HbA1c <12 percent.[41]

Authors reported adverse events were similar between MatriStem and Dermagraft.[46] Osteomyelitis and cellulitis occurred in more patients receiving Dermagraft than GrafixPrime (16.1% vs. 6.4%),[44] and five wound/foot infections were reported using EpiFix or Apligraf.[41] For additional information on clinical outcomes, see Table C-27 and Table C-28.

Cellular Dermal Substitutes versus Cellular Dermal Substitutes and Cellular Epidermal and Dermal Substitutes

Two studies compared a cellular dermal substitute with a cellular dermal substitute[44] or a cellular epidermal and dermal substitute in diabetic foot ulcers.[45] Authors of one study reported significant findings for GrafixPrime over Dermagraft for wounds ≤5 cm^2 healed at 8 weeks (81.3% vs. 37.5%; p=0.0118). Enrollees had a wound area <15 cm^2, a wound duration <52 weeks, and an ABI between 0.7 and 1.3.[44]

Authors reported statistically significant benefits to Theraskin over Dermagraft at 12 weeks including more diabetic foot ulcers healed, a shorter time to wound closure, and fewer grafts needed (4.36 Theraskin, 8.92 Dermagraft). At 20 weeks, however, no significant difference in wound healing was reported (90.91% Theraskin, 66.67% Apligraf; p=0.4282). Patients had wounds <10 cm^2, >30-days duration, and HbA1c <12 percent.[45] For additional information on clinical outcomes, see Table C-29 and Table C-30.

Cellular Epidermal and Dermal Substitutes versus Cellular Epidermal and Dermal Substitutes

Authors of one study reported no statistically significant difference between Apligraf and Theraskin for venous leg ulcer healing (at 12 and 20 weeks) and number of grafts per subject. Wounds remained healed at week 26. Eligible patients had wounds greater than 30-days duration and area less than 40 cm^2.[35] For additional information on clinical outcomes, see Table C-29 and Table C-30.

Table 19. Overview of 6 head-to-head comparative studies

Skin Substitutes	Category	Study	Wound Type	Overview	Risk-of-bias Assessment
GrafixPrime® vs. Dermagraft®	Cellular dermal vs. Cellular dermal	Ananian et al. 2018[44]	DFU	Authors reported GrafixPrime (n=31) was not inferior to Dermagraft (n=31) for the percent of patients achieving complete closure of DFUs (9.68%, 90% CI: -10.67% to 28.94%). Significant findings for GrafixPrime over Dermagraft included wounds ≤5 cm^2 healed at 8 weeks (81.3% vs. 37.5%; p=0.0118). Osteomyelitis and cellulitis occurred in more patients receiving Dermagraft (5 vs. 2).	Moderate
Apligraf® vs. Theraskin®	Cellular epidermal and dermal vs. Cellular epidermal and dermal	Towler et al. 2018[35]	VLU	No statistically significant differences were reported between Apligraf (n=12) and Theraskin (n=15) for VLU healing (at 12 and 20 weeks) and number of grafts per subject. Wounds remained healed through week 26.	Moderate

Skin Substitutes	Category	Study	Wound Type	Overview	Risk-of-bias Assessment
DermACELL® vs. GraftJacket® Regenerative Tissue Matrix* vs. SOC	Acellular dermal vs. Acellular dermal	Cazzell et al. 2017[50]	DFU	Significant findings were reported favoring DermACELL (n=71) over SOC (n=69) for wounds healed at 16 weeks (66% vs. 37.7%; p=0.009) and 24 weeks (70% vs. 49.3%; p=0.044). The GraftJacket arm (n=28) was intentionally underpowered in this study. Serious treatment-related adverse events were comparable between arms (28.2% DermACELL, 28.6% GraftJacket, 27.9% SOC).	Low
Dermagraft vs. Theraskin	Cellular dermal vs. Cellular epidermal and dermal	Sanders et al. 2014[45]	DFU	Statistically significant benefits to Theraskin (n=11) over Dermagraft (n=12) included more DFUs healed, a shorter time to wound closure, and fewer number of grafts needed at 12 weeks. At 20 weeks, no statistically significant difference in wound healing was indicated (90.91% Theraskin, 66.67% Dermagraft; p=0.4282).	Moderate
MatriStem® Micromatrix and MatriStem Wound Matrix** vs. Dermagraft	Acellular dermal vs. Cellular dermal	Frykberg et al. 2016[46]	DFU	No statistically significant differences were reported for all outcomes (including wounds healed and time to closure) between MatriStem (n=27) and Dermagraft (n=29). 6-month recurrence and overall adverse events were similar.	Moderate
EpiFix vs. Apligraf	Acellular dermal vs. Cellular epidermal and dermal	Zelen et al. 2016[41]	DFU	Findings included a significantly shorter time to heal DFUs with EpiFix (n=32) vs. Apligraf (n=33) or SOC (n=35) and significantly fewer grafts used during 12-week study period with EpiFix (mean ±SD: 3.4±2.9 EpiFix, 5.9±3.6 Apligraf; p=0.003). Complete healing at 12 weeks was higher with EpiFix (97% EpiFix, 73% Apligraf, 51% SOC; adjusted p=0.00019). 7 wound/foot infections were reported, 2 in the SOC arm.	Low

CI=confidence interval; DFU=diabetic foot ulcer; SD=standard deviation; SOC=standard of care; VLU=venous leg ulcer
* Now GraftJacket RTM
** Now marketed as Cytal® Wound Matrix

Risk of Bias

We assessed risk of bias of primary studies using a 10-item risk-of-bias tool (see Methods section). Ten studies were rated moderate risk of bias; 12 were rated low risk of bias. No studies were rated high risk of bias.

The most common reasons for moderate risk of bias were selection bias, detection bias, and reporting bias. Most studies were at low risk of attrition bias due to use of intent-to-treat analysis. The most common causes of selection bias were greater than 15 percent differences between groups in number of baseline comorbidities, wound size, and wound duration, as well as failure

to report adequate randomization methods. Problems with detection bias and reporting bias included failure to blind wound assessors and failure to measure or report wound recurrence. For additional details of the risk-of-bias assessment, see Table C-31.

Guiding Question 4 Overview

Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes (21% of 76 commercially available skin substitutes), including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes. Studies examining acellular dermal substitutes versus standard of care reported more effective complete wound healing and a shorter time to heal with acellular skin substitutes for diabetic foot ulcers and venous leg ulcers. Standard of care varied across these studies, which may have contributed to differences in outcomes. Additional evidence from studies examining other skin substitute classifications versus standard of care and head-to-head comparisons of skin substitutes are necessary to establish whether any one skin substitute product is superior to another.

Studies rarely reported clinical outcomes such as hospitalization due to infection and amputations. Patient-related outcomes, such as functional capacity, pain, exudate, and odor control, were also under-reported. Need for hospitalization and pain reduction was reported in 14 percent of included studies (3 of 22); need for amputation, exudate, and odor control were reported in a single study (1 of 22); no studies reported return to baseline activities of daily living and functional capacity.

Guiding Question 5: What skin substitutes are currently being investigated in ongoing trials?

Our search of ClinicalTrials.gov[a] for RCTs and prospective nonrandomized comparative studies examining skin substitutes in chronic wounds of interest identified 16 ongoing clinical trials. We identified an additional five ongoing clinical trials during the SEADs submission. We provide information below on 21 ongoing clinical trials (all RCTs). For additional information on all ongoing trials, see Table E-1 in Appendix E.

The 21 ongoing clinical trials are examining 20 skin substitutes (1 unspecified). In addition to the 16 distinct skin substitutes examined in Guiding Questions 3 and 4, these ongoing clinical trials are examining an additional nine skin substitutes, including Absolve® Biologic Wound Matrix, Artacent™ Human Amniotic Membrane, Biovance®, Neox®Cord 1K, NuShield®, PriMatrix Dermal Repair Scaffold, PuraPly™ Antimicrobial Wound Matrix, Restrata™, and Revita. Based on the modified Davison-Kotler classification system, the 20 skin substitutes examined in these trials can be classified as acellular dermal, cellular dermal, and cellular epidermal and dermal substitutes.

The 21 ongoing clinical trials are examining diabetic foot ulcers (12 studies), pressure ulcers (2 studies), venous leg ulcers (5 studies), diabetic foot ulcers and venous leg ulcers (1 study), and chronic wounds (1 study).

Trial status includes recruiting (13 studies); active, not recruiting (4 studies); enrolling by invitation (3 studies); and unknown (1 study). Most RCTs are comparing skin substitutes with standard of care; three RCTs are comparing two skin substitutes.

[a] Listing a study on this site does not mean it has been evaluated by the U.S. Federal Government. Determining the safety and scientific validity of a study listed on ClinicalTrials.gov is the responsibility of the study sponsor and investigators.

Guiding Question 5 Overview

Twenty-one ongoing clinical trials are examining skin substitutes in chronic wounds of interest. These 21 RCTs are examining 20 skin substitutes with similar classifications as included studies; most studies are examining diabetic foot ulcers and currently recruiting.

Guiding Question 6: What best practices in study design could be used to produce high-quality evidence on skin substitutes?

Key Points

- Variation in study design reduces the ability to compare outcomes across studies.
- Comparisons across studies may be enhanced by standardizing approaches for inclusion criteria (wound size, wound duration before study inclusion, wound severity) by using a 2- to 4-week run-in period before study enrollment and a 12-week study period, by reporting wound recurrence up to 6 months as well as wounds healed during the study, and by blinded wound assessment.
- KIs suggested that patient inclusion criteria could be expanded to include patients more representative of clinical practice and of poorer health than typical patients included in RCTs. This would allow subanalysis of gender, race, ethnicity, age, and comorbidities that may help direct specific product use for different wound conditions.
- KIs suggested that failure to heal after 6 weeks of treatment with a skin substitute may be an appropriate criteria for discontinuing use of a skin substitute and switching to another advanced therapy option.
- KIs suggested that 40 percent to 50 percent wound closure in 4 weeks was a good predictor of successful wound closure.

Variations in Study Design

Our examination of the studies included in Questions 3 and 4 indicates that variation in study designs reduces the ability to compare outcomes across studies. For example, we identified 20 different criteria in 38 (published and ongoing) studies reporting wound size inclusion criterion (Figure 3). Sizes ranged from as small as 0.5 cm^2 to 100 cm^2. One to 25 cm^2 was the most common range used as a wound size inclusion criterion. More than 4 weeks was the most common wound duration inclusion criterion (25 studies) (Figure 4), while a few studies allowed up to 52 weeks. Three ongoing studies did not report wound duration as an inclusion/exclusion criterion. Only six published studies reported on wound recurrence after 12 weeks (Figure 5). Eight of the published studies and 14 of the ongoing clinical trials did not report recurrence as a primary or secondary outcome. Thirty-six percent of studies reported wound severity using classification systems (e.g., Texas Wound Classification System) at enrollment. The run-in period using standard of care before patients were randomly assigned to treatment was either 2 weeks or 4 weeks, and the percent wound healing used to determine eligibility for the trial varied from 20 percent to 50 percent. Given the variation in these and other study design features, we suggest that research in this field may benefit from a more standardized study design.

Figure 3. Wound Size Criterion: 22 included RCTs and 21 ongoing clinical trials

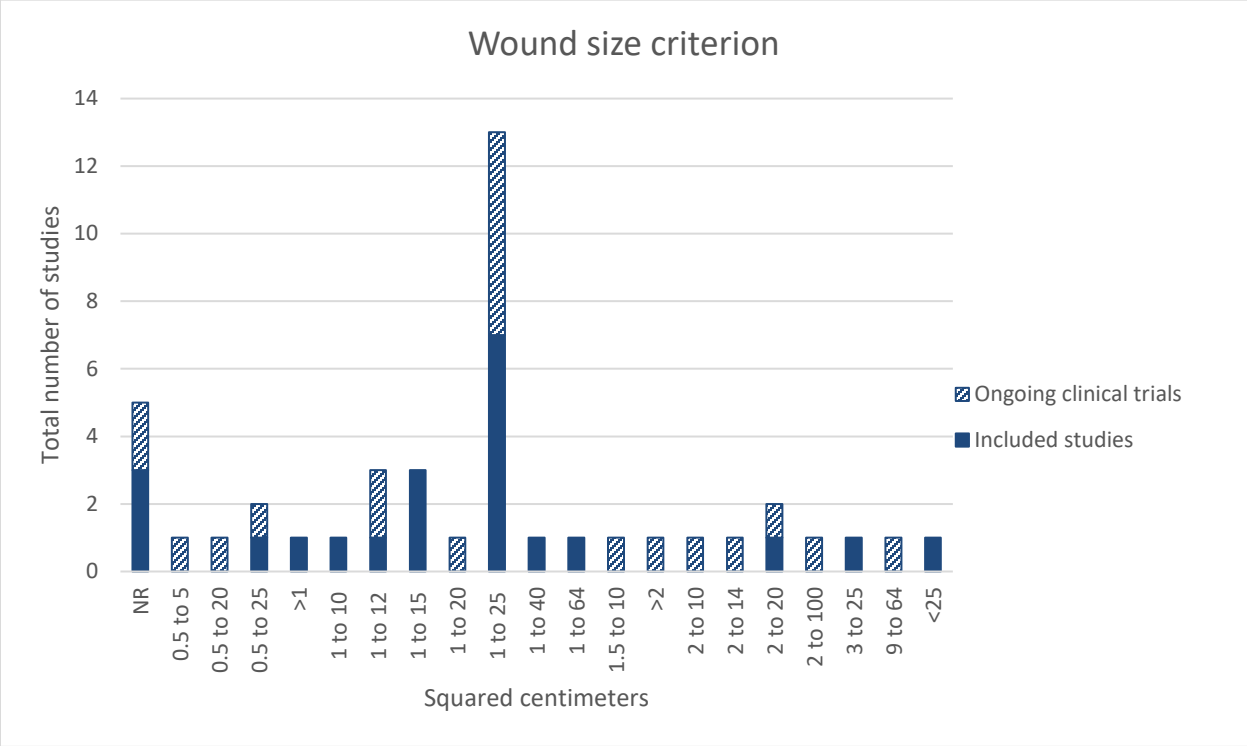


Figure 4. Wound Duration Criterion: 22 included RCTs and 21 ongoing clinical trials

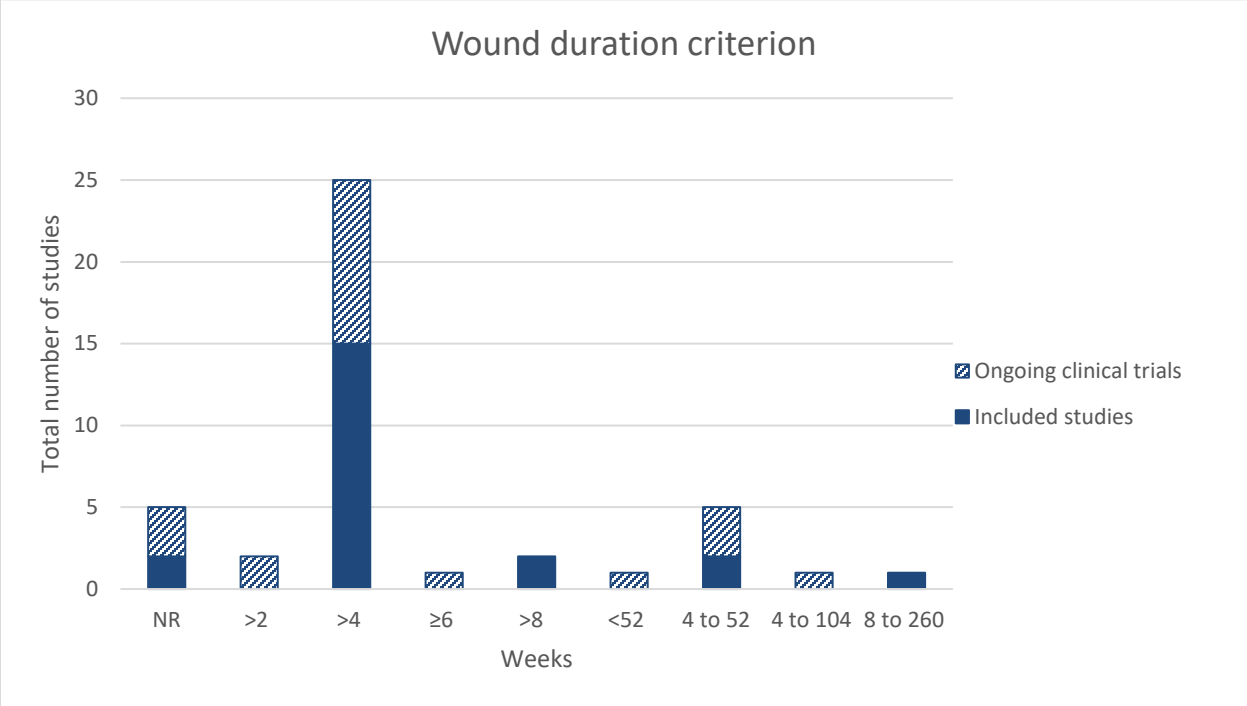
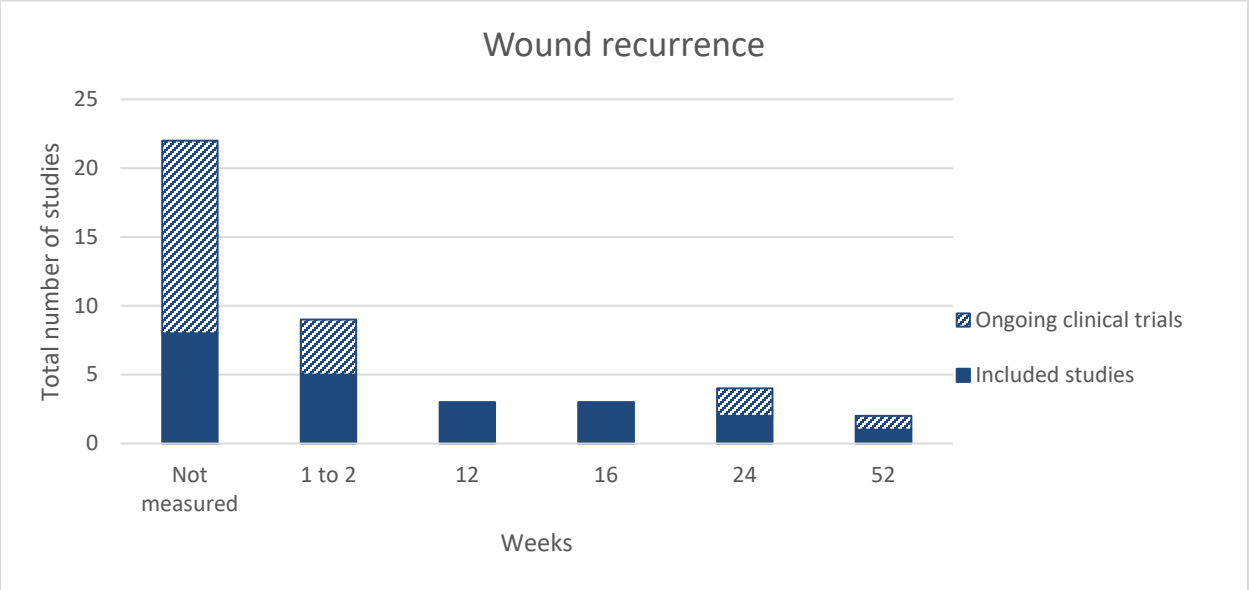


Figure 5. Wound Recurrence: 22 included RCTs and 21 ongoing clinical trials



Based on input from the KIs and our examination of the published and ongoing trials, we suggest the following design and conduct features for future studies of skin substitutes.

Patient Inclusion

Several KIs suggested that studies could include a broader selection of patients with comorbidities and poorer health that is more representative of the patient population seen in clinical practice. Most published studies identified for this report included patients without cardiovascular disease and kidney disease. Investigations of diabetic foot ulcers typically included only patients with HbA1c <12 percent. Some studies included smokers but did not assess healing rates in this population. Some expansion of patient inclusion criteria, such as including patients with HbA1c >12 percent, may provide information needed to better judge the effectiveness of skin substitutes in clinical practice. Larger trials would allow subgroup analysis according to initial wound size and duration and according to comorbidities and HbA1c levels; only four of the included studies reported a subgroup analysis by wound size and/or wound duration.[42,44,58,59] With expanded inclusion criteria, a broader range of wound sizes and durations could be included.

Four (18%) studies performed statistical analysis examining the influence of race[38,41,42,45] and Hispanic ethnicity[38] on healing of diabetic foot ulcers[41,42,45] and venous leg ulcers[38]. One study indicated that being Caucasian was significantly associated with healing within 12 weeks (hazard ratio, 3.01; 95% CI: 1.33 to 6.80; p=0.008).[42] Future research is needed in this area as well as an analysis of gender differences. We did not identify any studies that performed subgroup analysis by gender.

Registry studies may provide more data on patients outside the typical RCT. Data collected by the U.S. Wound Registry is intended to provide comparative-effectiveness data for patients with chronic wounds and ulcers being treated with cellular and/or tissue-based products that will include skin substitutes. Registry data may be used for subanalysis of key patient-related (e.g., gender, race, comorbidities) and wound-related characteristics (e.g., severity, wound duration)

that may not be available in typical RCTs. This information may help direct specific product use for different wound conditions.

Study Design

FDA's "Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds—Developing Products for Treatment" provides recommendations on clinical trial design for chronic wound studies.[83] FDA considered randomization particularly important for reducing bias "because standard wound care procedures and baseline wound characteristics generally have a profound effect on outcome." Other FDA recommendations include: "identical standard-of-care procedures in both the control and investigational product arms," "blinding of subjects and investigators to the assigned treatment reduces bias and should be employed when feasible," and "exclude subjects demonstrating substantial healing resulting solely from improved compliance with standard care."

Wound therapy for experimental and standard of care should be clearly described with all materials used on the wound attributed by product name and manufacturer. Serena et al. 2012 and the Alliance of Wound Care Stakeholders have emphasized the "need to explicitly state in detail what type of care was given to each type of wound in the study."[85] We suggest that unsuccessful therapies used before enrollment need to be described to distinguish patients who have received only standard of care from patients who may have received another advanced therapy. These requirements for describing both interventions and standard of care extend to registry studies as well as RCTs.

KIs recommended that studies include a 4-week run-in period before study enrollment and randomization; however, most included RCTs used a 2-week run-in period. Patients achieving 50 percent or better wound reduction during this period would continue with standard of care and would not be enrolled in the study. One KI indicated that a product that could accelerate healing with one application might still be appropriate to study in patients achieving 50 percent healing during a 4-week run-in period, given the potential for cost-savings.

In addition, KIs suggested that studies should treat patients for a minimum of 12 weeks to determine healing and then follow them until 6 months to determine wound recurrence. The Alliance of Wound Care Stakeholders recommends measuring wound recurrence.[85] Skin substitutes would be applied as recommended by the product labeling and by a trained health care provider. Failure to heal after 6 weeks of treatment with a skin substitute may be an appropriate criterion for discontinuing use of a skin substitute and switching to another advanced therapy option was also suggested.

Some KIs opined that studies of skin substitutes should be conducted in specialized wound centers with expertise in the use of wound care products. They felt such centers could determine whether proper standard of care had been used before the patient entered a trial. Two studies performed a subgroup analysis of patients with diabetic foot ulcers that received adequate debridement.[42,59] Both studies reported an increase in wounds healed with adequate debridement.

Blinding of patients and clinicians is difficult because skin substitutes are distinctly different from other products used to treat chronic wounds. However, allocation of treatment during randomization should always be blinded, and independent individuals blinded to wound treatment should assess wound healing. The Alliance of Wound Care Stakeholders has emphasized the need to "blind patients, clinical assessors, and analysts where possible."[85]

Additional studies not sponsored by industry would provide greater balance in this field.

Outcomes

Complete wound healing defined as complete reepithelization with no drainage or need for a dressing and confirmation 2-weeks later should be the primary outcome. FDA suggests this criteria in "Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds—Developing Products for Treatment."[83] Rate of wound closure should also be reported. KIs suggested that 40 percent to 50 percent wound closure in 4 weeks was a good predictor of successful wound closure. Evidence indicates that a 50 percent reduction in diabetic foot ulcers after 4 weeks of standard of care is a strong predictor of wound healing by 12 weeks with continued standard of care,[18] while percent change in wound area for venous leg ulcers after 4 weeks of standard of care is predictive of complete wound healing by 24 weeks with continued standard of care.[19]

Published studies seldom reported wound recurrence. In addition to reassessing healed wounds at 2 weeks, KIs suggested that wound recurrence be reported at 6-month followup after the wound has been designated healed. FDA recommends trial subjects be reevaluated at least 3 months following complete wound closure.[83] One KI mentioned use of teledermatology to track healing of chronic wounds. While we found no mention of measuring recurrence using teledermatology, perhaps future trials could incorporate this method of followup.

KIs suggested that patients be evaluated for pain using a visual analog scale (from 1-10), for wound odor and exudate, and for activities of daily living using a standardized validated assessment tool. Measuring pain in patients with diabetes with neuropathy may be challenging. As noted earlier, need for hospitalization and pain reduction was reported in only 14 percent of included studies; need for amputation, exudate, and odor control were reported in a single study (4.56%, 1/1722); return to baseline activities of daily living and functional capacity were not reported in any study. Quality-of-life scales used in included studies or ongoing clinical trials included wound-related quality-of-life scales (Cardiff Wound Impact Schedule, W-QoL) quality-of-life scales specific to diabetic wounds (Diabetic Foot Ulcer Scale), quality-of-life scales specific to venous leg ulcers (Sheffield Preference-based Venous Leg Ulcer 5D), and general quality-of-life scales (Short Form [SF]-36, SF-12v2). FDA also noted the importance of measuring quality of healing (e.g., cosmesis).[83] One ongoing clinical trial is measuring patient experience and perception of comfort and pain, as well as cost of treatment, including patient out-of-pocket payments (e.g., transport, medication for pain management, sleep) and patient/carer lost work time.

Lastly, reporting adverse events, such as wound infection during the study, allergic reactions to skin substitutes and wound therapy components, cellulitis, amputation, hospitalization due to infections, and deaths related to wounds, would benefit clinicians using these treatments. Documenting reasons for dropping out of a trial would also be helpful. The Alliance of Wound Care Stakeholders also recommends measuring dropout rates and reporting causes.[85]

Summary and Implications

Skin Substitutes Being Examined in Clinical Trials

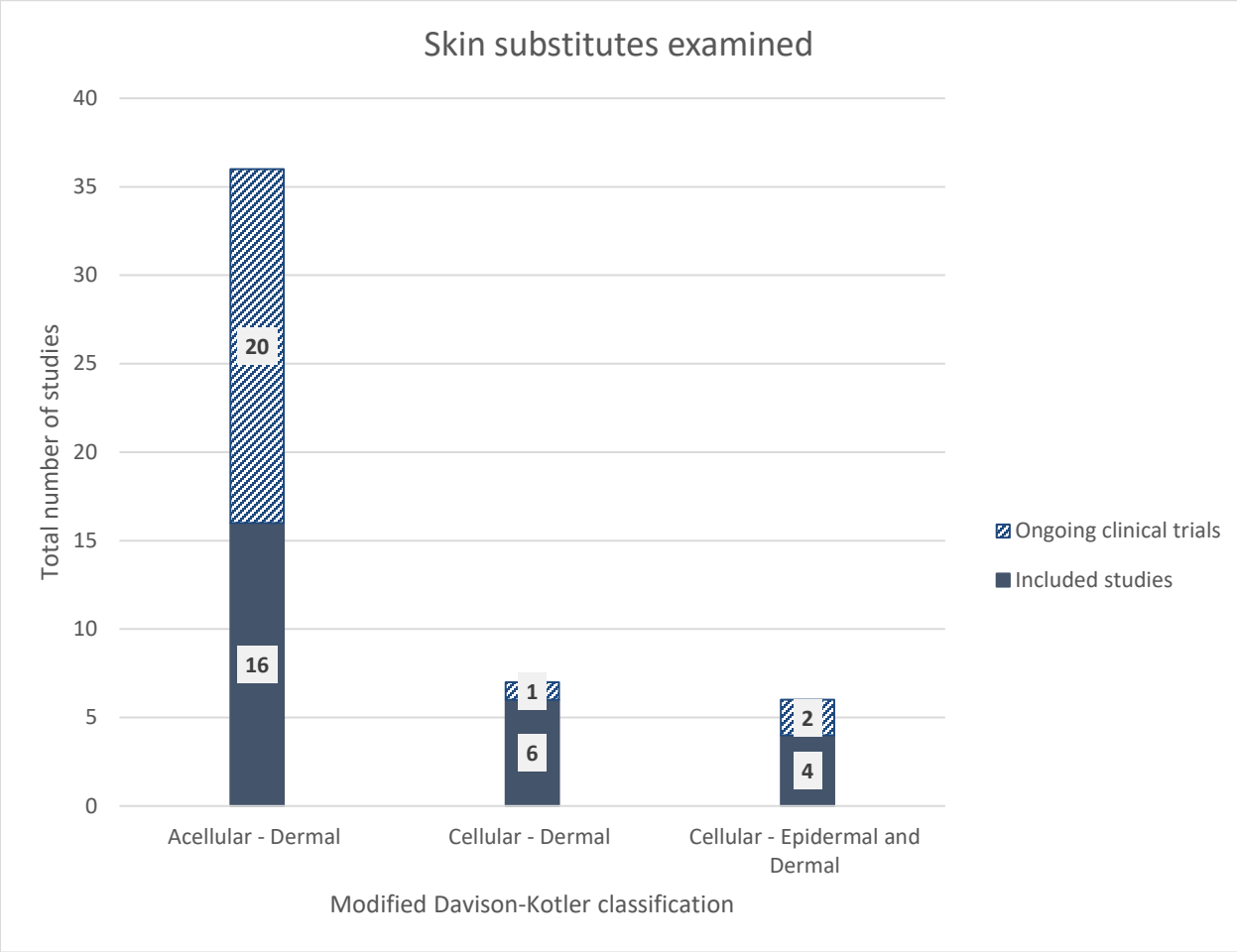
Of the 76 commercially available skin substitutes relevant to this report, included studies and ongoing clinical trials will have examined approximately 25 (33%) of these skin substitutes by early 2019. Using the modified Davison-Kotler classification system, studies will have examined acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes. Ongoing studies continue the trend of examining acellular dermal substitutes, mostly

replacements from human placental membranes. Figure 6 displays the skin substitutes that published and ongoing clinical trials are examining.

The 2012 report identified 57 skin substitute products, and 18 RCTs examined only 7 (12%) of these products. Five of these seven products were also examined in RCTs identified in the 2019 report. Apligraf was examined in three studies identified in the 2012 report and two studies identified in the 2019 report. TheraSkin was examined in one study identified in the 2012 report and two studies identified in the 2019 report. Dermagraft was examined in four studies identified in the 2012 report and four studies identified in the 2019 report. Graftjacket was examined in three studies identified in the 2012 report and one study identified in the 2019 report. Oasis Wound Matrix was examined in five studies identified in the 2012 report and one study identified in the 2019 report.

Disclaimer: A skin substitute's commercial availability is not a reflection of its legal status. Manufacturers self-determine whether their human cells, tissues, or cellular or tissue-based product can be marketed without FDA preapproval and often misunderstand or mischaracterize the criteria they must meet for the product to be regulated solely for communicable disease risk. See 21 CFR 1271.10(a). For more information, see "FDA Announces Comprehensive Regenerative Medicine Policy Framework."

Figure 6. Skin substitutes examined in 22 included RCTs and 21 ongoing clinical trials



The clearest implications of this Technical Brief are the lack of studies examining the effectiveness of most skin substitute products and the need for better-designed and better-reported studies providing more clinically relevant data. The 2012 report came to the same conclusion. The large majority of skin substitute products listed in the report did not have efficacy data from RCTs. The overall applicability of the 2012 evidence base was limited to a few skin substitutes examining diabetic foot ulcers and vascular leg ulcers and to patients in generally good health. The report noted that "various features of study design and conduct … could be improved in future wound care studies to ensure better study quality and low potential for bias."

Given that companies producing skin substitutes are promoting their products based on proprietary processing methods and claims of superior and more effective skin substitute composition as a result of these processes, each of these products needs to be examined in a properly designed and conducted clinical trial, as suggested above. Trial outcome information may then inform product labeling and assist clinicians using these products. Trial design can be standardized to ease comparisons across studies.

While most evidence continues to focus on use in diabetic foot ulcers, ongoing trials will provide additional published data on venous leg ulcers and pressure ulcers.

Wound Care Registries

Registries specific for wound care may provide additional effectiveness and harm data on use of skin substitutes for diabetic foot ulcers, venous leg ulcers, and pressure ulcers. Using real-world evidence derived from sources other than RCTs was emphasized in the 21st Century Cures Act.[86] The Act also emphasized the need for appropriate standards and methodologies for collecting and analyzing real-world evidence. According to AHRQ, a registry is "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical or policy purposes" and if "properly designed and executed, patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness."[87] Effective registries minimize potential sources of bias (systematic error) through planned design, conduct, and analysis. The population of interest, interventions of interest including exposure, outcomes of interest, intended users of the registry, and purpose of the registry should be decided on before or soon after the registry is started. The registry developer should provide guidance on patient enrollment, data collection, and verification to ensure the data's integrity. The 21st Century Cures Act states that clinician-led clinical data registries should meet "standards for data quality including systematically collecting clinical and other health care data, using standardized data elements and having procedures in place to verify the completeness and validity of those data."[86] The ACT also notes the need for "regular data checks or audits to verify completeness and validity."

Wound care registries should record detailed information on standard of care and how a skin substitute or other intervention are applied and for how long. Wound duration before advanced treatment, run-in period, and prior wound care should be noted. The intervention should be described in sufficient detail to distinguish a product's or device's various forms. Details of comorbidities, wound history, and other patient characteristics are also needed. Any publications originating from registry data should document standard of care received before and during use of a skin substitute. Details on study design, data collection, and quality assurance should be

publicly available. Developers of wound care registries may wish to review the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) for a checklist of items to include when describing a registry to the public.[88] The checklist includes items such as rationale, objectives, protocol, data collection process, risk-of-bias evaluation, interventions, comparators, outcomes, and funding source.

The Alliance for Wound Care Stakeholder's Panel on Wound Care Evidence-based Research has proposed criteria for observational studies designed to provide effectiveness data in real-world practice that are applicable to registry-based studies.[85] The Alliance is a non-profit multidisciplinary trade association that represents clinical societies and businesses with an interest in promoting quality care and access to products and services for people with wounds. According to the Alliance, appropriate reporting in any observational study publication should include defining the eligibility criteria for each group as well as sources and methods for selecting participants, properly defining allocation of treatment if relevant to study, defining primary and secondary outcomes, defining care guidelines especially if more than one center is involved, defining how missing data are handled (patients lost to followup), using appropriate followup that matches study goals, measuring dropout rates and causes, providing sufficiently detailed baseline data for all study groups, selecting experienced investigators and analysts at appropriate research sites, and using validated measurement tools. As mentioned above (pages 22-23), the registry studies submitted for review did not meet these criteria and were not originally created for investigating the effectiveness of skin substitutes for treating chronic wounds.

Delineating specific methods for registry studies is beyond the scope of this report. Additional information and guidance can be found in several publications. See the 3rd edition of AHRQ's publication "Registries for Evaluating Patient Outcomes: A User's Guide,"[87] a reference handbook with practical information on the design, operation, and analysis of patient registries. The Patient-Centered Outcomes Research Institute (PCORI) published "Standards in the Conduct of Registry Studies for Patient-Centered Outcomes Research" with a list of 17 recommended minimum standards for the design and conduct of disease or treatment registries and the design and analysis of studies using primarily or exclusively registry data.[89] The PCORI minimum standards are intended to help registries ensure "a minimum level of rigor and produce reliable, valid evidence." FDA issued guidance on "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[90] In the guidance, FDA notes that confidence in the reliability of real-world data and real-world evidence sources comes from ensuring data quality and following recommendations from organizations such as AHRQ and PCORI. In this document FDA emphasizes using real-world evidence primarily to support expanding indications for medical device use and for postmarket surveillance particularly involving medical device safety.

Findings

Of the 22 included RCTs[b], 16 studies compared a skin substitute with standard of care. Standard of care in these studies for each wound type included sharp debridement, glucose control, compression bandages for venous leg ulcers, pressure redistribution support surfaces for pressure ulcers, infection control, offloading, and daily dressing changes with a moisture-

[b] While AHRQ describes these studies as RCTs, no other component of Health and Human Services (HHS), including FDA, has examined the studies to determine the adequacy of these studies and whether such studies would qualify as adequate and well-controlled clinical trials under any HHS regulatory framework.

retentive dressing, such as an alginate or hydrocolloid. While 85 percent of studies examining acellular dermal substitutes described the experimental intervention as favorable over standard of care for wound healing and shorter time to heal, insufficient data are available to determine whether wound recurrence or other sequela are less frequent with acellular dermal substitutes. Only three studies compared cellular dermal substitutes with standard of care. Clinical evidence for cellular dermal substitutes may be limited by the lack of robust, well-controlled clinical trials of these products in this category.

Of the six head-to-head comparative studies, findings from five studies did not indicate significant differences between skin substitutes in outcomes measured at the latest followup (>12 weeks). The authors of one study ending at 12 weeks reported a significant difference in wound healing favoring an acellular dermal skin substitute over a cellular epidermal and dermal skin substitute.[41] The investigators in another study comparing two acellular dermal substitutes appear to have intentionally underpowered one arm of the study since statistical significance was not sought or expected for this study arm. Of the two studies reporting on recurrence, authors of one study reported similar recurrence,[46] while authors of another study reported no recurrence at 26 weeks.[35] We conclude that the current evidence base, as described by the authors in the referenced manuscripts, may be insufficient to determine whether one skin substitute product is superior to another.

The 2012 report had similar conclusions: "All the studies in the evidence base reported some benefit of skin substitutes over the control treatments when number of wounds completely healed was measured between 8 and 16 weeks but the reported results varied widely across studies." The 2012 report also found few studies comparing skin substitutes to each other; only two of the 18 RCTs featured head-to-head comparisons. The 2012 report stated: "Additional studies in this area of wound care would be helpful to provide treatment data for many of the other skin substitute products, to allow better comparisons between wound care products, and to provide better information on wound recurrence when using skin substitute products." In 2019, this still seems to be the case.

Evidence Gaps

The majority of studies examined treatment options for diabetic foot ulcers. More studies are needed on the treatment options for venous leg ulcers, pressure ulcers, and other chronic wounds to determine whether skin substitutes should be considered as an appropriate therapy for these wounds. RCTs are also needed comparing the different types of product categories as well as studies within categories. Because the acellular products use human dermis, placental membranes, or animal-sourced material, these products should be compared with standard of care and with each other. Results from an acellular dermal product created from human skin cannot be extrapolated to similar products or to acellular placental membrane and acellular animal products due to differences in processing, composition, and preservation methods. Processing methods differ between manufacturers, and each claims that its process is superior and preserves more of the factors the manufacturer claims may encourage wound healing, creating a need for more comparison studies between products. Manufacturer claims of superior wound healing cannot be verified without additional high-quality studies.

Industry funds most published studies. Industry funded 20 of 22 RCTs included in this report, which raises significant concerns about possible publication bias or selective outcome reporting in that results unfavorable to industry may not be reported or published. A reexamination of 15 ongoing clinical trials in the 2012 report *Skin Substitutes for Treating Chronic Wound*s[1] with

the status of completed/currently recruiting on ClinicalTrials.gov indicated a status of completed (10), terminated (4), and unknown (1). See Table E-2 in Appendix E. Of the 14 completed/ terminated trials, publications are available for five (35.7%) trials. Of the nine (64.3%) trials without publications, three trials were associated with discontinued products (NCT00399308, NCT01353495, NCT00270946); one trial completed in April 2018 (NCT01450943); while five trials completed before March 2017 (NCT01619670, NCT01729286, NCT01612806, NCT01270633, NCT00909870). We are unsure whether the lack of publications for these five trials is due to publication bias, but independent funding of skin substitute research would reduce potential for bias and make product comparisons more likely. The evidence gaps will be only partially addressed by currently registered ongoing trials, which are largely funded by industry. Only three of the ongoing RCTs are comparing two skin substitutes.

We found little information on the long-term effects of using skin substitutes. Wound recurrence was seldom reported, and potential toxic or carcinogenic effects are not known. Information on amputations and hospitalizations due to infections is also missing. Before findings can be relied upon, more data are needed on hospitalization, pain reduction, need for amputation, exudate and odor control, and return to baseline activities of daily living and function.

Next Steps

1. What Studies Should Be Conducted in the Future?

The current evidence base lacks studies comparing many of the skin substitutes to standard of care and to each other. These types of studies should be encouraged. Many clinicians lack access to information on these products specific to the course of healing and adverse events. The processing procedures used to create skin substitutes vary in terms of how they remove cells and DNA, preserve ECM structure, use or do not use cross-linking to reduce degradation, and how the product is eventually stored (frozen or room temperature). Studies could be conducted comparing similar products, such as acellular human dermis or placental membranes, and processed by different methods.

2. What Should Future Study Designs Have in Common?

Variation in study design reduces the ability to compare outcomes across studies. Researchers should be encouraged to use a more standardized study design approach when assessing skin substitutes and report on wound recurrence, patient pain, and activities of daily living as well as wound healing. Studies should adhere to a rigorous standard of care, ensuring adequate debridement, infection and diabetes management, offloading for diabetic foot ulcers, compression for venous leg ulcers, and pressure redistribution support surfaces for pressure ulcers. Studies could use a 4-week run-in period and enroll only patients who had not achieved 50 percent wound reduction during this period. Studies should document prior treatment with appropriate standard of care for at least 4 weeks before the run-in period to confirm wound chronicity. Studies should last a minimum of 12 weeks and then follow patients an additional 6 months to monitor wound recurrence. Allocation of treatment during randomization should always be blinded, and independent individuals blinded to wound treatment should assess wound healing. Trials might also use a standard method of measuring wound size and healing rate.

Adverse events (infections, amputations, allergic reactions, and deaths related to wounds) should be reported or stated as having not occurred, whichever is the case.

Clinicians would benefit from having additional clinical evidence of effectiveness in patients resembling those in clinical practice. Patients with cardiovascular disease, kidney disease, and poor glucose control or those who smoke could be included in studies large enough to allow subgroup analysis of these patient populations. Clinicians will also benefit from information on gender, race, ethnicity, age, and comorbidities. Long-term followup of patients may be particularly important to judge not only recurrence, but also potential toxic or other harmful effects. This information may become available in studies with long-term followup (e.g., 6 to 24 months).

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Abbreviations and Acronyms

ABI:	ankle brachial index
ACD:	acellular dermal matrix
ADA:	American Diabetes Association
ADM:	acellular dermal matrix
AE:	adverse event
AHRQ:	Agency for Healthcare Research and Quality
AIDS:	acquired immune deficiency syndrome
BMI:	body mass index
CAD:	coronary artery disease
CFR:	Code of Federal Regulations
CI:	confidence interval
CINAHL:	Cumulative Index to Nursing and Allied Health
cm:	centimeter
CMS:	U.S. Centers for Medicare & Medicaid Services
DAMA:	dehydrated amniotic membrane allograft
DFU:	diabetic foot ulcer
dHACA:	dehydrated human amnion and chorion allograft
DM:	diabetes mellitus
DPb:	composite dermal/epidermal, permanent, biological
ECM:	extracellular matrix
EPb:	epidermis, permanent, biological
EPC:	Evidence-Based Practice Center
FDA:	U.S. Food and Drug Administration
HbA1c:	Hemoglobin A1c test
HBOT:	hyperbaric oxygen therapy
HCT/P:	human cell, tissue, and cellular and tissue-based product
HFDS:	human fibroblast-derived dermal substitute
HR:	hazard ratio
HR-ADM:	human reticular acellular dermis matrix
HRQoL:	health-related quality of life
IDRT:	Integra dermal regeneration template
ITT:	intention-to-treat
KI:	Key Informant
LOCF:	last observation carried forward
MD:	mean difference
MLCT:	multilayer compression therapy
MMP:	matrix metalloproteases
MRI:	magnetic resonance imaging
NA:	not applicable
NHS:	National Health Service
NLM:	National Library of Medicine
NPWT:	negative pressure wound therapy
NR:	not reported
NYHA:	New York Heart Association
OR:	odds ratio
PAD:	peripheral artery disease
PHS:	public health service
PICOTS:	population, intervention, comparators, outcomes, timing, and setting
PMA:	premarket approval
PU:	pressure ulcer
PVD:	peripheral vascular disease
RCT:	randomized controlled trial
RR:	risk ratio
SAE:	serious adverse event
SAL:	sterility assurance level
SD:	standard deviation
SE:	standard error
SOC:	standard of care
TCOM:	transcutaneous oximetry
TRIP:	Turning Research Into Practice (database)
UK:	United Kingdom
vCPM:	viable cryopreserved placental membrane
VLU:	venous leg ulcer

Appendix A. Search Strategies

Resources Searched

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for each resource appear below.

Name	Date Limits	Platform/Provider
Cochrane Central Register of Controlled Trials (CENTRAL)	2012 through September 17, 2018	Wiley
Cochrane Database of Systematic Reviews (Cochrane Reviews)	2012 through September 17, 2018	Wiley
Cumulative Index of Nursing and Allied Health Literature (CINAHL)	2012 through September 13, 2018	EBSCOhost
Database of Abstracts of Reviews of Effects (DARE) (part of the Cochrane Library)	2012 through September 17, 2018	Wiley
EMBASE (Excerpta Medica)	2012 through February 19, 2019	Embase.com
Health Technology Assessment Database (HTA) (part of the Cochrane Library)	2012 through September 17, 2018	Wiley
MEDLINE	Inception [1966] through November 1, 2016 (KQ1) Inception through June 22, 2016 (KQ2)	Embase.com
PubMed (In Process citations)	Inception [1966] through November 3, 2016 (KQ1) Inception through February 19, 2019	NLM
U.K. National Health Service Economic Evaluation Database (NHS EED) (part of the Cochrane Library)	2012 through September 17, 2018	Wiley

Other Gray Literature Resources

Name	Date Limits	Platform/Provider
ClinicalTrials.gov	Open/Ongoing trials Searched June 28, 2018, and February 20, 2019	www.clinicaltrials.gov/
Epistemonikos	Searched September 18, 2018	https://www.epistemonikos.org/
National Institute for Health and Care Excellence, U.K.	Searched September 18, 2018	NHS
TRIP (Turning Research Into Practice) Database	Searched September 18, 2018	Trip Database, Ltd.
U.S. Food and Drug Administration (FDA), including Medical Device databases	Searched September 18, 2018	FDA

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Topic-Specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Chronic wounds	**EMBASE (EMTREE)** 'chronic wound'/exp 'decubitus'/exp 'diabetic foot'/exp **MEDLINE/PubMed (MeSH)** **CINAHL** (MH "Diabetic Foot") (MH "Foot Ulcer+") (MH "Leg Ulcer+") (MH "Pressure Ulcer+") (MH "Venous Ulcer") (MH "Wounds, Chronic")	Bedsore* Combinations of: Injur* Sore* Wound* Ulcer* Chronic* Intractab* 'Non-healing' Nonhealing Persisten* Arterial Bed Diabet* Feet Foot Leg Legs Pressure Venous
Skin substitutes	**EMBASE (EMTREE)** 'acellular dermal matrix'/exp 'artificial skin'/exp 'biological dressing'/exp 'engineered cartilage graft'/exp 'engineered skin autograft'/ 'engineered skin graft'/exp 'tissue engineering'/exp 'tissue scaffold'/exp **MEDLINE/PubMed (MeSH)** **CINAHL** (MH "Biological Dressings") (MH "Skin, Artificial") (MH "Tissue Engineering") (MH "Tissue Scaffolds")	Combinations of: Acellular Allograft* Amniot* Artificial bilayer Bioengineer* Biologic* Biosynthetic* Bovine Cadaver Engineer* Equivalen* HADM Living cell Porcine Regenerat* Replac* Synthetic* Substitut* Templat* Collagen Dermal Dermis Dressing* Epidermal Epidermis Scaffold*

Concept	Controlled Vocabulary	Keywords
		Skin Tissue* Wound*
Tradenames		Affinity Amniotic Alloderm Allomax Allopatch Alloskin Allowrap AmnioBand Amnioexcel Amniofix Amniomatrix Aongen matrix Architect matrix Apligraf Artacent Arthrex amnion Atlas wound matrix Arthroflex Avagen wound dressing Biobrane Bionnekt Biodfence Biodexcel bioDFactor biodmatrix Biomembrane Bioskin Biovance amniotic Celaderm Clarix Collagen sponge Collaguard CollaSorb Collawound Collexa Conexa reconstructive matrix CorMatrix Cytal wound matrix Cygnus Cymetra Dermacell Dermagraft Dermapure Dermaspan Dermavest Dresskin Endoform Epicel Epicord Epidex Ez-derm Flex HD Floweramnioflo Floweramniopathc Flowerderm Flowerflo Fortaderm Gammagraft Gelapin

Concept	Controlled Vocabulary	Keywords
		Grafix GrafixPL Graftjacket Graftskin Helicoll Hyalograft Hyalomatrix Hmatrix Hyalomatrix tissue reconstruction matrix Integra Keramatrix Kerecis Kollagen Laserskin Lyofoam Lyomousse Matriderm Matristem Matrix hd Mediskin Memoderm Miroderm neoPatch NEOX wound allografts Nushield placental Oasis Omnigraft Orcel PalinGen amniotic Permacol Permaderm Plurivest Primatrix Promatrix Promogran Puraply Puros dermis Renoskin Repliform Repriza Revita Revitalon Stratagraft Strattice Suprathel Syspur-derm Syspurderm Talymed Tensix Theraskin Tielle non-adhesive Tissuemend Transcyte Tranzgraft Truskin Vitro-skin Woundex UBM hydrated wound dressing UBM lyophilized wound dressing Xcm biologic tissue matrix

Search Strategies

EMBASE/MEDLINE (searched via Embase.com)

Set Number	Concept	Search Statement
1	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 OR 'engineered skin graft'/exp
2		((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
3		(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
4		(affinity NEAR/2 amniotic) OR alloderm 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 dresskin 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'
5	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
6	Combine sets	(#1 OR #2 OR #3 OR #4) AND #5
7	Apply language and date restrictions. Remove unwanted study designs	#6 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)
8	RCTs	#7 AND ('randomized controlled trial'/de OR random*:ti)
9	Meta-Analyses	#7 AND ('meta analysis'/de OR ((meta* NEXT/1 anal*):ti))
10	Systematic Reviews	#7 AND ('systematic review'/de OR systematic*:ti)
11	Combine sets	#9 OR #10 OR #11

Set Number	Concept	Search Statement
12	Wounds except diabetic foot	#7 AND (Bedsore* OR 'decubitus'/exp OR ((bed OR foot OR feet OR leg OR legs OR pressure OR venous OR arterial) NEAR/2 (sore* OR ulcer*)):ti,ab)
13	Controlled trials	'controlled clinical trial'/exp OR ((controlled OR control*) NEAR/2 group) OR controls:ab
14	Combine sets	#12 AND #13
15	Combine sets	#11 OR #14

EMBASE.com Syntax:

* = truncation character (wildcard)

NEAR/*n* = search terms within a specified number (*n*) of words from each other in any order

NEXT/*n* = search terms within a specified number (*n*) of words from each other in the order specified

/ = search as a subject heading

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

mj = denotes a term that has been searched as a major subject heading

:de = search in the descriptors field (controlled terms and keywords)

:lnk = floating subheading

/lim = limiter

:it,pt. = source item or publication type

:ti. = limit to title

:ti,ab. = limit to title and abstract fields

PubMed (PreMEDLINE)

PubMed In-Process Citations

Set Number	Concept	Search Statement
1	Skin substitutes	(acellular[tiab] OR artificial*[tiab] OR bioengineer*[tiab] OR biosynthetic*[tiab] OR engineer*[tiab] OR equivalen*[tiab] OR regenerat*[tiab] OR replac*[tiab] OR synthetic*[tiab] OR substitut*[tiab] OR templat*[tiab]) AND (epidermal[tiab] OR epidermis[tiab] OR dermis[tiab] OR dermal[tiab] OR skin[tiab] OR tissue*[tiab])
2		(matrices[tiab] OR matrix[tiab]) AND (acellular[tiab] OR extracellular[tiab] OR decellular*[tiab] OR dermal[tiab] OR skin[tiab] OR tissue*[tiab] OR wound*[tiab])
3		scaffold*[tiab] AND (dermal[tiab] OR engineer*[tiab] OR repair*[tiab] OR tissue*[tiab] OR skin[tiab])
4		(acellular[tiab] AND allograft*[tiab]) OR ((amniot*[tiab] OR cadaver*[tiab]) AND (skin*[tiab] OR tissue*[tiab])) OR biologic*dressing*[tiab] OR (collagen[tiab] AND (bovine[tiab] OR porcine [tiab])) OR (regenerat*[tiab] AND (template*[tiab] OR matrix[tiab])) OR bilayer* living cell* OR hadm

Set Number	Concept	Search Statement
5		affinity amniotic OR alloderm OR allomax OR allopatch OR alloskin OR allowrap OR AMNIOwound OR AmnioBand OR amnioexcel OR amniofix OR amniomatrix OR aongen matrix OR architect matrix OR apligraf OR artacent OR arthrex 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"
6		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 dresskin 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
7		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
8		"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"
9	Combine skin substitute sets	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
10	Chronic wounds	bedsore* OR “chronic wound” OR decubitus ulcer* OR diabetic foot
11		(injur*[tiab] OR wound*[tiab] OR ulcer*[tiab]) AND (chronic* [tiab] OR intractab*[tiab] OR non-healing[tiab] OR nonhealing[tiab] OR persisten*[tiab])
12		(bed[tiab] OR foot[tiab] OR feet[tiab] OR diabet*[tiab] OR leg [tiab] OR legs[tiab] OR pressure[tiab] OR venous[tiab]) AND (sore*[tiab] OR ulcer*[tiab])
13		diabet*[tiab] AND (feet[tiab] OR foot[tiab])
14	Combine chronic wound sets	#10 OR #11 OR #12 OR #13
15	Combine sets	#9 AND #14
16	Limit to in process publications	#15 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb])
17	Remove animal studies	#16 NOT (mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rabbit*[ti] OR sheep[ti])
18	Meta-analyses & Systematic Reviews	#16 AND (meta-analysis OR meta-analysis[pt] OR “metaanalytic"[tiab] OR metaanaly*[tiab] OR "research synthesis"[tiab] OR systematic review[tiab] OR systematic[ti])
19	RCTs	#16 AND (“randomized controlled” OR random*[ti])
20	Non-RCT controlled trials	#16 AND ((control*[tiab] AND trial*[tiab]) OR “control group” OR controls[ab] OR “comparative effectiveness” OR “prospective controlled”
21	Combine sets	#18 OR #19 OR #20
22	Limit to English	#21 AND eng[la]

Set Number	Concept	Search Statement
23	Remove unwanted publication types	#22 NOT (year-old[tiab] OR "case report"[ti] OR comment[ti])
24	Limit by date	#23 AND 2012:2018[edat]

PubMed Syntax

* = truncation character (wildcard)

[mh]/[MesH] = controlled vocabulary term

[sb] = subset

[ti] = limit to title field

[tiab] = limit to title and abstract fields

[tw] = text word

CINAHL

Set Number	Concept	Search Statement
1	Skin substitutes	(MH "Biological Dressings") OR (MH "Skin, Artificial") OR (MH "Tissue Engineering") OR (MH "Tissue Scaffolds")
2		(acellular OR artificial* OR bioengineer* OR biosynthetic* OR engineer* OR equivalen* OR regenerat* OR replac* OR synthetic* OR substitut* OR templat*) N2 (epidermal OR epidermis OR dermis OR dermal OR skin OR tissue*)
3		(matrices OR matrix) N2 (acellular OR extracellular OR decellular* OR dermal OR skin OR tissue* OR wound*)
4		scaffold* N2 (dermal OR engineer* OR repair* OR tissue* OR skin)
5		(acellular N2 allograft*) OR ((amniot* OR cadaver*) N2 (skin* OR tissue*)
6		biologic* dressing* OR (collagen N2 (bovine OR porcine)) OR (regenerat* N2 (template* OR matrix)) OR bilayer* living cell* OR hadm
7		(affinity N2 amniotic) OR alloderm OR allomax OR allopatch OR alloskin OR allowrap OR AMNIOwound OR AmnioBand OR amnioexcel OR amniofix OR amniomatrix OR (aongen N2 matrix) OR (architect N2 matrix) OR apligraf OR artacent OR arthrex amnion OR atlas wound matrix OR arthroflex OR avagen wound dressing OR biobrane OR bio-connekt OR biodfence
8		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 dresskin OR Endoform
9		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

Set Number	Concept	Search Statement
10		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
11		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"
12	Combine skin substitutes sets	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
13	Chronic wounds	(MH "Pressure Ulcer+") OR (MH "Leg Ulcer+") OR (MH "Foot Ulcer+") OR (MH "Diabetic Foot") OR (MH "Venous Ulcer") OR (MH "Wounds, Chronic")
14		bedsore* OR decubitus ulcer*
15		(injur* OR wound* OR ulcer*) N2 (chronic* OR intractab* OR 'non-healing' OR nonhealing OR persisten*)
16		(bed OR foot OR feet OR diabet* OR leg OR legs OR pressure OR venous) N2 (sore* OR ulcer*)
17		(diabet* N2 (feet or foot)
18	Combine wound sets	S13 OR S14 OR S15 OR S16 OR S17
19	Combine sets	S12 AND S18
20	Meta-analyses	(MH "Meta Analysis")
21		TI meta* anal*
22	Systematic Reviews	(MH "Systematic Review")
23		TI systematic*
24	RCTs	(MH "Randomized Controlled Trials")
25		TI random*
26	Combine study types	S20 OR S21 OR S22 OR S23 OR S24 OR S25
27	Combine sets and apply limits	(S19 AND S26) AND Limiters-Exclude MEDLINE records;Published Date: 20120101-20181231; English Language

CINAHL Syntax

+ = explode

* = truncation character (wildcard)

N*n* = search terms within a specified number (*n*) of words from each other in any order

TI = limit to title field

AB = limit to title and abstract fields

MH = MeSH heading

MJ = MeSH heading designated as major topic

PT = publication type

FDA Classification Database

Highly relevant codes

Procode	Descriptor
MGR	device, dressing, wound and burn, interactive
PBD	composite cultured skin
PFC	cultured human cell skin dressing

Possibly relevant codes

Procode	Descriptor
MGP	dressing, wound and burn, occlusive
NAD	dressing, wound, occlusive

Other related codes

Procode	Descriptor
FTM	mesh, surgical
FTL	mesh, surgical, polymeric
MGQ	dressing, wound and burn, hydrogel w/ drug or biologic
FRO	dressing, wound, drug
KGN	dressing, wound, collagen
GER	gauze, external w/ drug/biologic/animal source material
OCE	cultured epithelial autograft

Appendix B. Excluded Studies Based on Review of Full-Length Articles

Duplicate Study or Duplicate Reporting of Patients

Oliveira Paggiaro André, Garcia Menezes Andriws, Donizetti Ferrassi Alexandra, Fernan des De Carvalho Viviane, Gemperl Rolf. Biological effects of amniotic membrane on diabetic foot wounds: a systematic review. Journal Of Wound Care. Feb 2018. 27:S19

Zelen CM, Orgill DP, Serena T, Galiano R, Carter MJ, DiDomenico LA, Keller J, Kaufman J, Li WW. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. International Wound Journal. 1 Apr 2017. 14:307-315

Santema TBK, Poyck PPC, Ubbink DT. Systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers: Highlights of a Cochrane systematic review. Wound Repair And Regeneration. 1 Jul 2016. 24:737-744

DiDomenico LA, Orgill DP, Galiano RD, Serena TE, Carter MJ, Kaufman JP, Young NJ, Zelen CM. Plast Reconstr Surg Glob Open. 2016 Oct 12;4(10):e1095. eCollection 2016 Oct.

Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. International Wound Journal. 1 Dec 2015. 12:724-732

Lavery Lawrence A, Fulmer James, Shebetka Karry Ann, Regulski Matthew, Vayser Dean, Fried David, Kashefsky Howard, Owings Tammy M, Nadarajah Janaki. The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International Wound Journal. Oct 2014. 11:554-561

Included in Skin Substitutes for Treating Chronic Wounds

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. Journal Of The American Academy Of Dermatology. June 2012. 66:e209-e215

No Outcomes of Interest

Stone RC, Stojadinovic O, Rosa AM, Ramirez HA, Badiavas E, Blumenberg M, Tomic-Canic M. A bioengineered living cell construct activates an acute wound healing response in venous leg ulcers. Science Translational Medicine. 4 Jan 2017. 9:#pages#

Not a Comparator of Interest (Inadequate Standard of Care)

Campitiello F, Mancone M, Della Corte A, Guerniero R, Canonico S. To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. Updates In Surgery. 1 Dec 2017. 69:523-529

Not a Comparator of Interest (Dissimilar Standard of Care)

Cazzell SM, Lange DL, Dickerson JE, Slade HB. The Management of Diabetic Foot Ulcers with Porcine Small Intestine Submucosa Tri-Layer Matrix: A Randomized Controlled Trial. Advances In Wound Care. 1 Dec 2015. 4:711-718

Not a Study of Interest

Luck J, Rodi T, Geierlehner A, Mosahebi A. Allogeneic Skin Substitutes Versus Human Placental Membrane Products in the Management of Diabetic Foot Ulcers: A Narrative Comparative Evaluation of the Literature. Int J Low Extrem Wounds. 2019 Jan 20;Epub ahead of print. Also available: **http://dx.doi.org/10.1177/1534734618818301**.

Tchero H, Herlin C, Bekara F, Kangambega P, Sergiu F, Teot L. Failure rates of artificial dermis products in treatment of diabetic foot ulcer: a systematic review and network meta-analysis. Wound Repair And Regeneration: Official Publication Of The Wound Healing Society [And] The European Tissue Repair Society. 2017 Aug. 25:691-6. Epub 2017 Jun 21

Game FL, Apelqvist J, Attinger C, Hartemann A, Hinchliffe RJ, Löndahl M, Price PE, Jeffcoate WJ. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: A systematic review. Diabetes/Metabolism Research And Reviews. 1 Jan 2016. 154-168

Pourmoussa A, Gardner DJ, Johnson MB, Wong AK. An update and review of cell-based wound dressings and their integration into clinical practice. Annals Of Translational Medicine. 2016. 4.

Santema TB, Poyck PPC, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Cochrane Database Of Systematic Reviews. 11 Feb 2016. 2016.

Holmes C, Wrobel JS, Maceachern MP, Boles BR. Collagen-based wound dressings for the treatment of diabetes-related foot ulcers: A systematic review. Diabetes, Metabolic Syndrome And Obesity: Targets And Therapy. 18 Jan 2013. 17-29

Hankin CS, Knispel J, Lopes M, Bronstone A, Maus E. Clinical and cost efficacy of advanced wound care matrices for venous ulcers. Journal Of Managed Care Pharmacy. 2012 Jun. 18: 375-84

Not a Study Design of Interest

Tchanque-Fossuo CN, Dahle SE, Lev-Tov H, Li CS, Isseroff RR. Cellular versus acellular grafts for diabetic foot ulcers: altering the protocol to improve recruitment to a comparative efficacy trial. Cutis. 2017 Nov 1;100(5):E18-E21.

Nherera Leo M, Romanelli Marco, Trueman Paul, Dini Valentina. An Overview of Clinical and Health Economic Evidence Regarding Porcine Small Intestine Submucosa Extracellular Matrix in the Management of Chronic Wounds and Burns. Ostomy Wound Management. Dec 2017. 63:38-48

Frykberg RG, Marston WA, Cardinal M. The incidence of lower-extremity amputation and bone resection in diabetic foot ulcer patients treated with a human fibroblast-derived dermal substitute. Advances In Skin & Wound Care. 1 Jan 2015. 28:17-20

Not an Intervention of Interest

Chicone Gisele, Fernandes de Carvalho Viviane, Oliveira Paggiaro André. Use of Oxidized Regenerated Cellulose/Collagen Matrix in Chronic Diabetic Foot Ulcers: A Systematic Review. Advances In Skin & Wound Care. Feb 2018. 31:66-72

Shu X, Shu S, Tang S, Yang L, Liu D, Li K, Dong Z, Ma Z, Zhu Z, Din J. Efficiency of stem cell based therapy in the treatment of diabetic foot ulcer: A meta-analysis. Endocrine Journal. 2018. 65:403-413

Dehghani M, Azarpira N, Mohammadkarimi V, Mossayebi H, Esfandiari E. Grafting with cryopreserved amniotic membrane versus conservative wound care in treatment of pressure ulcers: A randomized clinical trial. Bulletin of Emergency and Trauma. 1 Oct 2017. 5:249-258

Hu Z, Zhu J, Cao X, Chen C, Li S, Guo D, Zhang J, Liu P, Shi F, Tang B. Composite skin grafting with human acellular dermal matrix scaffold for treatment of diabetic foot ulcers: A randomized controlled trial. Journal Of The American College of Surgeons. 1 Jun 2016. 222:1171-1179

Kloeters Oliver, Unglaub Frank, de Laat Erik, van Abeelen Marjolijn, Ulrich Dietmar. Prospective and randomised evaluation of the protease-modulating effect of oxidised regenerated cellulose/collagen matrix treatment in pressure sore ulcers. International Wound Journal. Dec 2016. 13:1231-1237

You HJ, Han SK, Rhie JW. Randomised controlled clinical trial for autologous fibroblast-hyaluronic acid complex in treating diabetic foot ulcers. Journal Of Wound Care. 1 Nov 2014. 23:#pages#

Gottrup F, Cullen BM, Karlsmark T, Bischoff-Mikkelsen M, Nisbet L, Gibson MC. Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. Wound Repair And Regeneration. March-April 2013. 21:216-225

You HJ, Han SK, Lee JW, Chang H. Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes - A pilot study. Wound Repair And Regeneration. July-August 2012. 20:491-499

Hanumanthappa MB, Gopinathan S, Suvarna R, Guruprasad RD, Shetty G, Shetty K, Shetty S, Nazar Z. Amniotic membrane dressing versus normal saline dressing in non-healing lower limb ulcers: A prospective comparative study at a teaching hospital. Journal Of Clinical And Diagnostic Research. 1 May 2012. 6:423-427

Primary Studies Published Before 2012

Li X, Xu G, Chen J. Tissue engineered skin for diabetic foot ulcers: A meta-analysis. International Journal Of Clinical And Experimental Medicine. 30 Oct 2015. 8:18191-18196

Braun LR, Fisk WA, Lev-Tov H, Kirsner RS, Isseroff RR. Diabetic foot ulcer: An evidence-based treatment update. American Journal Of Clinical Dermatology. July 2014. 15:267-281

Greer N, Foman NA, MacDonald R, Dorrian J, Fitzgerald P, Rutks I, Wilt TJ. Advanced wound care therapies for nonhealing diabetic, venous, and arterial ulcers: A systematic review. Annals Of Internal Medicine. 15 Oct 2013. 159:532-542

Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. Cochrane Database Of Systematic Reviews. 31 Jan 2013. 2013.

Felder 3rd JM, Goyal SS, Attinger CE. A systematic review of skin substitutes for foot ulcers. Plastic And Reconstructive Surgery. Jul 2012. 130:145-164

Iorio ML, Shuck J, Attinger CE. Wound healing in the upper and lower extremities: a systematic review on the use of acellular dermal matrices. #journal#. Nov 2012. 130.

Voigt J, Driver VR. Hyaluronic acid and wound healing. Wound Repair And Regeneration. May-June 2012. 20:317-331

Game FL, Hinchliffe RJ, Apelqvist J, Armstrong DG, Bakker K, Hartemann A, Löndahl M, Price PE, Jeffcoate WJ. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes/Metabolism Research And Reviews. February 2012. 28:119-141

Appendix C. Clinical Evidence

Table C-1. Characteristics of systematic reviews

Citation	Objective	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Interventions	Relevant Findings	Authors' Conclusions
Paggiaro et al. 2018[51]	To analyze the scientific evidence on use of amniotic membranes to stimulate DFU healing.	Searches were completed in Lilacs, BVS, and PubMed for articles published between 2007 and 2017. 71 articles were considered for inclusion.	RCTs (published in Portuguese or English) using amniotic membrane dressings to treat DFUs and evaluating wound healing were included.	Studies: 6 RCTs (n=331) published from 2013 to 2017 were included. All studies were conducted in the United States. Enrollment (range): 25 to 100 Followup: 6 weeks (2 studies), 12 weeks (4 studies	1 study each examined SOC vs. Grafix, AmnioBand, EpiFix, and AmnioExcel. 1 study examined weekly vs. biweekly EpiFix; and 1 study examined EpiFix vs. Apligraf vs. SOC. Alginate and collagen alginate were 2 examples of standard wound care used.	Wound healing (yes or no) (5 studies, n=258): RR: 2.77, 95% CI: 1.76 to 4.36; I^2=41% Average wound healing time in days (3 studies, n=112): MD -32.28 days, 95% CI: -41.05 to -23.71; I^2=0%	The authors drew an erroneous conclusion based on the data they provide: "There is no statistical evidence to support the effectiveness of amniotic membrane in comparison with other conventional dressings. However, there is a clear tendency for the use of amniotic membrane treatment to result in a larger number of DFUs healing at a quicker rate." We replicated the meta-analyses, finding the same results for RR and mean difference as stated in the paper. Both outcomes are statistically significant and clinically important. In the text, the authors reference the p-values for the tests of heterogeneity, which have no bearing on the statistical significance of the difference between groups. We contacted the authors, who are now submitting an erratum to the journal.

Citation	Objective	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Interventions	Relevant Findings	Authors' Conclusions
Guo et al. 2017[52]	To compare ADM's efficacy and safety to those of SOC in DFU	PubMed, MEDLINE, EMBASE, and Cochrane library were searched up to August 2016 for comparative studies involving ADM in the management of DFU. 266 articles were eligible for inclusion.	RCTs (>10 patients per arm) comparing ADM to SOC in DFU reporting an outcome of interest (healing rate, time to heal, wound area reduction, and adverse events).	Studies: 6 RCTs (n=632) published from 2004 to 2015. ADM is human-derived in 5 studies and animal-derived in 1 study. Enrollment (range): 28 to 307 Followup: 4 weeks (1 study), 12 weeks (2 studies), 16 weeks (3 studies) Heterogeneity among studies: estimated using I^2 statistic. Substantial heterogeneity was represented by an I^2 value >50%.	1 study each examined SOC with AlloPatch Pliable, and Integra Dermal Regeneration Template. 3 studies examined GraftJacket vs. SOC; 1 study examined Graftjacket vs. DermACELL vs. SOC. SOC was described as including several "routine methods," including sharp debridement, glucose control, infection control, offloading, and daily dressing change. Dressings were described as alginate, advanced moist therapy, 0.9% sodium chloride/gel/foam/ gauze, alginate/ hydrocolloids/ hydrogel/foam, and wound gel with gauze dressings (2 studies).	Complete wound healing at 12 weeks (6 studies, n=632): RR 2.31, 95% CI: 1.42 to 3.76; I^2 =74% Complete wound healing at 16 weeks (3 studies, n=467): RR 1.57, 95% CI: 1.28 to 1.93; I^2 =37% Time to heal (weeks) (4 studies, n=193): MD -2.98, 95% CI: -5.15 to -0.82; I^2 =77% Adverse events (6 studies, n=632): RR 0.98, 95% CI: 0.58 to 1.67 Heterogeneity for the outcomes complete wound healing at 12 weeks (6 studies) and time to heal (4 studies) was significant. For complete wound healing, the authors noted moderate heterogeneity remained after removing 1 study measuring the healing rate in the first 4 weeks. For time to heal, 1 study was noted as having overly influenced heterogeneity.	"Compared with standard of care, acellular dermal matrix may accelerate the healing velocity of uninfected, non-ischemic, full-thickness diabetic foot ulcer. Acellular dermal matrix showed superiority compared with standard of care alone, while generating no more complications."

Citation	Objective	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Interventions	Relevant Findings	Authors' Conclusions
Haugh et al. 2017[53]	To describe and meta-analyze studies comparing commercially available amniotic tissue products with standard wound care in RCTs.	PubMed, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched. Publication dates were not reported.	RCTs comparing amniotic tissue products with SOC for use in nonhealing DFUs published in peer-reviewed English-language journals were included. Studies solely comparing amniotic tissue products with bioengineered skin substitutes were excluded. 596 articles were identified as relevant.	Studies: 5 RCTs (n=311) published from 2013 to 2016. 52 patients treated with a bioengineered skin substitute (Apligraf) were excluded, resulting in 259 being analyzed. 4 studies analyzed dehydrated amniotic products (EpiFix and AmnioExcel). 1 study analyzed a cryopreserved amniotic product (Grafix). Enrollment (range): 25 to 100 Followup: 6 weeks (2 studies), 12 weeks (3 studies) Heterogeneity among studies: heterogeneity was assessed using Q and I^2 statistics. I^2 values of 25%, 50%, and 75% were considered indicative of a low, moderate, and high amount of heterogeneity, respectively.	3 studies compared EpiFix with SOC. 1 study each compared SOC to AmnioExcel or Grafix. All 3 studies described standard of care. All 3 studies included debridement. 1 study also reported using appropriate moist wound therapy and compression dressings. 1 study reported hemostasis, moist wound dressings, offloading, and infection surveillance. 1 study also reported offloading and nonadherent dressings.	Complete wound healing (5 RCTs, n=311): RR: 2.75 (2.06 to 3.66; I^2=50.5%	"The current meta-analysis indicates that the treatment of [DFUs] with amniotic membrane improves healing rates in [DFUs]. Further studies are needed to determine whether these products also decrease the incidence of subsequent complications, such as amputation or death, in diabetic patients."

ADM=acellular dermal matrix; CI=confidence interval; DFU=diabetic foot ulcer; HR-ADM=human reticular acellular dermis matrix; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; MD=mean difference; RCT=randomized controlled trial; RR=risk ratio or relative risk; SOC=standard of care

Table C-2. Risk-of-bias assessments of individual studies included in systematic reviews

Citation	Title	Risk of Bias Tool	Risk-of-bias Assessment
Paggiaro et al. 2018[51]	*Biological Effects of Amniotic Membrane on Diabetic Foot Wounds: A Systematic Review*	Cochrane Handbook for systematic reviews of interventions Version 5.1.0	Authors noted selection bias (due to unclear/lack of allocation concealment in 50% of studies), detection bias (unclear/lack of blinding assessors in 50% of studies), and attrition bias (incomplete outcome data in 50% of studies) as study limitations.
Guo et al. 2017[52]	*Efficacy and Safety of Acellular Dermal Matrix in Diabetic Foot Ulcer Treatment: A Systematic Review and Meta-Analysis*	Cochrane Handbook for systematic reviews of interventions Version 5.1.0	Authors noted selection bias (due to unclear allocation concealment), performance bias (unclear/lack of blinding patients and personnel), detection bias (lack of blinding assessors in 50% of studies), and other bias (not described) as study limitations.
Haugh et al. 2017[53]	*Amnion Membrane in Diabetic Foot Wounds: A Meta-analysis*	Based on guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology Collaboration	Findings not reported.

Table C-3. Patient enrollment criteria for studies comparing acellular dermal substitutes with standard of care

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Brown-Etris et al. 2019[58]	1 cm^2 to 64 cm^2	NR	Individuals with Stage III and Stage IV ulcers diagnosed by clinical presentation, a viable wound bed with at least 80% granulation tissue, depth ≤1.5 cm, and undermining/ tunneling ≤1.5 cm. On a pressure-reducing support device. No wounds with heavy or high volume exudate; eschar; significant arterial disease (ABI less than 0.60).	Age ≥18 years and willing to sign consent. No medical conditions known to impair wound healing (including, but not limited to: malnutrition (Albumin<2.5 mg/dL). No cellulitis, osteomyelitis, necrotic or avascular ulcer beds. No uncontrolled diabetes (HbA1c >12%). No sickle cell disease, or taking concomitant medication known to impair wound healing (corticosteroids >10 mg daily, immune suppressives). No history of radiation therapy to the wound site; allergy to porcine products; clinical signs of infection at the target ulcer; undergoing hemodialysis; or having religious or cultural objections to the use of porcine products.	Type 1 and Type 2 diabetes, connective tissue disease, immunosuppression, peripheral vascular disease, dementia
Cazzell S. 2019[49]	≥1 cm^2 and <25 cm^2	≥60 days	Single target VLU with a CEAP Grade 6. No infection and wound depth ≤9 mm. No recent revascularization procedure to increase blood flow in the target limb. Determination of adequate circulation defined as having at least 1 of the following criteria within the past 60 days: $TcPO_2$ at the dorsum of the foot ≥30 mmHg, ABI ranging from 0.8-1.2, or at least biphasic Doppler arterial waveforms at the dorsalis pedis and posterior tibial arteries.	Age ≥21 and ≤80 years. No HbA1c "<12%" (we presume the authors intended >12%) within 90 days of screening visit, serum creatinine concentrations ≥3.0 mg/dL within 30 days of screening. No application of biomedical or topical growth factors or living skin equivalents to the target wound within 30 days prior to screening. No sensitivity to potential D-ADM processing reagents gentamicin, polymyxin B, vancomycin, N-lauroyl sarcosinate, Benzonase, or glycerol.	Type 2 diabetes, obese

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
				No presence of severe peripheral vascular disease, active infection, untreated malignancy, active Charcot's disease, necrosis, purulence, or sinus tracts in the ulcer that could not be removed by debridement. Ability to comply with offloading and dressing change requirements.	
Tettelbach et al. 2019[59]	1 cm^2 to 15 cm^2	≥30 days	Ulcer located below ankle. Completed 14-day run-in period with ≤30% wound area reduction post-debridement. Adequate circulation to the affected extremity. Index ulcer not penetrating down to tendon or bone. No ulcer within 3 cm of index ulcer. No active Charcot deformity. No major structural abnormalities of the foot. No clinical signs and symptoms of infection, known or suspected ulcer malignancy, or wound duration >1 year without intermittent closure. No known osteomyelitis or active cellulitis at wound site. No amputation or revascularization (surgical or stenting) to the affected leg or foot in the last 6 months.	History of Type 1 or Type 2 diabetes. Age ≥18 years. Willing and able to provide informed consent and participate in all procedures and followup evaluations necessary to complete the study. No NPWT or HBOT in the last 7 days. No chemical debridement, Dakin's solution, or medical honey therapy in the last 10 days. No cytotoxic chemotherapy, topical steroids, use of ≥14 days of immune suppressants, any biological skin substitutes, or use of investigational drugs or therapeutic devices in the last 30 days. No HbA1c >12 in the last 60 days prior to randomization. No history of immune system disorders including systemic lupus erythematosus, fibromyalgia, AIDS, or HIV. Not currently receiving radiation therapy or chemotherapy. Not currently on dialysis or planning to start dialysis.	Diabetic, obese, smoker, alcohol use, cardiovascular disease

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Tettelbach et al. 2019[42]	≥1 cm^2 and < 25 cm^2	≥4 weeks, unresponsive to SOC	No clinical signs of infection. Adequate circulation to the affected extremity, as demonstrated dorsum transcutaneous oxygen test ≥30 mm Hg; ABI between 0.7 and 1.2; or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg. No ulcer duration of >52 weeks without intermittent healing. No index ulcer probing to tendon, muscle, capsule, or bone. No wounds improving greater than 25% over the 2-week run-in period of the trials using SOC dressing and Camboot offloading.	Aged ≥18 years. Type 1 or type 2 diabetes. Able and willing to provide consent and agrees to comply with study procedures and followup evaluations. Serum creatinine <3.0 mg/dL. HbA1c <12%. Not currently receiving radiation or chemotherapy. No known or suspected malignancy of current ulcer. No diagnosis of autoimmune connective tissue disorder. No use of biomedical/topical growth factor within previous 30 days. Not pregnant or breast feeding. Not taking medication considered to be immune system modulators. No allergy or known sensitivity to gentamicin or streptomycin. Not taking Cox-2 inhibitors. No planned use of Dakin's solution, Mafenide acetate, scarlet red dressing, Tincoban, zinc sulfate, povidone-iodine solution, Mafenide acetate, Polymyxin/nystatin, or chlorhexidine during trial.	Diabetic, obese (BMI ≥30), alcohol use, smokers, recurring ulcers, history of cardiovascular abnormalities, prior amputation
Bianchi et al. 2018[37,38]	1 cm^2 to 25 cm^2	≥30 days	ABI >0.75. No VLU penetrating into muscle, tendon or bone. No signs of ulcer infection or cancer. No VLU located on the dorsum of the foot or more than 50% of the ulcer below the malleolus. Wounds did not reduce in size by at least 25% with moist dressings and multilayer compression during the 2 week run-in.	No NPWT or HBOT in the last 7 days or treatment with other advanced wound care products within the past 30 days.	Hypertension, diabetes, smokers, alcohol use, obesity

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
DiDomenico et al. 2018[60]	>1 cm^2	4 weeks	Anatomically on the foot as defined by beginning below the malleoli of the ankle. Additional wounds may not be within 3 cm of the study wound. Adequate circulation to the affected extremity, as demonstrated by 1 of the following in the past 60 days: dorsum transcutaneous oxygen test ≥30 mm Hg; ABI with results of ≥0.7 and ≤1.2; or Doppler arterial waveforms, which are triphasic or biphasic at the ankle of affected leg. No wound probing to bone (UT grade IIIA-D). No index wound >25 cm^2. No active infection at index wound site. No patients with wounds healing >20% during the screening period.	Type 1 or type 2 DM (ADA diagnostic criteria). Serum creatinine <3 mg/dL. HbA1c <12% at randomization or no HbA1c >12% in previous 90 days. No serum creatinine level ≥3 mg/dL. No patients currently receiving radiation therapy or chemotherapy. No patients with known or suspected local skin malignancy to the index wound. No patients with uncontrolled autoimmune connective tissues diseases. No nonrevascularizable surgical sites. No pathology that would limit the blood supply and compromise healing. No patients who have received a biomedical or topical growth factor for their wound within the previous 30 days. No patients who are pregnant or breast feeding. No patients who are taking medications considered immune system modulators that could affect graft incorporation. No patients taking a Cox-2 inhibitor.	Obesity, smoker, alcohol use
Zelen et al. 2018[54]	<25 cm^2	≥4 weeks	Noninfected wound, diabetic in origin, larger than 1 cm^2, and located on the foot (beginning below the malleoli of the ankle). Wound with documented failure of prior treatment to heal the wound. No additional wounds present within 3 cm of the index wound. HbA1c <12% (before randomization). No wound probing to bone (UT Grade IIIA-D). No active infection at index wound site. Adequate circulation to the affected extremity, as demonstrated by 1 of the following in the past 60 days: dorsum TCOM ≥30 mm Hg, ABI ≥0.7 and ≤1.2, triphasic or biphasic doppler arterial waveforms at the ankle of affected leg.	Type 1 or type 2 DM (based on ADA diagnostic criteria). Serum creatinine <3.0 mg/dL. No wound treated with a biomedical or topical growth factor in the previous 30 days. No HbA1c >12% in previous 90 days. No patients with known or suspected local skin malignancy to the index wound. No patients with ongoing radiation therapy or chemotherapy. No patients with uncontrolled autoimmune connective tissues diseases. No nonrevascularizable surgical sites. No pathology that would limit the blood supply and compromise healing. No pregnancy or breastfeeding. No patients taking immune system modulators that could affect graft incorporation. No Cox-2 inhibitor. No wounds heal >20% during the screening period.	Diabetes, obese, smokers, drinks alcohol

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Alvarez et al. 2017[48]	NR	>2 months	DFU located on the plantar surface of the foot with a grade I-A DFU (University of Texas Classification System). Adequate arterial circulation to the foot (e.g., ABI >0.75, toe-brachial index >0.65, toe systolic pressure >50 mmHg. No clinical signs of infection. No evidence of osteomyelitis. No nondiabetic etiology.	Type 1 or type 2 DM. No previous cancer (other than cutaneous epithelioma) or in remission. Not pregnant or lactating. Not receiving oral or parenteral corticosteroids. No other advance wound therapy (e.g., autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, ECM). Not receiving topical collagenase. Aged 18 to 85 years.	Type 1 or type 2 DM, Charcot foot, partial amputation
Alvarez et al. 2017[57]	NR	NR	NR	NR	Obese
Snyder et al. 2016[55]	1 cm^2 to 25 cm^2	≥1 month	At least 1 wound that is Wagner grade 1 or superficial 2. No signs of infection or osteomyelitis. Closed <30% in area during screening period. Located on the foot, distal to malleolus. Adequate circulation to the affected extremity (ABI 0.7 to 1.2, or triphasic or biphasic Doppler arterial waveform at the ankle of the affected leg, or dorsum transcutaneous oxygen test ≥30 mm Hg. No active Charcot deformity of the study foot. No known or suspected malignancy of the current ulcer. No exposed bone, tendon, or joint capsule in the study ulcer.	Diagnosis of type 1 or 2 DM. HbA1c <12%, serum creatinine of <3.0 mg/dL or CrCl >30 mL/min. No receiving radiation or chemotherapy. No active malignant disease. Not receiving hemodialysis or peritoneal dialysis. No sickle cell anemia or Raynaud's syndrome. No diagnosis of autoimmune connective tissue disease. Not receiving a biologic agent, growth factor, xenograft, or skin equivalent to the ulcer 30 days before consent. Not taking medications considered to be immune system modulators.	Type 1 or 2 DM, obesity

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Driver et al. 2015[56]	≥1 cm^2 and ≤12 cm^2	≥30 days	Adequate vascular perfusion of the affected limb. Ulcer was diagnosed as a full-thickness DFU located distal to the malleolus. Minimum 2 cm margin between the qualifying study ulcer and any other ulcers on the specified foot (postdebridement). Wagner grade 1 or 2. Depth ≤5 mm with no exposed capsule, tendon, or bone and no tunneling, undermining, or sinus tracts. No suspected or confirmed signs/symptoms of gangrene or wound infection on any part of the affected limb. No osteomyelitis with necrotic soft bone. No study ulcer size following debridement decreased by more than 30% during the run-in period.	Type 1 or 2 diabetes. HbA1c ≤12%. Not pregnant. Able to maintain the required offloading and dressing changes. No sensitivity of bovine collagen and/or chondroitin. No excessive lymphedema that could interfere with wound healing. No unstable Charcot foot or Charcot with boney prominence. No ulcers secondary to a disease other than diabetes. No Chopart amputation. No history of bone cancer or metastatic disease of the affected limb. No chemotherapy within the 12 months before randomization. No treatment with wound dressings that include growth factors (or engineered tissues or skin substitutes) within 30 days of randomization or scheduled to receive such treatment during the study. No treatment with HBOT within 5 days of screening or schedule to receive this treatment during the study. No nonstudy ulcer requiring treatment that could not be treated during the study with moist wound therapy. No history of intercurrent illnesses or conditions (other than diabetes) that would compromise the subject's safety or the normal wound healing process.	Type 1 or 2 DM

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Serena et al. 2014[40]	2 cm^2 to 20 cm^2	≥1 month	ABI >0.75. VLU extending through the skin's full thickness but not down to muscle, tendon, or bone. Treated with compression therapy for at least 14 days. Ulcer has a clean, granulating base with minimal adherent slough. No ulcer caused by a medical condition other than venous insufficiency. No clinical signs and symptoms of infection. No history of radiation at ulcer site. Not undergone 12 months of continuous high-strength compression therapy over ulcer duration. Not previously treated with tissue-engineered materials (e.g., Apligraf, Dermagraft) or other scaffold materials (e.g., Oasis, MatriStem) in the last 30 days. No ulcers on the dorsum of the foot or with more than 50% of the ulcer below the malleolus.	No uncontrolled diabetes (HbA1c >10%). No suspicion of cancer. No history of more than 2 weeks treatment with immunosuppressants, cytotoxic chemotherapy, or application of topical steroids within 1 month. No investigational drug(s) or therapeutic device(s) within 30 days. No known history of AIDS or HI. Not needing NPWT or HBOT. No NYHA Class III and IV CHF. Not pregnant or breast feeding. No allergy to gentamicin and streptomycin.	Obesity
Zelen et al. 2013[39]	>1 and <25 cm^2	≥4 weeks	No clinical signs of infection. Serum creatinine <3 mg/dl. HbA1c <12%. Adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test ($TcPO_2$) ≥30 mmHg, ABI between 0.7 and 1.2 or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg. No Charcot foot. No index ulcer probing to bone.	History of type 1 or 2 diabetes. Agrees to adhere with study procedures and followup evaluations. Not currently receiving radiation or chemotherapy. No known or suspected malignancy of current ulcer. No diagnosis of autoimmune connective tissue disease. Not receiving a biomedical or topical growth factor for their wound within the previous 30 days. Not pregnant or breast feeding. Not taking medications considered to be immune system modulators. No allergy to gentamicin or streptomycin.	Type 1 and 2 diabetes, obesity

ABI=ankle brachial index; ADA=American Diabetes Association; AIDS=acquired immune deficiency syndrome; CEAP: Clinical-Etiology-Anatomy-Pathophysiology; ECM=extracellular matrix; HBOT=hyperbaric oxygen therapy; DM=diabetes mellitus; HIV=human immunodeficiency virus; NPWT=negative pressure wound therapy; NR=not reported; TCOM=transcutaneous oximetry; VLU=venous leg ulcer

* Age of enrollment ≥18 years unless noted

Table C-4. Patient characteristics in studies comparing acellular dermal substitutes with standard of care

Study	Characteristic	Skin Substitute	Control
Brown-Etris et al. 2019[58]	Number of patients	Oasis® Wound Matrix (n=67)	SOC (n=63)
	Mean age±SEM (years)	76±2	78±2
	% male	52%	52%
	Race/Ethnicity	82% Caucasian, 15% black, 3% Other	86% Caucasian, 11% black, 3% Other
	Wound type	Pressure ulcer	Pressure ulcer
	Average wound size (cm^2) (range)	1-63	1-60
	Mean wound duration (weeks) (range)	0-3 months (37%), 4-6 months (19%), 7-12 months (19%), >1 year (22%), unknown (1%)	0-3 months (44%), 4-6 months (21%), 7-12 months (16%), >1 year (16%), unknown (3%)
	Wound severity	Stage III (58%), Stage IV (42%)	Stage III (52%), Stage IV (44%), unknown (3%)
	Comorbidities	Type 1 and Type 2 diabetes, connective tissue disease, immunosuppression, peripheral vascular disease, dementia; percent of comorbidities not reported however authors noted no significant difference between arms per comorbidity	Type 1 and Type 2 diabetes, connective tissue disease, immunosuppression, peripheral vascular disease, dementia
	Completion rate	76.1%	68.2%
Cazzell S. 2019[49]	Number of patients	DermACELL (n=18)	SOC (n=10)
	Mean age ±SD (years)	64.6±12.9	61.8±16.9
	% male	NR	NR
	Race/Ethnicity	NR	NR
	Wound type	VLU	VLU
	Average wound size (cm^2)	7.3	10.1
	Mean wound duration (days)	661	466
	Wound severity	CEAP 6	CEAP 6
	Comorbidities	44.4% Type 2, obese (mean±SD BMI 33.5±10.9)	30% Type 2, obese (mean±SD BMI 32.9±9.1)
	Completion rate	94.7%	90%
Tettelbach et al. 2019[59]*	Number of patients	EpiCord (n=101)	SOC (n=54)
	Mean age ±SD (years)	58.3±10.9	56.3±10.2
	% male	81.2%	81.5%
	Race/Ethnicity	80.2% Caucasian, 11.9% African American, 27.7% Hispanic	81.5% Caucasian, 14.8% African American, 33.3% Hispanic
	Wound type	DFU	DFU
	Average wound size ±SD (cm^2)	2.6±2.2	2.8±2.6
	Mean wound duration ±SD (weeks)	20.5±13.7	20.3±13.2
	Wound severity	NR	NR
	Comorbidities	67.3% obese BMI ≥30, diabetic (% Type 1 and Type 2 NR), 37.6% smokers, 49.5% alcohol users, 38.6% history of cardiovascular abnormalities	55.6% obese BMI ≥30, diabetic (% Type 1 and Type 2 NR), 52.8% smokers, 47.2% alcohol users, 37.7% history of cardiovascular abnormalities
	Completion rate	85.1%	88.8%
Tettelbach et al. 2019[42]	Number of patients	EpiFix (n=54)	SOC (n=56)
	Mean age ±SD (years)	57.4±10.6	57.1±10.5
	% male	73% male	74% male
	Race/Ethnicity	87% Caucasian, 11% African American, 41% Hispanic	82% Caucasian, 14% African American, 36% Hispanic
	Wound type	DFU	DFU

Study	Characteristic	Skin Substitute	Control
	Average wound size (cm^2)	3.2±2.8	3.9±3.8
	Mean wound duration (weeks)	20.8±18.5	21.4±15.8
	Wound severity	NR	NR
	Comorbidities	diabetic (% Type 1 and Type 2 NR), 72% obese (BMI ≥30), 40% alcohol use, 41% smokers, 23% recurring ulcers, 43% history of cardiovascular abnormalities, 20% prior amputation	diabetic (% Type 1 and Type 2 NR, 63% obese (BMI ≥30), 40% alcohol use, 32% smokers, 18% recurring ulcers, 45% history of cardiovascular abnormalities, 29% prior amputation
	Completion rate	85%	88%
Bianchi et al. 2018[37,38]	Number of patients	EpiFix plus MLCT (n=64)	SOC (dressings and MLCT) (n=64)
	Mean age ±SD (years)	62.2±14.3	60.3±11.4
	% male	66%	69%
	Race/Ethnicity	80% Caucasian, 13% African American, 7% Other; no percent reported for Hispanic ethnicity, although examined in regression modeling	78% Caucasian, 17% African American, 5% Other; no percent reported for Hispanic ethnicity, although examined in regression modeling
	Wound type	VLU	VLU
	Median wound size (cm^2) (range)	5.1 (range, 1.0 to 24.3)	6.3 (range, 1.2 to 24.8)
	Mean wound duration (weeks) (range)	40.0±55.6	61.5±71.6
	Wound severity	NR	NR
	Comorbidities	34% smokers, 39% alcohol use, obese (BMI 35.4±10.7), 23% diabetes, 16% hypertension	48% smokers, 44% alcohol use, obese (BMI 36.6±10.8), 33% diabetes, 13% hypertension
	Completion rate	81.2%	89%
DiDomenico et al. 2018[60]	Number of patients	Amnioband (n=40)	SOC (n=40)
	Mean age ±SD (years)	60.1±11.77	61.0±10.66
	% male	55%	80%
	Race/Ethnicity	95% Caucasian, 5% African American, 0% Hispanic	93% Caucasian, 5% African American, 2% Hispanic
	Wound type	DFU	DFU
	Average wound size (cm^2) (SD)	2.1±1.46	3.1±3.58
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	NR	NR
	Comorbidities	% Type 1 and Type diabetes NR, obese (mean BMI 34), 10% smokers, 20% drank alcohol	Obese (mean BMI 34.5), 8% smokers, 20% drank alcohol
	Completion rate	100%	92%
Zelen et al. 2018[54]	Number of patients	AlloPatch Pliable (n=40)	SOC (n=40)
	Mean age ±SD (years)	59±12	62±13
	% male	70%	60%
	Race/Ethnicity	90% white, 10% African American	95% white, 5% African American
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	3.2±4.0	2.7±2.4
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	NR (excluded UT Grade IIIA-D)	NR (excluded UT Grade IIIA-D)
	Comorbidities	% Type 1 and Type 2 diabetes NR, obese (mean±SD BMI 35±7.9), 28% smokers, 18% drinks alcohol	Obese (mean±SD BMI 34±8.8), 18% smokers, 23% drinks alcohol
	Completion rate	87.5%	42.5%

Study	Characteristic	Skin Substitute	Control
Alvarez et al. 2017[48]	Number of patients	MatriStem Wound Matrix** (urinary bladder matrix (UBM) (n=11)	SOC (n=6)
	Mean age ±SD (years)	57.5	55.2
	% male	82%	84%
	Race/Ethnicity	NR	NR
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	14±12.3	17±13.4
	Mean wound duration (months) (range)	6.5	4.8
	Wound severity	Grade I-A (University of Texas Wound Classification System)	Grade I-A (University of Texas Wound Classification System)
	Comorbidities	1% Charcot foot, 54.5% partial amputation	1% Charcot foot, 33.3% partial amputation
	Completion rate	100%	100%
Alvarez et al. 2017[57]	Number of patients	Hyalomatrix Wound Matrix plus compression (n=9)	SOC (nonadherent primary dressing plus a multilayer compression bandage) (n=7)
	Mean age ±SD (years)	60	58
	% male	44.6%	36.8%
	Race/Ethnicity	NR	NR
	Wound type	VLU	VLU
	Average wound size (mm^2) (range)	489 (range NR)	535 (range NR)
	Mean wound duration (months)	10	7
	Wound severity	NR	NR
	Comorbidities	Obese (mean BMI 30)	Obese (mean BMI 29)
	Completion rate	100%	100%
Snyder et al. 2016[55]	Number of patients	AmnioExcel dehydrated amniotic membrane allograft (n=15)	SOC (n=14)
	Mean age ±SD (years)	57.9±12.49	58.6±6.97
	% male	80%	92.9%
	Race/Ethnicity	78.6% Caucasian, 14.3% black/ African American, 0% American Indian or Alaska Native, 7.1% Other; 14.3% Hispanic/Latino	53.3% Caucasian, 20% black/ African American, 6.7% American Indian or Alaska Native, 20.0% Other; 26.7% Hispanic/Latino
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	4.7 (range, 1.2 to 16.5)	6.9 (range, 1.1 to 21.1)
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	Percent Wagner grade 1 or superficial 2 not reported	Percent Wagner grade 1 or superficial 2 not reported
	Comorbidities	Type 1 or 2 DM (% NR), obese (mean BMI 34.9; range, 24.9 to 55.7)	Type 1 or 2 DM (% NR), obese (mean BMI, 35.1; range, 28.2 to 50.2)
	Completion rate	73.3%	71.4%
Driver et al. 2015[56]	Number of patients	Integra Dermal Regeneration Template (n=154)	SOC (n=153)
	Mean age ±SD (years)	55.8±10.6	57.3±9.7
	% male	76.6%	74.5%
	Race/Ethnicity	76.6% Caucasian, 18.2% black/ African American; 29.9% Hispanic/ Latino	72.5% Caucasian, 22.2% black/ African American; 24.2% Hispanic/ Latino
	Wound type	DFU	DFU
	Average wound size (cm^2) at end of 2-week run in	3.53±2.5	3.65±2.7
	Mean wound duration (days ±SD)	308±491	303±418

Study	Characteristic	Skin Substitute	Control
	Wound severity	70.8% Wagner grade 2	75.8% Wagner grade 2
	Comorbidities	18.2% tobacco use, mean±SD BMI 34.0±7.2	12.4% tobacco use, mean±SD BMI 34.1±8.4
	Completion rate	83.1% completed treatment phase, 68.8% completed followup phase	76.4% completed treatment phase, 53.5% completed followup phase
Serena et al. 2014[40]	Number of patients	EpiFix plus MLCT (n=53)	MLCT (n=31)
	Mean age ±SD (years)	59.0±17.75	62.6±13.53
	% male	58.5%	48.4%
	Race/Ethnicity	NR	NR
	Wound type	VLU	VLU
	Average wound size (cm^2) (range)	6.0±4.33	6.3±5.27
	Mean wound duration (weeks) (range)	13.8±20.83	13.0±16.40
	Wound severity	NR	NR
	Comorbidities	69.8% obese	74.2% obese
	Completion rate	96.2%	94.1%
Zelen et al. 2013[39]	Number of patients	EpiFix (n=13)	SOC (n=12)
	Mean age ±SD (years)	56.4±14.7	61.7±10.3
	% male	NR	NR
	Race/Ethnicity	NR	NR
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	2.6±1.9	3.4±2.9
	Mean wound duration (weeks) (range)	14.1±13.0	16.4±15.5
	Wound severity	NR	NR
	Comorbidities	Obese (mean BMI 30.4), percent Type 1 and Type diabetes NR	Obese (mean BMI 35.4), percent Type 1 and Type DM not reported
	Completion rate	92.3%	16.6%

BMI=body mass index; CEAP: Clinical-Etiology-Anatomy-Pathophysiology; DFU=diabetic foot ulcer; DM=diabetes mellitus; MLCT=multi-layer compression therapy; NR=not reported; SD=standard deviation; SOC=standard of care; UBM=urinary bladder matrix; UT=University of Texas

* Tettelbach et al. 2019[59] noted a recurrent index ulcer at baseline in 41 patients (26 EpiCord, 15 SOC) and prior amputation in 27 patients (17 EpiCord, 10 SOC).

** Now branded as Cytal Wound Matrix (ACell, Inc., Columbia, MD)

Table C-5. Basic study design and conduct information for studies comparing acellular dermal substitutes with standard of care

Study	Study Detail	Description
Brown-Etris et al. 2019[58]	Specific wound treatment comparison	Oasis® Wound Matrix (n=67) vs. SOC (n=63)
	Wound type	Pressure ulcer
	Country	USA
	Institutes involved	12 institutions
	Method of patient recruitment	Not reported
	Patients enrolled	130
	Date range of study	NR
	Care setting	15% home care, 27% outpatient, 58% long-term care
	Use of run-in	No
	Method of measuring wound condition at enrollment	Photographs and wound measurements including ulcer length, width, and depth
	Stratification of results (wound severity or comorbidities)	Wound severity, size and duration
	Use of intent-to-treat	Yes
	Handling of drop outs	NR
	Statistical power calculations	Sample size was calculated using estimated healing rates of 27% for the standard of care arm and 47% for the SIS treatment group. Two groups of 69 patients each were required to demonstrate a 20% difference between the interventions, with α=0.05, power=0.80. The total enrollment target was 140 patients (70 per group), of which 130 patients were eventually enrolled. Actual study power was therefore 0.78.
	Length of study	36 weeks (12-week treatment, 24 week followup)
	Source of funding	Cook Biotech Incorporated
Cazzell S. 2019[49]	Specific wound treatment comparison	DermACELL (n=18) vs. SOC (n=10)
	Wound type	VLU
	Country	USA
	Institutes involved	7 medical centers in 5 states
	Method of patient recruitment	NR
	Patients enrolled	28
	Date range of study	NR
	Care setting	Medical center
	Use of run-in	No
	Method of measuring wound condition at enrollment	Silhouette Advanced Wound Assessment and Management System
	Stratification of results (wound severity or comorbidities)	Wound size and duration for wound area reduction (not an outcome of interest)
	Use of intent-to-treat	No
	Handling of drop outs	NR
	Statistical power calculations	Authors noted “as an exploratory pilot study, there was no expectation of statistical significance.”
	Length of study	24 weeks
	Source of funding	LifeNet Health, Inc.

Study	Study Detail	Description
Tettelbach et al. 2019[59]	Specific wound treatment comparison	EpiCord (n=101) vs. SOC (n=54)
	Wound type	DFU
	Country	USA
	Institutes involved	11 study sites
	Method of patient recruitment	Contacted (not specified)
	Patients enrolled	202 enrolled, 155 randomized
	Date range of study	Enrollment from August 2016 to March 2018
	Care setting	Hospital-based and private clinics in urban and rural areas
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Silhouette Advanced Wound Assessment and Management System and camera
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	The PASS 2013 statistical software was used to determine the sample size needed to detect a difference of 30% between the two treatment groups in the percentage of healed subjects. Under the above assumption, 20 subjects for treatment group 1 (alginate controls) and 40 subjects for treatment group 2 (EpiCord) would be required to meet the Type I error rate (P-value) of 0.05 with 80% power for a total of 60 subjects for the study.
	Length of study	16 weeks (12-week treatment, 4-week followup)
	Source of funding	MiMedx Group Inc.
Tettelbach et al. 2019[42]	Specific wound treatment comparison	EpiFix (n=54) vs. SOC (n=56)
	Wound type	DFU
	Country	USA
	Institutes involved	14 outpatient centers throughout the USA
	Method of patient recruitment	NR
	Patients enrolled	218 enrolled, 126 randomized
	Date range of study	October 2014 through June 2017
	Care setting	Hospital-based and private clinic settings in urban and rural areas
	Use of run-in	2-week
	Method of measuring wound condition at enrollment	SilhouetteStar camera and Silhouette Connect system
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	Using nQuery Advisor 7.01, the sample size calculation was based on the assumption that there is a difference of 35% between the two treatment groups in the percentage of healed subjects. Under the above assumptions, at least 35 subjects per treatment group were required to meet the Type I error rate (p-value) of 0.05 and 85% power of a total of 70 subjects for the study. To accommodate for potential discontinuations and study dropouts and to make the study more clinically relevant, the authors sought to enroll a minimum of 100 subjects.

Study	Study Detail	Description
	Length of study	12 weeks
	Source of funding	MidMedx Group, Inc.
Bianchi et al. 2018[37,38]	Specific wound treatment comparison	EpiFix® plus multilayer compression therapy (MLCT) vs. dressings and MLCT
	Wound type	VLU
	Country	USA
	Institutes involved	15 centers distributed throughout the USA; 9 private practice and 6 hospital-based centers
	Method of patient recruitment	Patients presenting for VLU care
	Patients enrolled	189 enrolled, 128 randomized
	Date range of study	March 19, 2015, to March 3, 2017
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photos and measurements using the Silhouette® camera
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	No
	Handling of dropouts	19 SOC patients who did not achieve 40% wound reduction by week 8 exited the study to receive advanced wound care. These patients were classified as completers and their non-healed status at 8 weeks with SOC was pulled forward for final analysis.
	Statistical power calculations	A 2-side log rank test indicated that an overall sample size of 120 subjects (60 in each group) would achieve approximately 87% power at a 5% significance level to detect a difference of 30% between the proportions of subjects whose ulcers are unhealed by 12 weeks in each arm.
	Length of study	16 weeks
	Source of funding	MiMedx Group, Inc., Marietta, GA, USA
DiDomenico et al. 2018[60]	Specific wound treatment comparison	Amnioband (dehydrated human amnion and chorion allograft) (n=40) vs. SOC (n=40)
	Wound type	DFU
	Country	USA
	Institutes involved	5 centers
	Method of patient recruitment	NR
	Patients enrolled	95 screened, 80 randomized
	Date range of study	March 23, 2015 to January 21, 2018
	Care setting	Outpatient wound care centers
	Use of run-in	2 weeks
	Method of measuring wound condition at enrollment	Tracings, photos at a distance of 30 cm with a graded centimeter ruler present, with a legible label directly adjacent to the ulcer
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	Group sample sizes of 40 in Group 1 and 40 in Group 2 were sufficient to achieve an 80% power to detect a difference of 0.3 between the group proportions. The proportion in Group 1 (the treatment group) was assumed to be 0.3 under the null hypothesis and 0.6 under the alternative hypothesis.

Study	Study Detail	Description
		The proportion in Group 2 (the control group) was 0.3. The test statistic used was the 2-sided Z test with pooled variance. The test's significance level was targeted at 0.05, and the significance level actually achieved by this design was 0.0484.
	Length of study	12 weeks
	Source of funding	Musculoskeletal Transplant Foundation (dba MTF Biologics), Edison, NJ, USA
Zelen et al. 2018[54]	Specific wound treatment comparison	AlloPatch Pliable (n=40) vs. SOC (n=40)
	Wound type	DFU
	Country	USA
	Institutes involved	5 centers
	Method of patient recruitment	NR
	Patients enrolled	92 screened, 80 randomized
	Date range of study	December 16, 2014, to March 29, 2017
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photo, tracings
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	"The sample size of 40 in each group was enough to detect a difference of 0.3 between the group proportions with 80% power. The proportion in the HR-ADM group was assumed to be 0.3 under the null hypothesis and 0.6 under the alternative hypothesis. The proportion in the SOC group was 0.3. The test statistic used was the 2-sided Z test with pooled variance, with significance level targeted at 0.05. The significance level actually achieved by this design was 0.048."
	Length of study	12 weeks
	Source of funding	Musculoskeletal Transplant Foundation (dba MTF Biologics) , Edison, NJ, USA
Alvarez et al. 2017[48]	Specific wound treatment comparison	MatriStem Wound Matrix* (urinary bladder matrix [UBM]) (n=11) vs. SOC (n=6)
	Wound type	DFU
	Country	USA
	Institutes involved	1 center
	Method of patient recruitment	NR
	Patients enrolled	17
	Date range of study	NR
	Care setting	Outpatient wound care center
	Use of run-in (length)	No
	Method of measuring wound condition at enrollment	Photodigital planimetry
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	NR
	Statistical power calculations	No

Study	Study Detail	Description
	Length of study	1 year
	Source of funding	ACell, Inc. (Columbia, MD)
Alvarez et al. 2017[57]	Specific wound treatment comparison	Hyalomatrix Wound Matrix plus compression vs. SOC (nonadherent primary dressing plus a multilayer compression bandage)
	Wound type	VLU
	Country	USA
	Institutes involved	University Wound Care Center, Center for Vascular Health (Bronx, NY)
	Method of patient recruitment	NR
	Patients enrolled	16 enrolled, 16 randomized
	Date range of study	NR
	Care setting	Outpatient wound care center
	Use of run-in (length)	No
	Method of measuring wound condition at enrollment	Photodigital planimetry
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	No
	Handling of drop outs	No
	Statistical power calculations	No
	Length of study	16 weeks
	Source of funding	Medline Industries, Inc. (Mundelein, IL)
Snyder et al. 2016[55]	Specific wound treatment comparison	AmnioExcel (n=15) vs. SOC (n=14)
	Wound type	DFU
	Country	USA
	Institutes involved	8 clinical study sites
	Method of patient recruitment	NR
	Patients enrolled	49 screened, 29 randomized
	Date range of study	NR
	Care setting	NR
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photo
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	NR
	Statistical power calculations	NR
	Length of study	6 weeks
	Source of funding	Derma Sciences, Princeton, NJ
Driver et al. 2015[56]	Specific wound treatment comparison	Integra Dermal Regeneration Template (IDRT) (n=154) vs. SOC (n=153)
	Wound type	DFU
	Country	USA
	Institutes involved	32 sites
	Method of patient recruitment	NR
	Patients enrolled	545 assessed, 307 randomized
	Date range of study	April 2010 to November 2013
	Care setting	Academic and private practice sites
	Use of run-in (length)	2 weeks

Study	Study Detail	Description
	Method of measuring wound condition at enrollment	Photo, tracings
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	A sample size of 296 subjects in the randomization/ treatment phase was needed to have 80% power to detect a clinically meaningful difference of 18% (46% in the active group vs. 28% in the control group) for the primary outcome using a 2-sided 0.05 level test and assuming a 20% dropout rate.
	Length of study	28 weeks (16-week treatment, 12-week followup)
	Source of funding	Integra LifeSciences Corp.
	Handling of drop outs	NR
	Statistical power calculations	Based on closure rates of 30% and 50% in the control arm and Grafix arm, respectively, with a 30% dropout rate, 94 patients, who completed the treatment, in each treatment arm were required to meet the 2-sided type 1 error rate of 0.05 with 80% power.
	Length of study	24 weeks
	Source of funding	Osiris Therapeutics, Inc.
Serena et al. 2014[40]	Specific wound treatment comparison	EpiFix plus MLCT (n=53) vs. MLCT (n=31)
	Wound type	VLU
	Country	USA
	Institutes involved	8 centers in PA, MA, FL, OK, IN, and TX
	Method of patient recruitment	Patients presenting for care of a VLU
	Patients enrolled	88 screened, 84 randomly assigned
	Date range of study	March 2012 to March 2014
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Digital photo. Area calculated by multiplying length with width.
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	Sample sizes of 30 in each group were calculated to achieve a power of 81% when the difference between proportions healed at 4 weeks was 0.30 and the proportion healed in the MLCT group was 0.2. The test statistic used was the 2-sided likelihood ratio test with a significance level of 0.047.
	Length of study	4 weeks
	Source of funding	MiMedx Group, Inc., Marietta, GA.

Study	Study Detail	Description
Zelen et al. 2013[39]	Specific wound treatment comparison	EpiFix (n=13) vs. SOC (n=12)
	Wound type	DFU
	Country	USA
	Institutes involved	1 research institute in southwest Virginia
	Method of patient recruitment	NR
	Patients enrolled	25
	Date range of study	March and August 2012
	Care setting	Research institute
	Use of run-in	No
	Method of measuring wound condition at enrollment	Ulcer measurement with a graded centimeter ruler (length, width and depth)
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	No
	Handling of drop outs	NR
	Statistical power calculations	NR
	Length of study	12 weeks
	Source of funding	MiMedx (Kennesaw, GA)

DFU=diabetic foot ulcer; LOCF=last observation carried forward; MLCT=multilayer compression therapy; NR=not reported; SOC=standard of care; VLU=venous leg ulcer

* Now branded as Cytal Wound Matrix (ACell, Inc., Columbia, MD)

Table C-6. Patient enrollment criteria for studies comparing cellular dermal substitutes with standard of care

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health and Age Requirements*	Comorbidities
Serena et al. 2019[36]	0.50-25 cm^2	≥4 weeks	Wound located below the medial aspect of the malleolus extending at least through the epidermis into dermis, subcutaneous tissue, muscle, or tendon but not into bone. Adequate lower-extremity perfusion (TCOM or SPP measurement of ≥30 mmHg; ABI between 0.7 and ≤1.3; or TBI ≥0.6 within 3 months of first screening visit). No evidence of unresolved gross soft-tissue infection or osteomyelitis.	Well-controlled glucose (HbA1c <12%). Age ≥18 years. No evidence of underlying comorbid conditions that would adversely affect wound closure (cancer, Raynaud's syndrome, severe venous insufficiency, or uncorrected arterial insufficiency). No use of cytotoxic drugs or chemotherapeutics. No evidence of skin cancer within or adjacent to the ulcer site, symptoms of osteomyelitis, ulcers of the calcaneus, renal impairment (creatinine >2.5 mg/dL), hepatic impairment (≥2x ULN), hematologic disorders, cellulitis, ulcers with sinus tracts, active deep vein thrombosis, uncontrolled diabetes, and severely immune compromised.	Type 1 and 2 DM
Lavery et al. 2014[47]	1 and 15 cm^2	4 to 52 weeks	Wound located below the malleoli on plantar or dorsal surface of the foot and ulcer. No evidence of active infection including osteomyelitis or cellulitis. Adequate circulation to the affected foot (ABI 0.70 to 1.30, or toe brachial index ≤0.5 or Doppler study with inadequate arterial pulsation. No exposed muscle, tendon, bone, or joint capsule. No reduction of wound area by ≥30% during the screening period.	Type I or type II diabetes. No hemoglobin A1c above 12%. Age between 18 and 80 years.	Type 1 and 2 DM, obesity
Harding et al. 2013[43]	3-25 cm^2	≥2 months, <5 years	Patients were required to have a VLU located between the knee and ankle (at the level of, and including, the lateral and medial malleolus). No exposure of muscle, tendon, or bone and clean, granulating base with	Age ≥18 years. No morbid obesity, malignant disease within 5 years, severe PVD or renal disease, CHF, cell anemia, thalassemia, or uncontrolled diabetes. No use of immune suppressants, systemic	NR

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health and Age Requirements*	Comorbidities
			minimal adherent slough, suitable to receive a skin graft. Sufficient circulation to the study leg to make wound healing possible. ABI between 0.8 and 1.2 and venous disease had to be confirmed by duplex ultrasonography to demonstrate reflux of >0.5 seconds in saphenous, calf perforator, or popliteal veins. Ulcers that reduced in size (cm^2) by less than 50% while under compression therapy during the study's 2-week screening period were eligible for randomization into the study. No ulcers caused by a medical condition other than venous insufficiency. No evidence of sinus tracts in their ulcer or evidence of a wound infection (purulence and/or odor), cellulitis, and/or confirmed osteomyelitis. No skin diseases near study ulcer.	corticosteroids, cytotoxic chemotherapy, or topical steroids for more than 2 weeks and within 1 month of initial screening or who had a history of radiation at the ulcer site. No known allergy to bovine products or components of the compression bandage or who could not tolerate compression bandage therapy, had received an investigational drug within 30 days of randomization, or had been previously treated with HFDS and/or other tissue-engineered materials.	

ABI=ankle brachial index; CHF=congestive heart failure; DM=diabetes mellitus; HFDS=human fibroblast-derived dermal substitute; NR=not reported; PVD=peripheral vascular disease; SPP=skin perfusion pressure; TBI=toe-brachial index; TCOM=transcutaneous oxygen measurement; VLU=venous leg ulcer

Table C-7. Patient characteristics in studies comparing cellular dermal substitutes with standard of care

Study	Characteristic	Skin Substitute	Control
Serena et al. 2019[36]	Number of patients	Affinity (n=38)	SOC (n=38)
	Mean age ±SD (years)	59.2±7.61	59.6±10.72
	% male	78.9%	76.3%
	Race/Ethnicity	NR	NR
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	3.12±3.86	3.33±4.62
	Mean wound duration (days±SD)	NR	NR
	Wound severity	14 Wagner grade 1, 24 Wagner grade 2	15 Wagner grade 1, 23 Wagner grade 2
	Comorbidities	Type 1 and 2 DM (% NR)	Type 1 and 2 DM (% NR)
	Completion rate	100%	100%

Study	Characteristic	Skin Substitute	Control
Lavery et al. 2014[47]	Number of patients	Grafix (n=50)	SOC (n=47)
	Mean age ±SD (years)	55.5±11.5	55.1±12.0
	% male	66.0%	74.5%
	Race/Ethnicity	70% white/Caucasian, 26% black/African American, 2% American Indian or Alaska Native, 2% Other	68.1% white/Caucasian, 25.5% black/African American, 2.1% American Indian or Alaska Native, 4.3% Other
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	3.41±3.23	3.93±3.22
	Mean wound duration (days±SD)	115.0±72.6	122.9±83.9
	Wound severity	NR	NR
	Comorbidities	72% obese	53.2% obese
	Completion rate	84%	76.5%
Harding et al. 2013[43]	Number of patients	Dermagraft plus 4-layer compression therapy (n=186)	4-layer compression therapy (n=180)
	Mean age ±SD (years)	67.9±13.8	69.1±12.4
	% male	46.2%	46.1%
	Race/Ethnicity	93% white, 2.7% black, 1.6% Asian, 2.7% Other	91.1% white, 4.4% black, 0.6% Asian, 3.9% Other
	Wound type	VLU	VLU
	Median wound size (cm^2) (range)	7.4 (2.4 to 28.2)	7.2 (2.3 to 26.6)
	Median wound duration (weeks) (range)	49.7 (range, 8.9 to 262.1)	45.3 (range, 9.9 to 470.4)
	Wound severity	NR	NR
	Comorbidities	NR	NR
	Completion rate	100%	99.4%

DFU=diabetic foot ulcer; DM=diabetes mellitus; NR=not reported; SD=standard deviation; SOC=standard of care; VLU=venous leg ulcer

Table C-8. Basic study design and conduct information for studies comparing cellular dermal substitutes with standard of care

Study	Study Detail	Description
Serena et al. 2019[36]	Specific wound treatment comparison	Affinity vs. SOC
	Wound type	DFU
	Country	USA
	Institutes involved	14 centers (not specified)
	Method of patient recruitment	NR
	Patients enrolled	76
	Date range of study	NR
	Care setting	NR
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Digital planimetry
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of dropouts	LOCF
	Statistical power calculations	NR
	Length of study	12 weeks
	Source of funding	Organogenesis, Inc.
Lavery et al. 2014[47]	Specific wound treatment comparison	Grafix vs. SOC
	Wound type	DFU
	Country	USA
	Institutes involved	NR
	Method of patient recruitment	NR

Study	Study Detail	Description
	Patients enrolled	139 screened, 97 randomized
	Date range of study	May 2012 through April 2013
	Care setting	Research centers throughout the USA
	Use of run-in (length)	1 week
	Method of measuring wound condition at enrollment	Tracing, photos
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of dropouts	NR
	Statistical power calculations	Based on closure rates of 30% and 50% in the control arm and Grafix arm, respectively with a 30% dropout rate, 94 patients, who completed the treatment, in each treatment arm were required to meet the two-sided type 1 error rate of 0·05 with 80% power.
	Length of study	24 weeks
	Source of funding	Osiris Therapeutics, Inc.
Harding et al. 2013[43]	Specific wound treatment comparison	Dermagraft plus 4-layer compression therapy vs. 4-layer compression therapy
	Wound type	VLU
	Country	UK
	Institutes involved	25 centers (19 UK, 1 Canada, 5 USA)
	Method of patient recruitment	Referred to participating hospital or community-based VLU clinics in the UK, USA, or Canada
	Patients enrolled	573 screened, 366 randomly assigned
	Date range of study	NR
	Care setting	Hospital and community-based VLU clinics
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Tracing, planimetry analysis
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	Yes
	Handling of dropouts	NR
	Statistical power calculations	A sample size analysis indicated that 166 patients in each treatment group were required to detect a 15% difference in the proportion of patients who achieve complete healing at week 12. This calculation was based on a healing rate of 32% for controls and 47% for HFDS with a 0.05 two-sided significance level and at least 80% power.
	Length of study	24 weeks
	Source of funding	Financial support for editorial assistance was provided by Smith & Nephew Wound Management, Hull, UK, and Shire Regenerative Medicine, San Diego, CA, USA.

DFU=diabetic foot ulcer; HFDS=human fibroblast-derived dermal substitute; LOCF=last observation carried forward; NR=not reported; SOC=standard of care; VLU=venous leg ulcer

Table C-9. Patient enrollment criteria for studies comparing acellular dermal substitutes with acellular dermal substitutes

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health and Age Requirements*	Comorbidities
Cazzell et al. 2017[50]	≥1 cm^2 and <25 cm^2	30 days	Single-target DFU with a Wagner Ulcer Classification of 1 or 2 and absence of infection. Adequate circulation to the affected area, defined as having at least 1 of the following criteria within the past 60 days: transcutaneous oxygen measurement at the dorsum of the foot ≥30 mmHg, ABI ranging from 0.8-1.2, or at least biphasic Doppler arterial waveforms at the dorsalis pedis, and posterior tibial arteries. No wound treatments involving biomedical or topical growth factors 30- days before screening.	No circulating hemoglobin A1c exceeding 12% within 90 days of the screening visit, serum creatinine concentrations of 3.0 mg/dL or greater within 30 days before screening. No presence of peripheral vascular disease, active infection or untreated malignancy, Charcot's disease, or necrosis, purulence, or sinus tracts that could not be removed by debridement. No revascularization procedure aimed at increasing blood flow in the target limb or received a living skin equivalent within 4 weeks before screening. No sensitivity to lincomycin, gentamicin, polymyxin B, vancomycin, polysorbate 20, N-lauroyl sarcosinate, Benzonase, or glycerol. Age between 21 and 80 years.	Type 1 and 2 diabetes

ABI=ankle brachial index; DFU=diabetic foot ulcer
* Age of enrollment ≥18 years unless noted

Table C-10. Patient characteristics in studies comparing acellular dermal substitutes with acellular dermal substitutes

Study	Characteristic	Skin Substitute	Skin Substitute	Control
Cazzell et al. 2017[50]	Number of patients (ITT population)	DermACELL (n=71)	GraftJacket (n=28)	SOC (n=69)
	Mean age ±SD (years)	59.1±12.76	58.5±9.83	56.9±10.86
	% male	80.3%	71.4%	73.9%
	Race/Ethnicity	NR	NR	NR
	Wound type	DFU	DFU	DFU
	Average wound size (cm^2) (range)	3.9±4.15	3.3±2.69	3.6±3.61
	Mean wound duration (weeks) (range)	40.0 (6.0-479.0)	36.8 (2.0-226.0)	36.4 (2.0-167.0)
	Wound severity	12 (16.9%) Grade 1 Wagner, 59 (83.1%) Grade 2 Wagner	5 (17.9%) Grade 1 Wagner, 23 (82.1%) Grade 2 Wagner	14 (20.3%) Grade 1 Wagner, 55 (79.7%) Grade 2 Wagner
	Comorbidities	4 (5.6%) type 1 DM, 64 (90.1%) type 2 DM, 11 (15.5%) current smokers	2 (7.1%) type 1 DM, 26 (92.9%) type 2 DM, 9 (13.0%) current smokers	2 (2.9%) type 1 DM, 67 (97.1%) type 2 DM, 2 (7.1%) current smokers
	Completion rate	75%	82.1%	81.1%

DFU=diabetic foot ulcer; DM=diabetes mellitus; ITT=intent-to-treat; SD=standard deviation; SOC=standard of care

Table C-11. Basic study design and conduct information for studies comparing acellular dermal substitutes with acellular dermal substitutes

Study	Study Detail	Description
Cazzell et al. 2017[50]	Specific wound treatment comparison	DermACELL vs. GraftJacket vs. SOC
	Wound type	DFU
	Country	USA
	Institutes involved	13 centers in 9 states
	Method of patient recruitment	Patients presenting to the clinic for care of DFU
	Patients enrolled	203 enrolled, 168 randomly assigned
	Date range of study	NR
	Care setting	Outpatient wound care centers
	Use of run-in (length)	30 days
	Method of measuring wound condition at enrollment	Tracings
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	Yes
	Handling of dropouts	3 subjects were removed from the per-protocol population, including 1 subject who was withdrawn after missing 15 visits, 1 who was withdrawn after week 7 for lung cancer, and a conventional care subject who withdrew consent at week 3.
	Statistical power calculations	A power analysis determined 66 patients would be needed to be enrolled in the DermACELL and SOC arm to have an 80% chance of obtaining a statistically significant result. Statistical significance was not sought or expected for the GraftJacket arm so it was not included in the power analysis.
	Length of study	24 weeks
	Source of funding	LifeNet Health, manufacturer of DermACELL

DFU=diabetic foot ulcer; NR=not reported; SOC=standard of care

Table C-12. Patient enrollment criteria for studies comparing acellular dermal substitutes with cellular dermal substitutes and cellular epidermal and dermal substitutes

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities
Frykberg et al. 2016[46]	NR	≥4 weeks	Extends through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone, or joint capsule. Postdebridement, wound is free of necrotic debris and appears made up of healthy vascularized tissue. Adequate circulation to the study foot as evidenced by a Doppler measure ABI of ≥0.7 after 10 minutes of rest. No decrease in ulcer size by ≥30% during the screening period. No increase in ulcer size by ≥50% during the screening period. No ulcer has tunnels or sinus tracts that cannot be completely debrided.	Individuals with HbA1c <12%, no severe malnutrition (albumin <2.0 g/dl), and no random blood sugar reading >450 mg/dl.	Type 1 and 2 DM
Zelen et al. 2016[41]	≥1 cm^2 and <25 cm^2	≥4 weeks	No clinical signs of infection. Adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test ≥30 mmHg or ABI between 0.7 and 1.2 or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg. No index wound duration of >52 weeks without intermittent healing. No ulcer probing to tendon, muscle, capsule, or bone. No known or suspected malignancy of current ulcer. No wounds improving greater than 20% over the 2-week run-in period of the trial using standard of care dressing and Camboot offloading.	Type 1 or 2 diabetes, serum creatinine <3.0 mg/dl and HbA1c <12%. No diagnosis of autoimmune connective tissue disease, use of biomedical/topical growth factor within previous 30 days, pregnancy or breast feeding, taking medications considered to be immune system modulators, and taking Cox-2 inhibitors. Not currently receiving radiation or chemotherapy. No diagnosis of autoimmune connective tissue disease. No use of biomedical/topical growth factor in previous 30 days. Not pregnant or breast-feeding. Not taking medications considered to be immune system modulators. No allergy or known sensitivity to Gentamicin, Streptomycin, bovine collagen, or components of linear polysaccharide shipping medium. No use of Cox-2 inhibitors or planned use of Dakin's solution, mafenide acetate, scarlet red dressing, tincoban, zinc sulfate, povidone-iodine solution, polymyxin/nystatin, or chlorhexidine during trial.	Smoking use, hypertension, CAD, CHF, obesity

ABI=ankle brachial index; CAD=coronary artery disease; CHF=congestive heart failure; DM=diabetes mellitus; PAD=peripheral artery disease
Note: Age of enrollment ≥18 years unless noted

Table C-13. Patient characteristics for studies comparing acellular dermal substitutes with cellular dermal substitutes and cellular epidermal and dermal substitutes

Study	Characteristic	Skin Substitute	Skin Substitute	Control
Frykberg et al. 2016[46]	Number of patients	MatriStem MicroMatrix and MatriStem Wound Matrix (n=27)	Dermagraft (n=29)	N/A
	Mean age±SD (years)	57.0±9.8	58.5±11.4	N/A
	% male	77.8%	75.9%	N/A
	Race/Ethnicity	81.5% Caucasian, 18.5% Non-Caucasian; 37% Hispanic/Latino, 63% Non-Hispanic/Latino	88.2% Caucasian, 13.8% Non-Caucasian; 44.8% Hispanic/Latino, 55.2% Non-Hispanic/ Latino	NR
	Wound type	DFU	DFU	N/A
	Average wound size (cm^2) (range)	4.3±5.7	3.2±4.5	N/A
	Mean wound duration (days) (range)	263 days overall (range, 30 to 1095)	263 days overall (range, 30 to 1095)	N/A
	Wound severity (based on University of Texas Grade)	100% A1	93.1% A1, 6.9%>A1	N/A
	Comorbidities	11.1% type 1 DM, 88.9% type 2 DM	17.2% type 1 DM, 82.7% type 2 DM	N/A
	Completion rate	100%	100%	N/A
Zelen et al. 2016[41]	Number of patients	Apligraf (n=33)	EpiFix (n=32)	SC (n=35)
	Mean age±SD (years)	63.8±11.86	63.3±12.25	60.6±11.55
	% male	13.9%	18.8%	21.8%
	Race/Ethnicity	91% Caucasian; 9% AA	96% Caucasian; 4% AA	NR
	Wound type	DFU	DFU	DFU
	Average wound size (cm^2) (range)	1.7 (range, 1.0 to 14.7)	1.7 (range, 1.0 to 16.9)	1.8 (range, 1.0 to 15.5)
	Mean wound duration (weeks) (range)	NR	NR	NR
	Wound severity	NR	NR	NR
	Comorbidities	% DM not reported, 18.2% smokers, 72.7% hypertension, 15.2% CAD, 15.2% CHF, 19.8% obese	% DM not reported, 28.1% smokers, 68.8% hypertension, 18.8% CAD, 6.3% CHF, 19.8% obese	% DM not reported, 34.3% smokers, 74.3% hypertension, 28.6% CAD, 8.6% CHF, 22.8% obese
	Completion rate	85.2%	91.4%	48%

BMI=body mass index; CAD=coronary artery disease; CHF=congestive heart failure; DFU=diabetic foot ulcer; DM=diabetes mellitus; N/A=not applicable; NR=not reported; SC=standard of care; PAD=peripheral artery disease; SD=standard deviation

Table C-14. Basic study design and conduct information for studies comparing acellular dermal substitutes with cellular dermal substitutes and cellular epidermal and dermal substitutes

Study	Study Detail	Description
Frykberg et al. 2016[46]	Specific wound treatment comparison	MatriStem MicroMatrix and MatriStem Wound Matrix vs. Dermagraft
	Wound type	DFU
	Country	USA
	Institutes involved	13 unnamed
	Method of patient recruitment	NR
	Patients enrolled	95 enrolled, 56 randomly assigned
	Date range of study	NR
	Care setting	VA medical facilities (2), outpatient research clinics (4), private practice clinics (5), and hospital-based outpatient clinics (2).
	Use of run-in (length)	4 weeks
	Method of measuring wound condition at enrollment	Photos, tracings, and measurement of depth via Visitrak Depth Probe.
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of dropouts	To account for a 10% dropout rate, the sample size was upwardly adjusted to 102 subjects.
	Statistical power calculations	92 subjects are needed for enrollment to have 90% power at a 10% noninferiority margin.
	Length of study	6 months
	Source of funding	NR: 1 author is chief scientific officer and stockholder in ACell, Inc. (commercializes MatriStem)
Zelen et al. 2016[41]	Specific wound treatment comparison	Apligraf vs. EpiFix vs. SOC
	Wound type	DFU
	Country	USA
	Institutes involved	3 centers (unspecified) in Virginia, 1 center (unspecified) in Oklahoma.
	Method of patient recruitment	Presenting to the clinic with type 1 or 2 diabetes for care of a lower-extremity ulcer.
	Patients enrolled	126 enrolled, 104 randomly assigned
	Date range of study	September 2013 to August 2015
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photos and tracings
	Stratification of results (wound severity or comorbidities)	Hazard ratios were calculated using covariates of hypertension (vs. no hypertension), initial wound area (1.2 to 2.5 cm^2 and >2.5 vs. <1.2 cm^2), and location of DFU (forefoot, midfoot, rearfoot/ankle vs. toes).
	Use of intent-to-treat	Yes
	Handling of dropouts	LOCF
	Statistical power calculations	Sample size calculations (PASS 11) showed that group sample sizes of 23 in group 1 and 23 in group 2 could achieve 81% power to detect a difference between the group proportions of 0,4 (proportion healed); however, study enrollment continued until 100 patients meeting inclusion/exclusion criteria were recruited.
	Length of study	12 weeks
	Source of funding	NR

DFU=diabetic foot ulcer; HFDS=human fibroblast-derived dermal substitute; ITT=intent-to-treat; LOCF=last observation carried forward; NR=not reported; SOC=standard of care; vCPM=viable cryopreserved placental membrane

Table C-15. Patient enrollment criteria for studies comparing cellular skin substitutes with cellular skin substitutes

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities
Ananian et al. 2018[44]	≥1 cm^2 and <15 cm^2	4 to 52 weeks	Extends through the dermis with no exposed muscle, tendon, bone, or joint capsule. ABI between 0.7 and 1.3. Toe brachial index of ≥0.5, or a Doppler waveform demonstrating biphasic or triphasic flow in the foot. No index ulcers that decreased ≥20% in size during the 1-week screening period.	Diagnosed with type 1 or 2 DM. Aged between 18 years and 80 years.	Type 1 and 2 DM, obesity, smoking use, heart disease, mild PAD
Towler et al. 2018[35]	>1 cm^2 and <40 cm^2 and <5 mm deep	>30 days	ABI >0.5 or biphasic or triphasic Doppler signals in the dorsalis pedis and posterior tibial arteries of the affected extremity. No suspected gangrene or wound infection on any part of the affected limb. No leg ulcers secondary to a disease other than venous ulcers.	No history or end-stage renal disease, immunosuppression, severe malnutrition, severe liver disease, aplastic anemia, scleroderma, positive for AIDS or HIV, connective tissue disorder, sickle cell anemia, osteomyelitis, bone cancer or metastatic disease of the affected limb, irradiation of the affected extremity, and chemotherapy in the last 12 months. No hypersensitivity to bovine collagen or agarose (listed Apligraf directions for use). Has not received or currently receiving (within 30 days of randomization) or scheduled to receive a medication or treatment known to interfere with or affect the wound healing rate. Has not been treated with growth factors, engineered tissue, or skin substitutes within 30 days of randomization.	Diabetes, morbid obesity, peripheral vascular disease, smoking use, lymphedema, neuropathy
Sanders et al. 2014[45]	>1 cm^2 and <10 cm^2	>30 days	Minimum 2 cm margin between study ulcer and other ulcers. ABI >0.65. Toe pressure >50 mm Hg. $tcPO_2$>20 mm Hg. No gangrene or wound infection of the foot.	Individuals with type 1 or 2 diabetes and HbA1c <12%. No end-stage renal disease, immunosuppression, aplastic anemia, scleroderma, AIDs or HIV-positive, severe malnutrition, liver disease, connective tissue disorders, or sickle cell anemia. No mental or physical incapacity that could interfere with adherence; substance abuse; excessive lymphedema, unstable or deformed Charcot foot; vasculitis, neoplasms, or hematologic disorders; cellulitis, osteomyelitis, or wound infection; history of bone cancer or metastatic disease. No hypersensitivity to bovine collagen and/or chondroitin. No hypersensitivity to gentamycin, vancomycin, or the reagents listed in the TheraSkin® Instructions for Use. No oral parenteral corticosteroids, immunosuppressive, or cytotoxic drugs with 12 months. Treatment with growth factors or bioengineered skin substitutes within 30 days.	Type 1 and 2 DM, neuropathy, PAD, smoking use

ABI=ankle brachial index; AIDS=acquired immune deficiency syndrome; DM=diabetes mellitus; PAD=peripheral arterial disease
Note: Age of enrollment ≥18 years unless noted

Table C-16. Patient characteristics in studies comparing cellular skin substitutes with cellular skin substitutes

Study	Characteristic	Skin Substitute	Control
Ananian et al. 2018[44]	Number of patients	GrafixPrime (n=38)	Dermagraft (n=37)
	Mean age±SD (years)	55.3±12.09	58.1±11.89
	% male	73.7%	86.5%
	Race/Ethnicity	84.2% white/Caucasian, 7.9% black/ African American, 2.6% American Indian/Alaska Native, 5.3% Other; 57.9% Hispanic/Latino, 42.1% not Hispanic/Latino	91.9% white/Caucasian, 2.7% black/ African American, 0% American Indian/Alaska Native, 5.4% Other; 56.8% Hispanic/Latino, 43.2% not Hispanic/Latino
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	7.15	5.70
	Mean wound duration (days) (range)	199.32 days	146.32 days
	Wound severity	NR	NR
	Comorbidities	68.4% BMI ≥30, 13.2% type 1 DM, 86.8% type 2 DM, 10.5% current smoker, 92.1% heart disease, 55.3% prior amputation, 31.6% mild PAD	54.1% BMI ≥30, 2.7% type 1 DM, 97.3% type 2 DM, 5.4% current smoker, 94.6% heart disease, 54.1% prior amputation, 24.3% mild PAD
	Completion rate	86.8%	83.7%
Towler et al. 2018[35]	Number of patients	Apligraf (n=12)	Theraskin (n=15)
	Mean age±SD (years)	63.7±13.4	66.3±18.0
	% male	58.3%	66.7%
	Race/Ethnicity	NR	NR
	Wound type	VLU	VLU
	Average wound size (cm^2) (mean±SD)	6.37±6.95	4.94±4.43
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	NR	NR
	Comorbidities	33.3% diabetes, 50% morbidly obese, 8.3% peripheral vascular disease, 25% daily smokers, 8.3% lymphedema, 16.7% neuropathy	46.7% diabetes, 66.7% morbidly obese, 33.3% peripheral vascular disease, 25% daily smokers, 13.3% lymphedema, 13.3% neuropathy
	Completion rate	92% overall (of 4 dropouts, 1 received Apligraf, 3 did not receive grafts)	100%
Sanders et al. 2014[45]	Number of patients	Dermagraft (n=12)	Theraskin (n=11)
	Mean age±SD (years)	56.58±14.96	60.0±15.74
	% male	50%	45.45%
	Race/Ethnicity	54.55% white, non-Hispanic, 5.45% black	66.67% white, non-Hispanic, 33.33% black
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	4.78 (0.86 to 14.45)	5.45 (0.50 to 18.02)
	Mean wound duration (weeks) (range)	11.71 (4 to 26.1)	43.58 (4 to 260)
	Wound severity	NR	NR
	Comorbidities	8.33% type 1 DM, 91.67% type 2 DM, 58.33% neuropathy, 16.67% PAD, 9.09% smokers	9.09% type 1 DM, 90.9% type 2 DM, 72.73% neuropathy, 0% PAD, 0% smokers
	Completion rate	100%	100%

DFU=diabetic foot ulcer; DM=diabetes mellitus; NR=not reported; PAD=peripheral arterial disease; SD=standard deviation; VLU=venous leg ulcer

Table C-17. Basic study design and conduct information for studies comparing cellular skin substitutes with cellular skin substitutes

Study	Study Detail	Description
Ananian et al. 2018[44]	Specific wound treatment comparison	GrafixPrime (n=38) vs. Dermagraft (n=37)
	Wound type	DFU
	Country	USA
	Institutes involved	7 centers
	Method of patient recruitment	NR
	Patients enrolled	105 screened, 75 randomly assigned
	Date range of study	January 2016 to May 2017
	Care setting	Wound clinics, medical centers
	Use of run-in (length)	1 week
	Method of measuring wound condition at enrollment	No
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Safety based on ITT, clinical outcomes based on per-protocol population
	Handling of dropouts	NR
	Statistical power calculations	"Powered to show that vCPM [GrafixPrime] is not inferior to hFDS [Dermagraft] for wound closure. A treatment effect difference of 20% for the non-inferiority (NI) test was used in this analysis based on published clinical outcomes of vCPM and hFDS. A conservative NI margin of 15% was used per U.S. FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness. Using these parameters, 74 patients was determined to be the sample size needed to meet the primary endpoint. In this analysis, noninferiority of vCPM compared to hFDS could be proven only if the lower bound of the Newcombe 90% confidence interval for the difference in the two proportions (difference=vCPM-hFDS) was greater than −15%."
	Length of study	9 weeks
	Source of funding	Osiris Therapeutics, Inc.
Towler et al. 2018[35]	Specific wound treatment comparison	Apligraf vs. Theraskin
	Wound type	VLU
	Country	USA
	Institutes involved	1, Bon Secours St Francis Wound Healing Center, Greenville, SC
	Method of patient recruitment	NR
	Patients enrolled	31 enrolled, 31 randomly assigned
	Date range of study	June 2013 to June 2016
	Care setting	Wound center
	Use of run-in (length)	Yes, 30 days
	Method of measuring wound condition at enrollment	Photos
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	NR
	Handling of dropouts	NR
	Statistical power calculations	Pilot study with a power calculation only to predict the risk of type 2 error.
	Length of study	20 weeks
	Source of funding	No funding

Study	Study Detail	Description
Sanders et al. 2014[45]	Specific wound treatment comparison	Dermagraft vs. Theraskin
	Wound type	DFU
	Country	USA
	Institutes involved	Bon Secours Wound Care Clinic at Mary Immaculate Hospital (Newport News, VA) and Washington Hospital Wound Center (Washington, PA)
	Method of patient recruitment	NR
	Patients enrolled	23
	Date range of study	NR
	Care setting	2 hospital-based outpatient wound care centers
	Use of run-in (length)	No
	Method of measuring wound condition at enrollment	Photos, tracings,
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	No
	Handling of drop outs	NR
	Statistical power calculations	Post-study calculation: 0.80 based on the closure rate of the wounds in each group.
	Length of study	20 weeks
	Source of funding	Soluble Systems, LLC, and LifeNet Health

DFU=diabetic foot ulcer; NR=not reported; SD=standard deviation; VLU=venous leg ulcer

Table C-18. Assessment of wound closure in 22 RCTs

Study	Comparison	Wound Type	Primary Outcome(s)	Definition of a "Healed Wound"	Reported Assessment and Reassessment of Wound Closure	Blinding of Assessors
Brown-Etris et al. 2019[58]	Oasis® Wound Matrix vs. SOC	PU	Incidence of 90% and 100% wound healing by 12 weeks.	Complete epithelialization of the wound.	Weekly through 12 weeks. Healed wounds were reassessed at 6-month followup.	No
Cazzell S. 2019[49]	DermACELL vs. SOC	VLU	Complete wound closure.	100% reepithelialization without drainage.	Weekly assessments until complete wound healing or until 24 weeks. Healed wounds were reassessed 4, 8, and 12 weeks after complete wound closure.	Yes
Serena et al. 2019[36]	Affinity® vs. SOC	DFU	Percent of wound closure by or on 12 weeks.	U achieving an area between 0 and 0.1 cm^2.	Weekly assessments until complete wound healing or until 12 weeks. Reassessment of healed wounds was scheduled 2 weeks after complete wound closure.	NR
Tettelbach et al. 2019[59]	EpiCord vs. SOC	DFU	Complete wound closure by 12 weeks.	100% epithelialization.	Weekly through 12 weeks. Healed wounds reassessed at 16-week followup.	Yes
Tettelbach et al. 2019[42]	EpiFix vs. SOC	DFU	Complete wound closure at 12 weeks.	Complete reepithelialization of the wound without drainage or need for dressing.	Weekly through 12 weeks. Healed wounds reassessed at 16 weeks.	Yes
Ananian et al. 2018[44]	GrafixPrime vs. Dermagraft	DFU	Proportion of patients who achieved complete closure of the index wound by the end of treatment.	100% reepithelialization.	Weekly through week 9 or until wound healed. Reassessment not described.	NR
Bianchi et al. 2018[37,38]	EpiFix plus multilayer compression therapy vs. SOC	VLU	Time to complete wound closure, as assessed over a 12-week period from treatment initiation.	100% reepithelialization without drainage.	Weekly through week 12 with 1 followup visit at week 16. Individuals who achieved healing before 12 weeks were required to be seen weekly for all 12 visits and return at week 16 for reassessment of healed wounds.	Yes
DiDomenico et al. 2018[60]	AmnioBand vs. SOC	DFU	To compare the proportion of wounds healed at 6 weeks.	Complete (100%) epithelialization without drainage and need for dressing.	Weekly assessments until complete wound healing or until 12 weeks. Reassessment of healed wounds was scheduled 1 week after complete wound closure.	Yes
Towler et al. 2018[35]	Apligraf vs. Theraskin	VLU	Complete wound closure, time to wound closure.	100% epithelialization without drainage.	Weekly through 12 weeks, followed until wound healed or up to 20 weeks. Reassessment not described.	NR
Zelen et al. 2018[54]	AlloPatch Pliable vs. SOC	DFU	Proportion (%) of ulcers healed at 6 weeks. Complete wound closure.	Complete (100%) reepithelialization without drainage and need for dressing.	Weekly through 12 weeks or until wound healed. Reassessment not described.	Yes
Alvarez et al. 2017[48]	MatriStem Wound Matrix* vs. SOC	DFU	Incidence of complete wound closure by 16 weeks.	Complete epithelialization without drainage or dressings required by 16 weeks.	Weekly through 16 weeks. Healed wounds were reassessed once/monthly up to 1 year.	NR
Alvarez et al. 2017[57]	Hyalomatrix Wound Matrix plus compression vs. SOC	VLU	Incidence of wound healing at 12 and 16 weeks.	NR	Weekly through week 16. Reassessment not described.	NR

Study	Comparison	Wound Type	Primary Outcome(s)	Definition of a "Healed Wound"	Reported Assessment and Reassessment of Wound Closure	Blinding of Assessors
Cazzell et al. 2017[50]	DermACELL vs. GraftJacket vs. SOC	DFU	To compare the proportion of chronic DFUs completely closed at the end of 12 weeks.	100% reepithelialization without drainage or dressing requirements confirmed at 2 consecutive study visits 2 weeks apart.	Weekly assessments until complete wound healing or until 24 weeks. Healed wounds were reassessed 4, 8, and 12 weeks after complete wound closure.	Yes
Frykberg et al. 2016[46]*	MatriStem vs. Dermagraft	DFU	Complete wound closure with up to 8 weekly device applications (day 56).	Complete reepithelialization with no wound drainage present and no dressing required.	Weekly assessments through wound closure or until subject received once/weekly (±3 days) treatment applications without complete wound closure, whichever came first. At 8 weeks, nonhealers received 3 additional SOC-only visits to determine delayed healing. Healed wounds (by day 70) were reassessed at 6 months.	Yes
Snyder et al. 2016[55]	AmnioExcel vs. SOC	DFU	Proportion of subjects with complete wound closure before or on week 6 after initiation of treatment.	100% complete skin reepithelialization without drainage or dressing requirements.	Weekly through week 6. No reported reassessment for closed wounds.	NR
Zelen et al. 2016[41]	Apligraf vs. EpiFix vs. SOC	DFU	To compare healing characteristics between groups.	Complete (100%) reepithelialization without drainage or need for dressing.	Once every 7 days (±3 days) for up to 12 weeks or until 1 week after complete healing.	Yes
Driver et al. 2015[56]	Integra Dermal Regeneration Template vs. SOC	DFU	Percentage of subjects with complete closure of the study ulcer, as assessed by the investigator, during the treatment phase.	100% reepithelialization of the wound surface with no discernable exudate and without drainage or dressing requirements.	Weekly through 16 weeks or until wound closure. Reassessment of wound closure was 1 week later and a second consecutive study visit.	Yes
Lavery et al. 2014[47]	Grafix vs. SOC	DFU	Proportion of patients with complete wound closure by 12 weeks.	100% reepithelialization with no wound drainage.	Weekly for 12 weeks. Healed wounds were reassessed 2 weeks postclosure. The followup phase consisted of 2 visits during the first month and then monthly for 2 additional visits.	Yes
Sanders et al. 2014[45]	Dermagraft vs Theraskin	DFU	Complete wound closure, number of grafts required by week 12.	100% epithelialization without drainage.	Weekly assessments through 12 weeks, followed until wound healed or up to 20 weeks. Reassessment of a healed wound occurred in 1 "confirmatory visit"; timing not reported.	NR
Serena et al. 2014[40]	EpiFix plus MLCT vs. MLCT	VLU	Proportion of patients with ≥40% reduction of wound size at 4 weeks.	100% epithelialization without drainage.	Weekly assessments through week 4. Reassessment of a healed wound 1 week later.	NR
Harding et al. 2013[43]	Dermagraft plus f4-layer compression therapy vs. 4-layer compression therapy	VLU	Proportion of patients with completely healed study ulcers by 12 weeks.	Full epithelialization of the wound with the absence of drainage for 2 consecutive weekly visits.	Weekly assessments until complete wound healing or until 24 weeks. Healed wounds were reassessed in a consecutive week.	NR

Study	Comparison	Wound Type	Primary Outcome(s)	Definition of a "Healed Wound"	Reported Assessment and Reassessment of Wound Closure	Blinding of Assessors
Zelen et al. 2013[39]	EpiFix vs. SOC	DFU	Reduction of wound size and the proportion of ulcers completely healed after 4 and 6 weeks.	Complete epithelialization of the open area of the wound.	At time 0 and at least once every 7 days (±3 days) for up to 12 weeks or until complete healing, whichever occurred first.	NR

DFU=diabetic foot ulcer; MLCT=multi-layer compression therapy; NR=not reported; PU: pressure ulcer; SOC=standard of care; VLU=venous leg ulcer
* Now branded as Cytal Wound Matrix (ACell, Inc., Columbia, MD)

Table C-19. Definition of failure to heal during treatment phase in 22 RCTs

Study	Comparison	Wound Type	Failure to heal
Bianchi et al. 2018[37,38]	EpiFix plus multilayer compression therapy vs. multilayer compression therapy	VLU	Standard of care group subjects whose VLU wound area did not decrease in area by at least 40% by week 8 were classified as study failures and were allowed to receive advanced treatments.
Zelen et al. 2018[54]	AlloPatch Pliable vs. SOC	DFU	Failed to decrease in size by 50% in 6 weeks.
DiDomenico et al. 2016[60]	AmnioBand vs. SOC	DFU	Failed to reduce in area by 50% or more.
Zelen et al. 2016[41]	Apligraf vs. EpiFix vs. SOC	DFU	Failed to heal by ≥50% within the first 6 weeks of study enrollment.
Zelen et al. 2013[39]	EpiFix vs. SOC	DFU	Did not achieve 50% area reduction at 6 weeks.

DFU=diabetic foot ulcer; SOC=standard of care; VLU=venous leg ulcer

Table C-20. Description of treatments in 22 RCTs

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Brown-Etris et al. 2019[58]	NR	Debridement, cleansing with normal saline solution, covered with isotonic saline gel (Normlgel®, Mölnlycke Health Care) followed by a semi-occlusive absorbent film dressing (Alldress®, Mölnlycke). Appropriate pressure redistribution support surfaces (e.g., dynamic or static air mattress overlay or full dynamic air mattress).	Oasis® Wound Matrix: applied directly to the wound bed and reapplied weekly. Cut to size slightly larger than the ulcer and placed upon the wound bed. Covered with isotonic saline gel and secured using a semi-occlusive absorbent film dressing.	SOC	NR
Cazzell S. 2019[49]	NR	Debridement, moist-wound treatment (e.g., alginate, foam, or hydrogel dressings), and coverage with moist or dry gauge. Dressings covered the wound for at least 5 days, but no more than 9 days, (7 days±2 days) until the next study visit. Compression therapy.	DermACELL: applied and covered with an appropriate nonadherent dressing. A second application was allowed no fewer than 2 weeks and no later than 12 weeks after the first application. Maximum of 2 applications allowed.	SOC	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Serena et al. 2019[36]	NR	Sharp debridement, cleansing with normal, sterile saline. Off-loading with total contact casting for plantar ulcers, and fixed ankle walker boots (infected wounds), or other appropriate means at the investigator's discretion.	Affinity®: applied directly with the stromal side in contact with the wound on the open ulcer bed at weekly intervals or until healed. Outer dressings applied.	SOC	NR
Tettelbach et al. 2019[59]	NR	Debridement, alginate wound dressing followed by a non-adherent silicone dressing (ADAPTIC TOUCH, Acelity), an absorbent nonadhesive hydropolymer secondary dressing (TIELLE Max, Acelity), and gauze wrap. Offloading with Active Offloading Walker (boot and/or shoe) or a similar device.	EpiCord: applied weekly, hydrated with sterile normal saline, followed by a non-adherent silicone dressing and nonadhesive absorbent hydropolymer secondary dressing and wrapped with an outer layer of gauze.	SOC	NR
Tettelbach et al. 2019[42]	NR	Cleansed, debrided, and dressed with a standard alginate dressing and an absorbent nonadhesive hydropolymer secondary dressing and wrapped with gauze. Dressings changed weekly at the study site unless they became wet or soiled. If additional dressing changes were required in the treatment group, only the outer dressings were changed. Offloading using cam-walker, offloading boot, shoe, or complete contact cast.	EpiFix: applied weekly, hydrated with sterile saline, followed by a non-adherent silicone dressing and nonadhesive absorbent hydropolymer secondary dressing and wrapped with an outer layer of gauze.	SOC	NR
Ananian et al. 2018[44]	Cleaning and debriding at the investigator's discretion	Offloading with a standardized fixed ankle walker (plantar wounds) or standard postoperative shoe (dorsal wounds). Alternative offloading devices permitted.	GrafixPrime: up to 8 applications available in 5 cm x 5 cm and 2 cm x 3 cm. Covered with a nonadherent dressing and a secondary dressing.	Dermagraft: up to 8 applications available in a 5 cm x 7.5 cm size. Covered with a nonadherent dressing and a secondary dressing.	NR
Bianchi et al. 2018[37,38]	Moist dressings and multilayer compression	Cleaning, debridement, standard moist wound dressings (Adaptic Touch™-primary wound contact layer and TIELLE® Max nonadhesive hydropolymer dressing-absorbent secondary dressing), and multilayer compression bandages.	EpiFix® dehydrated human amnion/chorion membrane allograft (MiMedx Group, Inc., Marietta, GA): up to 12 weekly applications; nonadherent moist wound dressings placed over the allograft, followed by dry gauze wrap and multilayer compression.	SOC	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
DiDomenico et al. 2018[60]	Debridement, offloading, collagen alginate and a 3-layer dressing	Saline irrigation, debridement, dressed daily with collagen alginate (Fibracol, Systagenix, Gargrave, Yorkshire, United Kingdom); by patients or their caregivers at home 6 days a week and by the site investigator 1 day a week. Offloading using a removable diabetic offloading cam-walker (Royce Medical, Inc., Camarillo, California; or similar generic device)—the removable walker could be converted instantly to a total contact cast if patients were nonadherent.	Amnioband (dehydrated human amnion and chorion allograft (dHACA)): cut to size, rinsed with sterile saline, and placed over the entire wound surface. Graft was covered with a nonadherent dressing (Adaptic Touch, Systagenix, Yorkshire, United Kingdom) topped with a moisture-retentive dressing (hydrogel bolster) and a padded 3-layer dressing (Dynaflex, Systagenix). Weekly applications of dHACA were allowed.	SOC	Infection management: If suspected, both anaerobic and aerobic cultures were obtained from wound swabs and appropriate systemic antibiotic treatment was initiated and continued until the infection was clinically resolved. If the infection precluded dHACA application in the treatment group or caused problems with scheduled visits in either group, the patient was withdrawn from the trial and the treatment was considered to be a failure. Diabetes management: Individuals with poor metabolic control were referred to their primary care physician or endocrinologist to ensure adequate diabetes management
Towler et al. 2018[35]	Compression and local wound care	For 12 weeks, debridement Dressing changes with a nonadherent contact layer (Mepilex transfer foam, Mölnlycke Health Care, Norcross, GA; or Adaptic, Systagenix, Quincy, MA); Multilayer compression dressing. Highly exudate wounds received biweekly changes. Weeks 12 to 20 for nonhealers: multilayer compression therapy alone.	Apligraf: Weekly evaluations by study investigators. Weekly grafts through week 12 unless repeat grafts were contraindicated, based on clinical assessment (i.e., infection) or if a graft was not available on the schedule date of application. Grafting continued until wound healing occurred or until further grafts were not covered or authorized by insurance. Grafts were covered with Mepilex transfer foam or Adaptic.	Theraskin: similar application as Apligraf	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
			Subjects were followed through week 20 or until the study wound was completely healed (100% epithelialization without drainage).		
Zelen et al. 2018[54]	Cleaned and surgically debrided	Irrigation with sterile normal saline, debrided, daily dressing changes with a collagen alginate (Fibracol, Systagenix, Gargrave, Yorkshire, UK), followed by a 3-layer padded generic dressing of gauze, soft roll, and a compressive wrap; offloading using a removable cast walker (Royce Medical, Inc., Camarillo, CA), total contact cast, or similar generic device.	AlloPatch Pliable (human reticular acellular dermal matrix (HR-ADM)): Weekly applications of HR-ADM during the study period. Following immersion in sterile saline for 5 to 10 seconds, the graft was pie-crusted with a 15-scalpel blade, not greater than ×1.5 to ×1.0, and cut to size using sterile scissors and applied to the entire ulcer surface ensuring maximum surface contact. A nonadherent dressing (Adaptic Touch, Systagenix) was applied over the graft, followed by a moisture-retentive dressing (hydrogel bolster) and a padded 3-layer dressing (Dynaflex, Systagenix or equivalent) until complete closure.	SOC	Systemic antibiotics were administered until the infection was clinically resolved. Patients were withdrawn from the study if the infection worsened such that it interrupted HR-ADM treatment or interfered with study visits.
Alvarez et al. 2017[48]	Extensive debridement	Nonadherent (siliconized) medical-grade foam (Mepilex Wound Dressing; Mölnlycke Health Care, Norcross, GA), offloading with a total contact cast.	MatriStem Wound Matrix* (urinary bladder matrix): weekly applications through week 16 or until healing was achieved. Trimmed to fit, then moistened with saline and applied directly to the wound bed. Secured with adhesive skin closure strips, then a secondary dressing.	SOC weekly for 16 weeks or until healing was achieved.	NR
Alvarez et al. 2017[57]	NR	Nonadherent silicone foam dressing and either 2-layer short-stretch compression bandage or 4-layer compression bandage.	Hyalomatrix Wound Matrix: application not reported.	SOC	NR
Cazzell et al. 2017[50]	Debridement	Debridement followed by moist-wound treatment with alginate, foam, or hydrogel dressings. Dressings covered the wound for at least 5 days, but no more than 9 days, (7 days±2 days) until the next study visit. Dressings were changed only by the study team.	DermACELL: meshed, 4 x 4 cm (thickness range, 0.5-1.0 mm) D-ADM was applied and covered with an appropriate nonadherent dressing. A second ADM application was allowed to be administered if determined medically necessary by the investigator, no fewer than 3 weeks but no longer than 12 weeks (weeks 3-12) after the first application of ADM.	GraftJacket: meshed, 4 x 4 cm (thickness range, 0.38-1.02 mm) with similar application as DermACELL.	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Frykberg et al. 2016[46]	Debridement, saline irrigation, primary dressing, and offloading boot	Sharp debridement, saline irrigation, foot offloading.	MatriStem MicroMatrix (MSMM) and MatriStem Wound Matrix (MSWM): A sheet of MSWM was placed over the wound area followed by a nonadherent dressing and hydrogel dressing. Weekly application of both MSMM and MSWM occurred until a service-level granulation tissue was observed. Subsequently on weekly visits, only Wound Matrix and hydrogel were applied. Up to 8 applications of MatriStem were allowed. Healthcare provider applying grafts not reported.	Dermagraft: applied weekly per-product specifications. Up to 8 applications were allowed.	NR
Snyder et al. 2016[55]	Cleaned, debrided	Debridement, moist wound dressings, offloading with a DH Walker boot, infection surveillance, and management.	AmnioExcel dehydrated amniotic membrane allograft (DAMA): cut to fit the DFU. Dressed with Adaptic (Systagenix, Gatwick, UK) and covered with a foam nonadhesive dressing. Wrapped with the conforming bandage and lightly secured. Cover dressing consisting of a compression dressing of the cohesive bandage wrap was applied. DAMA could be reapplied weekly upon the investigator's discretion.	SOC: in addition to SOC received by all patients, controls also received Xtra-Sorb foam nonadhesive dressing (Derma Sciences, Princeton, NJ). After hemostasis was achieved, the wound was wrapped with Duform Synthetic Conforming Bandage (Derma Sciences) and lightly secured. Lastly, a compression dressing (Duban Cohesive Bandage, Derma Sciences) was applied as a cover dressing.	"Infection surveillance and management"

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Zelen et al. 2016[41]	Debridement, collagen-alginate dressings and gauze, offloading cast walker	Debridement, saline irrigation, collagen-alginate dressing, offloading.	Apligraf: weekly application followed by a nonadherent dressing (Adaptic Touch, Systagenix, San Antonio, TX or equivalent), a moisture-retentive dressing (NuGel, Systagenix, San Antonio, TX, or equivalent) and a compressive dressing. Dressings were changed weekly. Healthcare provider applying grafts not reported.	EpiFix: similar application as Apligraf	NR
Driver et al. 2015[56]	See SOC	Sharp debridement, moist wound therapy consisting of 0.9% sodium chloride gel plus a secondary dressing (a nonadherent foam dressing, an outer gauze wrap, and an offloading/protective device [Active Offloading Walker boot and/or shoe]).	Integra Dermal Regeneration Template (IDRT): applied in the outpatient setting. Fenestrating and meshing of the IDRT was permitted to allow for drainage and in the presence of exudating wounds or hematomas. The IDRT was trimmed to size and secured with sutures or staples and covered with a secondary dressing. The silicone layer of IDRT was removed when the collagen layer was replaced by new tissue, typically 14-21 days after application. Reapplication of IDRT was performed at the investigator's discretion. The secondary dressing changes for the active treatment group were performed weekly by site personnel.	See SOC	NR
Lavery et al. 2014[47]	NR	Surgical debridement, offloading and nonadherent dressings. All patients received a nonadherent dressing (Adaptic® (Systagenix, Gatwick, UK) and either saline-moistened gauze or Allevyn® (Smith & Nephew, London, UK) for moderately draining wounds. An outer dressing was then applied. Patients were provided walking boots or a post-op shoe depending on wound location. Custom offloading boots were also available.	Grafix: applied once a week (±3 days) for up to 84 days; the human viable wound matrix (hVWM) was placed to come in full contact with the wound and edges.	SOC: once a week (±3 days) for up to 84 days.	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Sanders et al. 2014[45]	NR	Saline irrigation, debridement offloading. Graft covered with dressing changes with either Mepitel or PolyMem (Ferris Manufacturing Corp., Fort Worth, TX); weeks 12 to 20 for nonhealers: saline-moistened gauze and debridement.	Dermagraft: Weekly evaluations by study investigators. Weekly grafts through week 12. Grafts were covered with Mepilex or PolyMem. Subjects were followed through week 20 or until the study wound was completely healed (100% epithelialization without drainage). One visit (timing not reported) was scheduled to confirm healed wound.	Theraskin: similar care except grafts were applied every other week.	NR
Serena et al. 2014[40]	Cleaned, debrided	Cleaned, debrided, MLCT bandage (Coban2, 3M St. Paul, MN) applied at every visit.	EpiFix (1 or 2 applications) plus MLCT: The dHACM was applied once in the 1 dHACM application treatment group at day 0 and applied twice in the 2 dHACM applications treatment group at day 0 and week 2.	MLCT: see SOC	Topical antimicrobials or oral antibiotics were permissible, but topical antibiotics were not.
Harding et al. 2013[43]	Debridement, saline rinse, and standard dressing regimen, including 4-layer compression bandaging. Wounds were covered with a nonadherent dressing (Dermanet®, DeRoyal, Powell, TN). Deeper ulcers received gauze on top of the Dermanet. Heavily exuding ulcers could receive additional absorbent dressings at the investigator's discretion. Dressings were changed weekly or earlier if clinically indicated.	Identical to prior wound therapy.	Dermagraft plus 4-layer compression therapy: applied weeks 0, 1, 4, and 8. Cut to fit the shape of the ulcer (accommodating any epithelial islands) then placed into the wound bed with no overlap onto the intact skin surrounding the ulcer and smoothed to ensure that the entire piece of Dermagraft was in contact with the wound surface.	4-layer compression therapy: using the Profore™ 4-layer compression system (Smith & Nephew, Hull, UK).	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Zelen et al. 2013[39]	No	Debridement, appropriate moist wound therapy (Silvasorb gel and Aquacel AG), a compression dressing, and offloading with a removable cast walker (Active Offloading Walker; Darco, Huntington, WV).	EpiFix, a dehydrated amniotic membrane allograft: applied and covered with a nonadherent dressing (Adaptic®), followed by a moisture-retentive dressing (hydrogel bolster) and a compression dressing. Weekly dressing changes and EpiFix applications weeks 2, 4, 6, 8, and 10, if nonhealing ulcer.	See SOC	NR

ADM=acellular dermal matrix; MLCT=multilayer compression therapy; NR=not reported; SOC=standard of care
* Now branded as Cytal Wound Matrix (ACell, Inc., Columbia, MD)

Table C-21. Clinical results related to wound healing in studies comparing acellular skin substitutes versus standard of care

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
Brown-Etris et al. 2019[58]	Wounds closed at 12 weeks (number, %)	Complete epithelialization of the wound	27/67 (40%) Oasis® Wound Matrix	18/63 (29%) SOC	p=0.111
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with Stage III ulcers	N/A	49%	36%	p=0.34
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with Stage IV ulcers	N/A	29%	21%	p=0.76
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with ulcers <6 cm^2	N/A	44%	45%	p=1.00
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with ulcers ≥6 cm^2	N/A	29%	10%	p=0.12
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with ulcer duration <6 months	N/A	50%	37%	p=0.26
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with ulcer duration ≥6 months	N/A	25%	15%	p=0.49
	Wounds healed after 12 weeks (24 weeks) (number, %)	N/A	10/21 (47.6%)	7/14 (50%)	No statistical analysis performed
	Average time to wound closure (weeks [SD])	N/A	NR	NR	N/A
	Number of patients with **infected** wounds and **increase** in wound size	N/A	3/11 (27%) infection only	5/12 (41.6%) infection only	NR
	Wound worsening and/or desired change in treatment	N/A	7/16 (44%) noncompleters	7/20 (35%) noncompleters	NR
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	2	0	NR
	Hospitalization and/or deteriorating health	N/A	4/16 (25%) noncompleters	1/20 (5%) noncompleters	NR
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Cazzell 2019[49]	Wounds closed at 24 weeks (number, %) per protocol population	100% reepithelialization without drainage	5/17 (29.4%) DermACELL	3/9 (33.3%) SOC	NS
	Average time to wound closure (weeks [SD])	N/A	NR	NR	N/A
	Number of patients with **infected** wounds and **increase** in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
	Recurrence	N/A	1 (data missing on 1/5 wounds healed)	2	p=0.3074
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Tettelbach et al. 2019[59]	Wounds closed at 12 weeks (number, %)	100% epithelialization	71/101 (70%) EpiCord	26/54 (48%) SOC	p=0.0089
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	74/101 (73%)	29/54 (54%)	p=0.0199
	Average time to wound closure (weeks [SD])	N/A	NR	NR	Kaplan-Meier plot of time-to-heal within 12 weeks demonstrated "a superior wound-healing trajectory for EpiCord-treated ulcers versus alginate-treated ulcers. The log-rank test of equality of the healing function over the two study groups produced a $\chi 2$ test statistic of 5.89, with a p=0.0152."
	Number of patients with **infected** wounds and **increase** in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Median number of grafts (range)	N/A	7 (range 2-12)	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	3	4	NR
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
Tettelbach et al. 2019[42]	Wounds closed at 12 weeks (number, %)	Complete epithelialization of the wound	38/54 (70%) EpiFix	28/56 (50%) SOC	p=0.0338 Cox regression analysis indicated that treatment with EpiFix (HR 2.15), and Caucasian race (HR 3.01) were significantly associated with healing at 12 weeks. Inadequate debridement (HR 0.36), history of recurring DFU (HR 0.42), and baseline ulcer size ≥2.2 cm^2 (HR 0.44) were negatively associated with healing at 12 weeks.
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	36/54 (66%)	24/56 (42%)	NR
	Average time to wound closure (weeks [SD])	N/A	NR	NR	Statistically significantly shorter time to closure with EpiFix (p=0.0187; Kaplan-Meier analysis)
	Number of patients with **infected** wounds and **increase** in wound size	N/A	6 infections only	5 infections only	NR
	Wound worsening and/or desired change in treatment	N/A	NR	NR	N/A
	Other wound healing outcomes Number of grafts (median, range)	N/A	5 (range, 1-12)	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	2	4	NR
	Hospitalization and/or deteriorating health	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
Bianchi et al. 2018[37,38]	Wounds closed at 12 weeks (number, %)	100% reepithelialization without drainage	32/64 (50%) EpiFix plus multilayer compression therapy	20/64 (31%) SOC (dressings and multilayer compression therapy alone)	p=0.0473
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	38/64 (59%)	25/64 (39%)	p=0.0335
	Average time to wound closure (Kaplan-Meier analysis: time to heal within 12 weeks)	N/A	NR	NR	Significantly improved time to healing using EpiFix (log-rank p=0.032)
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
DiDomenico et al. 2018[60]	Wounds closed at 12 weeks (number, %) per protocol population	100% reepithelialization without drainage	34/40 (85%) AmnioBand	13/40 (33%) SOC	$p=6.0 \times 10^{-6}$
	Average time to wound closure (days [95% CI])	N/A	37 (95% CI: 29.5 to 44.4)	67.3 (95% CI: 59.0 to 79.6)	$p=6.0 \times 10^{-6}$ Statistically significantly shorter time to closure with AmnioBand after controlling for initial wound area ($p=2.2\times 10^{-5}$; Kaplan-Meier analysis)
	Number of patients with **infected** wounds and **increase** in wound size	N/A	1 SAE, possibly infection-related and requiring hospitalization	3 SAE, possibly infection-related and requiring hospitalization	NR
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	0	2	NR
	Hospitalization	N/A	1 SAE, possibly infection-related and requiring hospitalization	3 SAE, possibly infection-related and requiring hospitalization	NR
	Return to function or activities of daily living	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Zelen et al. 2018[54]	Wounds closed at 6 weeks (number, %)	Complete (100%) reepithelialization without drainage and need for dressing	27/40 (68%) AlloPatch Pliable (human reticular acellular dermal matrix)	6/40 (15%) SOC	$p=2.7 \times 10^{-6}$ (statistically significant)
	Wounds healed after 6 weeks (12 weeks) (number, %)	N/A	32/40 (80%)	12/40 (30%)	$p=8.4 \times 10^{-6}$ (statistically significant)
	Average time to wound closure at 6 weeks (days [95% CI])	N/A	27 days (95% CI: 23 to 32)	41 days (95% CI: 39 to 42)	$p=9.9 \times 10^{-7}$
	Average time to wound closure at 12 weeks (days [95% CI])	N/A	38 days (95% CI: 29 to 47)	72 days (95% CI: 66 to 79)	$p=3.9 \times 10^{-7}$(statistically significant)
	Number of patients with infected wounds and increase in wound size	N/A	6/40 (15%) infections requiring hospitalization and IV antibiotic	2/40 (5%) infections requiring hospitalization and IV antibiotic	NR
	Other wound healing outcomes Average number of grafts at 6 weeks (weeks [SD])	N/A	3.4±2.1	N/A	N/A
	Average number of grafts at 12 weeks (weeks [SD])	N/A	4.7±3.4	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	3 from infection	5 from infection	NR
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Alvarez et al. 2017[48]	Wounds closed at 12 weeks (number, %)	Complete epithelialization without drainage or dressings required by 16 weeks	10/11 (91%) MatriStem Wound Matrix*	2/6 (33%) SOC	p=0.041
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	11/11 (100%)	5/6 (83%)	p value NR
	Average time to wound closure (days [SD])	N/A	62.4 days	92.8 days	p=0.031
	Number of patients with infected wounds and increase in wound size	N/A	Local wound infection reported in 6 patients (arm unspecified)	Local wound infection reported in 6 patients (arm unspecified)	N/A
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence at 1 year	N/A	1/11 (10%)	3/6 (50%)	p value NR
	Hospitalization	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Alvarez et al. 2017[57]	Wounds closed at 12 weeks (number, %)	NR	66.6% Hyalomatrix Wound Matrix plus compression	14.2% SOC (nonadherent primary dressing plus a multilayer compression bandage)	p=0.066
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	87.5%	42.8%	p=0.059
	Average time to wound closure (days)	N/A	41	104	p=0.029
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Snyder et al. 2016[55]	Wounds closed at 6 weeks (number, %)	100% complete skin reepithelialization without drainage or dressing requirements	5/15 (35%) AmnioExcel dehydrated amniotic membrane allograft	0/14 (0%) SOC	p=0.0170, 95% CI of responder ratio: 25.0 to 46.4 AmnioExcel, 0.00 to 0.00 SOC; p=0.0407
	Wounds healed after 6 weeks (number, %)	N/A	NR	NR	N/A
	Average time to wound closure (weeks[SD])	N/A	NR	NR	Statistically significantly shorter time to closure with AmnioExcel (p<0.0001; Kaplan-Meier analysis)
	Number of patients with infected wounds and increase in wound size	N/A	1 (6.7%) wound infection	1 (7/1%) diabetic foot infection	N/A
	Other wound healing outcomes Total number of grafts (mean±SD)	N/A	4.3±1.7; 1 piece applied weekly (7.3±0.6 days)	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Driver et al. 2015[56]	Wounds closed at 12 weeks (number, %); 16 weeks was end of treatment phase	100% reepithelialization of the wound surface with no discernable exudate and without drainage or dressing requirements	70/154 (45%) Integra Dermal Regeneration Template (IDRT)	31/153 (20%) SOC	p<0.001 OR 3.3, 95% CI: 2.0 to 5.4; p<0.001
	Wounds healed after 12 weeks (16 weeks, end of treatment) (number, %)	N/A	79/154 (51%) IDRT	49/153 (32%) SOC	p=0.001 OR 2.2, 95% CI: 1.4 to 3.5; p=0.001
	Median time to wound closure (days)	N/A	43	78	NR
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Median number of grafts/patient	N/A	1 (range, 1 to 15)	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence at end of followup phase (28 weeks)	N/A	19%	26%	p=0.32
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	Significant difference in body pain favoring Integra (p=0.033)
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Serena et al. 2014[40]	Wounds closed at 4 weeks (number, %)	100% epithelialization without drainage	6/53 (11.3%) EpiFix plus MLCT	4/51 (7.8%) MLCT	NR
	Wounds healed after 4 weeks (20 weeks) (number, %)	N/A	NR	NR	N/A
	Average time to wound closure (weeks [SD])	N/A	NR	NR	N/A
	Number of patients with infected wounds and increase in wound size	N/A	1 infection and increase drainage and abscess	2 infections only and 1 maceration around the wound with increased drainage	NR
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	26 patients received 1 application of EpiFix at day 0. 27 patients received 2 applications of EpiFix at day 0 and week 2.	N/A	N/A
	Amputation	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between-Group Difference
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	Of 89.8% reporting pain at randomization, 79.5% reported a reduction	Of 75.0% reporting pain at randomization, 52.4% reported a reduction	NR
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Zelen et al. 2013[39]	Wounds closed at 4 weeks (number, %)	Complete epithelialization of the open area of the wound	10/13 (77%) EpiFix	0/12 (0%) SOC	p<0.001
	Wounds healed after 4 weeks (6 weeks) (number, %)		12/13 (92%)	1/12 (8%)	p<0.001
	Average time to wound closure (weeks)		2.5±1.9	5	NR
	Number of patients with **infected** wounds and **increase** in wound size		0 infection only	2 infections only	NR
	Other wound healing outcomes Average number of grafts (weeks[SD])		NR	N/A	N/A
	Amputation		NR	NR	N/A
	Reoccurrence		NR	NR	N/A
	Hospitalization		NR	NR	N/A
	Return to function or activities of daily living		NR	NR	N/A
	Pain		NR	NR	N/A
	Exudate		NR	NR	N/A
	Odor		NR	NR	N/A

CI=confidence interval; MLCT=multilayer compression therapy; N/A=not available; NR=not reported; NS=not significant; OR=odds ratio; SD=standard deviation; SOC=standard of care
* Now branded as Cytal Wound Matrix (ACell, Inc., Columbia, MD)

Table C-22. Reports of adverse events in studies comparing acellular skin substitutes versus standard of care

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Brown-Etris et al. 2019[58]	Oasis Wound Matrix (n=11)	NR	1	1	1	NR	No significant difference between groups for proportion of patients experiencing an infection-related AE (p=0.483) and at least 1 AE (p=0.477).
	SOC (n=12)	NR	3	1	0	NR	
Cazzell 2019[49]	DermACELL (n=18)	NR	NR	NR	NR	NR	AEs were not reported.
	SOC (n=10)	NR	NR	NR	NR	NR	
Tettelbach et al. 2019[59]	EpiCord (n=101)	NR	NR	NR	NR	NR	Authors noted 75 patients with at least 1 AE (42 [42%] EpiCord, 33 [61%] SOC), no product-related AEs, and procedure-related AEs in 1 patient in each arm. Severe AEs occurred in 25 patients (15 EpiCord, 10 SOC).
	SOC (n=54)	NR	NR	NR	NR	NR	
	EpiFix (n=54)	7	NR	NR	3	NR	Most common AE: developing an additional ulcer (n=34).

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Tettelbach et al. 2019[42]	SOC (n=56)	8	NR	NR	1	NR	53 ulcer-related AEs (30 EpiFix, 23 SOC). 11 target ulcer infections (6 EpiFix, 5 SOC) 3 events were possibly product-related (1 case of wound maceration, 2 positive wound cultures (1 *Providencia stuartii*, 1 *Pseudomonas aeruginosa*).
Bianchi et al. 2018[37,38]	EpiFix plus multilayer compression therapy (n=52)	0	0	0	0	0	Severe AE: 9 EpiFix, 4 SOC; p=0.140 Authors noted severe AEs include death (cardiac arrest because of coronary artery disease), trauma, alcohol poisoning, and ulcer worsening resulting in additional interventional.
	SOC (dressings and multilayer compression therapy alone) (n=57)	0	0	0	0	0	
DiDomenico et al. 2018[60]	AmnioBand (n=40)	NR	NR	NR	1 (see General Comments)	NR	4 SAEs (1 AmnioBand, 3 SOC) Authors noted all the SAEs involving foot infections (number not specified) required hospitalization, and most progressed to osteomyelitis. No AE's were graft-related.
	SOC (n=40)	NR	NR	NR	3 (see General Comments)	NR	
Zelen et al. 2018[54]	AlloPatch Pliable (human reticular acellular dermal matrix) (n=40)	0	0	0	0	0	Serious AEs: 3 AlloPatch Pliable, 6 SOC 8 of the 9 SAEs were due to diabetic foot infections that required hospitalization and IV antibiotics. 1 SAE that occurred in the SOC arm was due to an acute Charcot foot. 7 nonserious AEs also occurred but were not related to treatment.
	SOC (n=40)	0	0	0	0	0	
Alvarez et al. 2017[48]	MatriStem Wound Matrix* (n=11)	See General Comments	0	See General Comments	0	0	AEs included local wound infection (n=6) and dermatitis (n=4). Serious AEs included cellulitis (n=1), urinary tract infection (n=1), and congestive heart failure (n=1). Authors indicated no events were related to the intervention.
	SOC (n=6)	See General Comments	0	See General Comments	0	0	
Alvarez et al. 2017[57]	Hyalomatrix Wound Matrix plus compression (n=9)	NR	NR	NR	NR	NR	NR
	SOC (nonadherent primary dressing plus a multilayer compression bandage) (n=7)	NR	NR	NR	NR	NR	
Snyder et al. 2016[55]	AmnioExcel dehydrated amniotic membrane allograft (n=15)	0	0	0	1 (6.7%)	0	1 wound infection (AmnioExcel), 1 diabetic foot infection (SOC), and 1 localized infection (AmnioExcel) were reported. Deep vein thrombosis occurred in 1 patient (SOC).
	SOC (n=14)	1 (7.1%)	0	0	0	0	
Driver et al. 2015[56]	Integra Dermal Regeneration Template (IDRT)	0	0	0	0	0	Significantly more severe AEs (15.6% IDRT vs. 26.8% SOC; p=0.016) and moderate AEs in SOC (31.8% IDRT vs. 42.5% SOC; p=0.053). Potentially study-related AEs were noted as similar (7/154 [4.5%] Integra vs. 8/153 [5.2%] SOC).
	SOC	0	0	0	0	0	

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Serena et al. 2014[40]	EpiFix plus MLCT (n=53)	2	0	0	0	0	In EpiFix plus MLCT arm, 2 cases of cellulitis on the affected extremity, 1 wound infection, and 1 wound with increased drainage and abscess. In the MLCT arm, AEs of 5 patients included maceration around the wound with increased drainage and 2 wound infections.
	MLCT (n=51)	0	0	0	0	0	
Zelen et al. 2013[39]	EpiFix (n=13)	0	0	0	0	0	AEs: 1 EpiFix, 4 SOC SOC: 1 patient each experienced a gastrointestinal bleed and acute pyelonephritis. EpiFix: 1 patient experienced pneumonia, respiratory distress and acute renal failure not believed to be product-related
	SOC (n=12)	2	0	0	0	0	

AE=adverse event; MLCT=multilayer compression therapy; NR=not reported; SAE=serious adverse event; SOC=standard of care
* Now branded as Cytal Wound Matrix (ACell, Inc., Columbia, MD)

Table C-23. Clinical results related to wound healing in studies comparing cellular dermal substitutes with standard of care

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between Group Difference
Serena et al. 2019[36]	Wounds closed at 12 weeks (number, %)	Ulcer achieving an area between 0 and 0.1 cm^2	21/38 (55%) Affinity	11/38 (29%) SOC	p=0.02
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	22/38 (58%) Affinity	11/38 (29%) SOC	p=0.01
	Median time to wound closure (weeks)	N/A	11	19	42% faster; p value NR
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalizations related to infections	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Lavery et al. 2014[47]	Wounds closed at 12 weeks (number, %)	100% reepithelialization with no wound drainage	31/50 (62.0%) Grafix	10/47 (21.3%) SOC	p=0.0001 OR 6.037, 95% CI: 2.449 to 14.882
	Wounds healed after 12 weeks (24 weeks) (number, %)	N/A	NR	NR	N/A
	Median time to wound closure (days)	N/A	42.0	69.5	p=0.019
	Probability of complete wound closure (Kaplan-Meier analysis)	N/A	67.1%	27.1%	Log-Rank, p<0.0001
	Number of patients with infected wounds and increase in wound size	N/A	9/50 (18.0%) infections only	17/47 (36.2%) infections only	p=0.044

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between Group Difference
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	NR	NR	N/A
	Amputation	N/A	0 (0%)	1 (2.1%)	NS
	Recurrence	N/A	5/28 (17.8%); report 31 healed, provide data only on 28/31 patients	3/10 (30%)	p=0.42
	Hospitalizations related to infections	N/A	6%	15%	p=0.15
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Harding et al. 2013[43]	Wounds closed at 12 weeks (number, %); ITT	Full epithelialization of the wound with the absence of drainage for 2 consecutive weekly visits	64 (34.4%) Dermagraft plus 4-layer compression therapy	56 (31.1%) 4-layer compression therapy	p=0.235, OR 1.40, 95% CI: 0.80 to 2.41
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with ulcer duration ≤12 months	N/A	49/94 (52.1%)	36/97 (37%)	p=0.029, OR 2.37, 95% CI: 1.08 to 5.14
	Wounds closed at 12 weeks (number, %); ITT, subgroup analysis for patients with ulcers ≤10 cm^2:	N/A	55/117 (47%)	47/120 (39.2%)	p=0.223
	Wounds healed after 12 weeks (24 weeks) (number, %)	N/A	96/186 (52%)	88/180 (49%)	p=NR
	Average time to wound closure (weeks[SD])	N/A	NR	NR	p=0.660, HR 1.07, 95% CI: 0.80 to 1.43
	Number of patients with infected wounds and increase in wound size	N/A	55 (29.4%) infection only	43 (24.0%) infection only	NR
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence through 24 weeks	N/A	15%	23%	NR
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Venous ulcer pain	N/A	10 (5.3)	9 (5.0)	NR
	Pain in extremity	N/A	9 (4.8%)	10 (5.6%)	NR
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; N/A=not applicable; NR=not reported; OR=odds ratio; SD=standard deviation

Table C-24. Reports of adverse events in studies comparing cellular dermal substitutes with standard of care

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Serena et al. 2019[36]	Affinity (n=38)	NR	NR	NR	NR	NR	Authors reported no systemic or localized AEs or SAEs were attributed to Affinity.
	SOC (n=38)	NR	NR	NR	NR	NR	
Lavery et al. 2014[47]	Grafix (n=50)	0	0	0	0	0	At least 1 AE occurred in fewer patients receiving Grafix (44% vs. 66%; p=0.031).
	SOC (n=47)	0	0	0	0	0	
Harding et al. 2013[43]	Dermagraft plus 4-layer compression therapy (n=187)	12 (6.4%)	0	10 (5.3%)	0	13 (7%)	Study site infection: 43 (23%) Dermagraft plus 4-layer compression therapy, 46 (26%) 4-layer compression therapy. Wound infection (purulence and/or odor): 55 (29.4%) Dermagraft plus 4-layer compression therapy, 43 (24.0%) 4-layer compression therapy. Serious/severe AE: 24 Dermagraft plus 4-layer compression therapy, 33 four-layer compression therapy.
	4-layer compression therapy (n=179)	18 (10.1%)	0	6 (3.4%)	0	5 (2.8%)	

AE=adverse event; SAE=serious adverse event

Table C-25. Clinical results related to wound healing in studies comparing acellular dermal substitutes with acellular dermal substitutes

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Skin Substitute	Control	Between Group Difference (versus SOC)
Cazzell et al. 2017[50]	Wounds closed at 16 weeks (number, %); ITT population	100% reepithelialization without drainage or dressing requirements confirmed at 2 consecutive study visits 2 weeks apart	66% DermACELL single-application	NR for GraftJacket	37.7% SOC	HR: 1.918, 95% CI: 1.139 to 3.23; p=0.0093 No significant differences for GraftJacket vs. SOC or DermACELL vs. GraftJacket (data not reported).**
	Wounds healed at 24 weeks (number, %); ITT population	N/A	70.0%	NR for GraftJacket	49.3%	HR 1.589; 95% CI: 0.9824 to 2.572; p=0.0442
	Average time to wound closure (weeks [SD])	N/A	NR	NR	NR	N/A
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	NR	N/A
	Other wound healing outcomes Average number of grafts*	N/A	NR	NR	NR	N/A
	Amputation	N/A	NR	NR	NR	N/A
	Recurrence* (for ITT)	N/A	NR	NR	NR	N/A
	Hospitalization	N/A	NR	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	NR	N/A
	Pain	N/A	NR	NR	NR	N/A
	Exudate	N/A	NR	NR	NR	N/A
	Odor	N/A	NR	NR	NR	N/A

CI=confidence interval; HR=hazard ratio: ITT=intent-to-treat; NR=not reported; SD=standard deviation; SOC=standard of care

* Data not included for average number of grafts and recurrence since they were based on the "per protocol population." For recurrence, data for percentage of healed wounds that remained closed at post-termination visits were missing for 48.5% of patients.

** Authors noted that statistical significance was not sought or expected for the GraftJacket arm.

Table C-26. Reports of adverse events in studies comparing acellular dermal substitutes with acellular dermal substitutes

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Cazzell et al. 2017[50]	DermACELL (n=71)	0	1*	0	5.6%	0	Serious treatment-related adverse events: 28.2% DermACELL, 28.6% Graftjacket, 27.9% SOC
	GraftJacket (n=28)	0	0	0	10.7%	0	
	SOC (n=68)	0	0	0	5.9%	0	

SOC=standard of care
* Authors noted that the death was unrelated to product.

Table C-27. Clinical results related to wound healing in studies comparing acellular dermal substitutes with cellular dermal substitutes and cellular epidermal and dermal substitutes

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Skin Substitute	Control	Between Group Difference
Frykberg et al. 2016[46]	Wounds closed at day 56 (number, %)	Complete reepithelialization with no wound drainage present and no dressing required.	5 (18.5%) MatriStem	2 (6.9%) Dermagraft	N/A	p=0.244
	Wounds healed at day 70 (10 weeks) (number, %)	N/A	7 (25.9%)	9 (31.0%)	N/A	p=0.768
	Average time to wound closure (days [SE])	N/A	69.817±3.271	65.738±1.910	N/A	p=0.523
	Number of patients with infected wounds and increase in wound size	N/A	1 of 27 (3.7%) infected.	2 of 29 (6.9%) infected.	N/A	NR
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A	N/A
	Other wound healing outcomes Change in wound size over 8 week treatment period (cm^2, 8 weeks)	N/A	-2.277	-0.792	N/A	p=0.762
	Amputation	N/A	NR	NR	N/A	N/A
	Recurrence at 6 months (10 patients reporting)	N/A	Of the 5 returning, 1 reoccurred (20%). Of the 7 healed at 70 days, 1 reoccurred (14.2%).	Of the 5 returning, 2 reoccurred (40%). Of the 9 healed at 70 days, 2 reoccurred (22.2%).	N/A	NS
	Hospitalization	N/A	NR	NR	N/A	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A	N/A
	Pain	N/A	NR	NR	N/A	N/A
	Exudate	N/A	NR	NR	N/A	N/A
	Odor	N/A	NR	NR	N/A	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Skin Substitute	Control	Between Group Difference
Zelen et al. 2016[41]	Wounds closed at 12 weeks (number, %)	Complete (100%) reepithelialization without drainage or need for dressing.	24 (73%) Apligraf	31 (97%) EpiFix	18 (51%) SOC	Adjusted p=0.00019
	Wounds healed after 12 weeks (20 weeks) (number, %)	N/A	NR	NR	NR	N/A
	Average time to wound closure (days [95% CI])	N/A	47.9 (95% CI: 38.2 to 57.7)	23.6 (95% CI: 17.0 to 30.2)	57.4 (95% CI: 48.2 to 66.6)	Adjusted p=3.2 x 10^{-7}
	Number of patients with infected wounds and increase in wound size	N/A	7 overall infections were reported; 5 not attributed to a product.	7 overall infections were reported; 5 not attributed to a product.	2 infections	N/A
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	5.9±3.6	3.4±2.9	N/A	0.003
	Amputation	N/A	NR	NR	NR	N/A
	Recurrence	N/A	NR	NR	NR	N/A
	Hospitalization	N/A	1 unrelated to product	1 unrelated to product	2	N/A
	Return to function or activities of daily living	N/A	NR	NR	NR	N/A
	Pain	N/A	NR	NR	NR	N/A
	Exudate	N/A	NR	NR	NR	N/A
	Odor	N/A	NR	NR	NR	N/A

CI=confidence interval; ITT=intent-to-treat; N/A=not applicable; NR=not reported; NS=not significant; SD=standard deviation; SE=standard error; SOC=standard of care
* Non-inferiority test for complete closure (based on per protocol population) indicated GrafixPrime was not inferior to Dermagraft.

Table C-28. Reports of adverse events in studies comparing acellular dermal substitutes with cellular dermal substitutes and cellular epidermal and dermal substitutes

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Frykberg et al. 2016[46]	MatriStem (n=27)	3 (11.1%)	0	0	1 (3.7%)	0	Wound infection: 1 (3.7%) MatriStem, 2 (6.9%) Dermagraft. 1 death due to cerebrovascular accident was not considered product related. Overall incidence of AEs was reported as comparable (29.6% MatriStem, 34.5% Dermagraft), and none were reported as device- or procedure-related. Number of subjects with at least 1 AE: 8 (29.6%) MatriStem, 10 (34.5%) Dermagraft. AE severity was reported as mild (2 MatriStem, 5 Dermagraft), moderate (4 in each arm), and severe (2 MatriStem, 1 Dermagraft).
	Dermagraft (n=29)	1 (3.4%)	0	0	1 (3.4%)	0	

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Zelen et al. 2016[41]	Apligraf (n=33)	0	0	0	0	0	7 wound/foot infections were reported; 2 in SOC arm. 4 serious AEs included 2 hospitalizations in SOC arm for wound infections (1 diagnosed with osteomyelitis later withdrew). 1 patient each was hospitalized for a urinary tract infection (Apligraf) and a car accident (EpiFix).
	EpiFix (n=32)	0	0	0	0	0	
	SOC (n=35)	0	0	0	1	0	

AE=adverse event; SAE=serious adverse event; SOC=standard of care

Table C-29. Clinical results related to wound healing in studies comparing cellular skin substitutes with cellular skin substitutes

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Ananian et al. 2018[44]	Wounds healed at 8 weeks (number, %) per protocol population	100% reepithelialization	15/31 (48.39%) GrafixPrime	12/31 (38.71%) Dermagraft
	Wounds ≤5 cm^2 healed at 8 weeks (number, %) per protocol population	N/A	13/16 (81.3%)	6/16 (37.5%)
	Wounds >5 cm^2 healed at 8 weeks (number, %) per protocol population	N/A	NR	NR
	Average time to wound closure (days [SE]) per protocol population	N/A	38	31
	Number of patients with infected wounds and increase in wound size–ITT	N/A	1 case each osteomyelitis and cellulitis	5 osteomyelitis/cellulitis
	Other wound healing outcomes Average number of grafts	N/A	5.3	4.0
	Amputation	N/A	NR	NR
	Recurrence	N/A	NR	NR
	Hospitalization	N/A	NR	NR
	Return to function or activities of daily living	N/A	NR	NR
	Pain	N/A	NR	NR
	Exudate	N/A	NR	NR
	Odor	N/A	NR	NR
Towler et al. 2018[35]	Wounds closed at 12 weeks (number, %)	100% epithelialization without drainage	75% Apligraf	93.3% Theraskin; p=0.294
	Wounds healed after 12 weeks (20 weeks) (number, %)	N/A	83.3%	93.3%; p=0.569
	Average time to wound closure (weeks [SD])	N/A	NR	NR
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	3.33	2.27; p=0.119
	Amputation	N/A	NR	NR
	Recurrence	N/A	NR	NR
	Hospitalization	N/A	NR	NR
	Return to function or activities of daily living	N/A	NR	NR
	Pain	N/A	NR	NR

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
	Exudate	N/A	NR	NR
	Odor	N/A	NR	NR
Sanders et al. 2014[45]	Wounds closed at 12 weeks (number, %)	100% epithelialization without drainage	4 (33.3%) Dermagraft	7 (63.6%) Theraskin; p=0.0498
	Wounds healed after 12 weeks (20 weeks) (number, %)	N/A	66.67%	90.91%; p=0.4282
	Average time to wound closure (weeks [SD])	N/A	12.5 (range, 7 to 20)	8.9 (range, 5 to 20); p=0.0323
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR
	Other wound healing outcomes Average number of grafts (weeks [SD]): healing wounds	N/A	8.92 (range, 6 to 12)	4.36 (range, 2 to 7); p<0.0001, SE 0.77584
	Average number of grafts (weeks [SD]): non-healing wounds	N/A	12	6
	Amputation	N/A	NR	NR
	Recurrence	N/A	NR	NR
	Hospitalization	N/A	NR	NR
	Return to function or activities of daily living	N/A	NR	NR
	Pain	N/A	NR	NR
	Exudate	N/A	NR	NR
	Odor	N/A	NR	NR

N/A=not available; NR=not reported; SD=standard deviation; SE=standard error

Table C-30. Reports of adverse events in studies comparing cellular skin substitutes with cellular skin substitutes

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Ananian et al. 2018[44]	GrafixPrime (n=38)	1	0	0	1	0	Serious AEs: 4 GrafixPrime, 7 Dermagraft Of SAEs, number index ulcer-related: 2 (50%) GrafixPrime, 6 (85.7%) Dermagraft
	Dermagraft (n=37)	5 cellulitis and osteomyelitis	0	0	5 cellulitis and osteomyelitis	0	
Towler et al. 2018[35]	Apligraf (n=12)	0	0	0	0	0	None
	Theraskin (n=15)	0	0	0	0	0	
Sanders et al. 2014[45]	Dermagraft (n=12)	0	0	0	0	0	Dermagraft: maceration around the wound (2 patients) Theraskin: erythema (1 patient)
	Theraskin (n=11)	0	0	0	0	0	

Table C-31. Risk-of-bias assessments for 22 primary studies (rated as low, moderate, or high risk)

Study	1	2	3	4	5	6	7	8	9	10	Risk of Bias
Serena et al. 2019[36]	Y	Y	N	Y	N	Y	N	Y	Y	Y	Low
Brown-Etris et al. 2019[58]	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Low
Cazzell S. 2019[49]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Low
Tettelbach et al. 2019[59]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Low
Tettelbach et al. 2019[42]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Ananian et al. 2018[44]	Y	N	Y	N	N	N	N	N	Y	Y	Moderate
Bianchi et al. 2018[37,38]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Low

Study	1	2	3	4	5	6	7	8	9	10	Risk of Bias
DiDomenico et al. 2018[60]	Y	Y	N	N	N	Y	Y	N	Y	Y	Moderate
Towler et al. 2018[35]	Y	Y	N	N	N	Y	N	N	Y	Y	Moderate
Zelen et al. 2018[54]	Y	Y	N	N	N	Y	Y	N	Y	Y	Moderate
Alvarez et al. 2017[48]	N	N	N	N	N	Y	N	Y	Y	Y	Moderate
Alvarez et al. 2017[57]	N	N	N	Y	N	Y	N	N	Y	Y	Moderate
Cazzell et al. 2017[50]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Low
Frykberg et al. 2016[46]	N	N	N	N	N	Y	Y	Y	Y	Y	Moderate
Snyder et al. 2016[55]	Y	Y	N	N	N	Y	N	N	Y	Y	Moderate
Zelen et al. 2016[41]	Y	Y	N	Y	N	Y	Y	N	Y	Y	Low
Driver et al. 2015[56]	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Low
Lavery et al. 2014[47]	N	N	N	Y	Y	Y	Y	Y	Y	Y	Low
Sanders et al. 2014[45]	Y	Y	N	N	N	Y	N	N	Y	Y	Moderate
Serena et al. 2014[40]	Y	Y	N	Y	Y	Y	N	N	Y	Y	Low
Harding et al. 2013[43]	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Low
Zelen et al. 2013[39]	N	N	N	Y	Y	Y	N	N	Y	Y	Moderate

N=no; Y=yes

Appendix D. Commercially Available Skin Substitute Products

Table D-1. Acellular/Dermal replacement from donated human dermis (14 products in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
AlloPatch®	Musculoskeletal Transplant Foundation (dba MTF Biologics), Edison, NJ, USA	AlloPatch is human allograft skin minimally processed to remove epidermal and dermal cells. The process preserves the extracellular matrix of the dermis. AlloPatch is aseptically processed and is not terminally sterilized. AlloPatch is processed to remove cells while maintaining the integrity of the matrix to address the issues of the specific and nonspecific inflammatory responses. It is used to replace damaged or inadequate integumental tissue or to repair, reinforce, or supplement soft-tissue defects.	"Allopatch is minimally processed, which better preserves and maintains the graft's natural biomechanical and biochemical properties. Unlike other ECMs [extracellular membranes] that need to be hydrated for 60 minutes or more before being used, delaying procedure completion and prolonging OR time, Allopatch requires no refrigeration or hydration and is ready to use off the shelf almost immediately." 3-year shelf life at ambient temperature.
AlloPatch® Pliable	Musculoskeletal Transplant Foundation (dba MTF Biologics)	AlloPatch Pliable is an aseptically processed human reticular dermal tissue for use as a chronic or acute wound covering.	"AlloPatch Pliable tissue is processed from deep cut tissue from which the epidermal layer has been physically removed. The process utilized preserves the extracellular matrix of the dermis. The resulting allograft serves as a framework to support cellular repopulation and vascularization at the surgical site. Open tissue architecture optimal for cell infiltration and host tissue remodeling." 3-year shelf life at ambient temperature.
Alloskin™ AC Acellular Dermal Matrix	AlloSource, Centennial, CO, USA	AlloSkin AC is a meshed dermis-only human skin graft that has been decellularized while preserving the natural biologic components and structure of the dermal matrix.	"The graft provides a favorable microenvironment for bio-ingrowth to begin revascularization and cellular repopulation. Single application often sufficient to potentially help stimulate the wound healing process. Ready-to-use off the shelf. Pliable and stretchable for contouring to wound topography and maintenance of wound bed contact. Robust enough to suture or staple. Meshed (1:1) encouraging fluid drainage from wound." Ready-to-use, shelf-stable graft with room temperature storage, eliminating the need for costly cryo freezers.
AlloSkin™ RT	AlloSource	AlloSkin RT meshed human dermal graft is a sterile skin graft with broad clinical applications for acute and chronic wound therapy.	"Skin allografts mechanically protect the wound and provide biologic factors native to human skin, which may help stimulate the wound healing process. AlloSource's process uses electron beam irradiation to yield a ready-to-use, shelf-stable graft with room temperature storage, eliminating the need for costly cryo freezers. Pliable and stretchable, AlloSkin RT allows graft contouring to wound topography, yet is robust enough to suture or staple graft without tearing. In addition, 1:1 meshing encourages exudate drainage from wound, allowing the graft to be secure to the surface and avoid 'floating'." Ready-to-use, shelf-stable graft with room temperature storage, eliminating the need for costly cryo freezers

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Coll-e-derm™	Parametrics Medical, Leander, TX, USA	Coll-e-derm is a human derived dermal allograft that is decellularized using a proprietary method to preserve the biological properties for wound healing.	"The natural collagen and elastin matrix is ideal for neovascularization and cellular proliferation. Coll-e-Derm maintains the strength of human skin and provides a natural scaffold for cellular and capillary remodeling of a damaged site, which can expedite the healing process. Benefits: Terminally Sterile at 10-6 with low dose precision gamma irradiation, lowering risk of infection. Supplied lyophilized at room temperature for easy storage and handling."
DermACELL® Human Acellular Dermal Matrix. DermACELL AWM is intended for chronic wounds.	LifeNet Health®, Virginia Beach, VA, USA	DermACELL is a technologically advanced human acellular dermal matrix. DermACELL is decellularized using Matracell®, a proprietary and patented technology that removes ≥97% of donor DNA without compromising the graft's desired biomechanical or biochemical properties and allows for rapid cellular infiltration and revascularization.	"DermACELL is ready to use out of the package and stored at room temperature, eliminating the need for refrigeration and rehydrating processes. As a final step, all DermACELL grafts are terminally sterilized-rendering the graft sterile to medical device-grade standards with a SAL of 10-6." "Facilitates cell proliferation and migration, critical for wound management."
Dermapure®	Tissue Regenix Group, San Antonio, TX, USA	DermaPure is a decellurized human dermis product thatworks by taking donated human dermis and removing the nucleated cells and cellular debris, using the patented dCELL® Technology process to create a natural biological scaffold that is up to 99% DNA-free.	"The decellularized dermal allograft aids the natural healing process by providing an environment that supports cell migration to facilitate the body's repair, or replacement, of damaged or inadequate integumental tissue. DermaPure maintains the structure and biochemical characteristics of native dermis, fully integrating into the wound bed after application. It provides a scaffold into which the recipient's cells can grow, becoming vascularized and supporting the generation of a new epithelial layer, ultimately regenerating native skin." Ambient temperature storage.
DermaSpan™ Acellular Dermal Matrix	Zimmer Biomet. (manufactured by Biomet Orthopedics, Warsaw, IN, USA)	DermaSpan Acellular Dermal Matrix is derived from allograft human skin and carefully processed to offer biocompatibility as well as biomechanical strength. DermaSpan ACD can be used in various practices, including orthopedics, plastic surgery, and general surgery, to repair or replace damaged or inadequate integumental tissue (wound coverage).	"DermaSpan Acellular Dermal Matrix is very carefully processed to offer biocompatibility as well as biomechanical strength in tendon coverage or reinforcement and wound coverage procedures. DermaSpan Acellular Dermal Matrix has the added advantage of being supplied sterile…unlike many other dermal allograft products." Does not need refrigeration.
FlowerDerm™	Flower Orthopedics, Horsham, PA, USA	FlowerDerm is a meshed dermis-only decellularized human skin graft that preserves the natural biologic components and structure of the dermal matrix. The graft provides a favorable environment for revascularization and cellular repopulation.	"A single application of this product is often sufficient to stimulate the wound healing process. The pliable, flexible material adheres to wound topography and maintains contact with the wound bed. It's also durable enough to suture or staple and has a mesh construction to encourage fluid drainage. FlowerDerm is ready for use right off the shelf." Stored at room temperature, 2-year shelf life.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
GammaGraft™	Promethean LifeSciences, Inc., Pittsburgh, PA, USA	GammaGraft is an irradiated human skin allograft storable at room temperature. Used as a temporary skin graft on burns and chronic wounds.	"GammaGraft has unrivalled ease of use and safety and provides one of the easiest biological grafts for patient compliance. Promethean's proprietary technology sterilizes and preserves the tissues. This technique leads to safer grafts as well as ones that are easier to handle and use. Many doctors and nurses are skeptical that GammaGraft can be used without any other wound coverings after the GammaGraft has dried on the wound. This is possible because GammaGraft has a natural keratin layer that acts as a vapor barrier for the wound. This allows for moist wound healing and a moist wound bed, even though the GammaGraft is dry." Stored at ambient temperature
GraftJacket™ RTM	Wright Medical Group N.V., Memphis, TN, USA	GraftJacket Matrix is used to provide supplemental support, protection, and reinforcement of tendon and ligamentous tissue; to be used as a periosteal patch or covering; or for protection and support of bone and tendons in foot and ankle and hand surgery. It is a human dermal collagen matrix that is readily incorporated into the body. The matrix undergoes a patented process that renders the material essentially acellular and is freeze-dried with a proprietary process that prevents the formation of ice crystals to preserve the intact matrix, including vascular channels.	"The Graftjacket Matrix provides a scaffold for host cell repopulation, revascularization and, ultimately, conversion to host tissue. Coupled with excellent tensile and suture retention strength, the biological characteristics of the Graftjacket Matrix make it an excellent scaffold to reinforce primary soft-tissue repairs throughout the body while eliminating morbidity associated with harvesting autograft." Stored at room temperature, 2-year shelf life.
hMatrix® ADM	Bacterin International, Inc., Belgrade, MT, USA	hMatrix ADM is an allograft derived from donated human skin. The dermis is processed using a proprietary method to remove the cells to maximize graft incorporation. The natural collagen and elastin matrix is ideal for neovascularization and cellular proliferation and has the potential to expedite the healing process. hMatrix ADM is provided as a sterile product with a device-level (SAL) of 10-6.	"The successful treatment of deep wounds often requires the use of a dermoconductive graft material to facilitate formation of granulation tissue and aid in wound closure. One such graft material used for this purpose is allograft-derived acellular dermis. ADM are used as a primary grafting material that can replace damaged or inadequate dermal tissue while helping to reduce the size of the wound and providing protection to the site of injury. • Superior suture retention strength. • Flexible matrix for precise placement. • Lower inflammatory response vs. competitors. • Distributed as a frozen product. • Sterility assurance level (SAL) 10-6. • 5 year shelf life. • Frozen storage."
InteguPly®	Aziyo Biologics, Silver Spring, MD, USA	InteguPly is human ACD processed to maintain the biologic and structural integrity of the tissue's extracellular matrix components, while delivering a SAL of 10^{-6}. Promoted for treating chronic wounds.	"Supports the repair or replacement of integumental tissue, as well as closure of chronic diabetic foot ulcers, venous leg ulcers and pressure wounds." • "Intact extracellular matrix that promotes tissue remodeling. • Superior safety profile-over 20,000 applications with no adverse reactions reported."

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Matrix HD® Allograft	RTI Surgical, Alachua, FL, USA	Matrix HD allograft is an acellular human dermis allograft sterilized using the Tutoplast™ Tissue Sterilization process. This proprietary process retains the 3-dimensional intertwined multidirectional fibers and mechanical properties of the native dermis tissue.	"The Matrix HD graft provides a natural scaffold to support the body's regenerative process." "Sterile–Terminally sterilized to a SAL of $^{10-6}$. Validated viral inactivation. Biocompatible: Preserved vascular channels. Preserved key components of the native matrix." "Convenient: Room temperature storage. Five year shelf life. Simple, single-step rehydration."

ADM=acellular dermal matrix; OR=operating room; SAL=sterility assurance level

Table D-2. Acellular/Dermal replacement from human placental membrane (28 products in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
AlloWrap®	AlloSource, Centennial, CO, USA	AlloWrap is a human amniotic membrane containing bioactive proteins that support wound healing.	"Strong, pliable tissue conforms to wound topography. Amniotic tissue is naturally rich in growth factors to support the healing process, and provides an immune-privileged barrier to support the patient's body in preventing inflammation and scar tissue generation. Available in a moist configuration (AlloWrap DS) or dry (AlloWrap Dry) designed for ease of handling in wound care placements. Room temperature storage, with two-year shelf life, no need for expensive cryo freezer storage."
AltiPlast®	Aziyo Biologics, Silver Spring, MD, USA	AltiPlast is a cryopreserved placental matrix derived from human amniotic and chorionic membranes.	"AltiPlast provides a universal approach to treating complex, chronic wounds. Whether an irregular, tunneling or undermining wound, AltiPlast finds its way, reaching deep into the wound to treat hidden fissures. The matrix components intimately contact the wound bed to support closure. AltiPlast is adaptable and ready to integrate into your treatment approach." Frozen.
AmnioBand® Allograft Placental Matrix	MTF Biologics, Edison, NJ, USA	AmnioBand is a minimally processed human allograft that retains the structural properties of the extracellular matrix. The resulting dehydrated allograft serves as a wound covering.	"Maintains inherent growth factors and matrix proteins essential to wound healing and host tissue remodeling. Aseptic processing preserves tissue's natural structure. Ready, right out of the package. Can be used in the hydrated or dehydrated state. Shelf life of three years at ambient temperature. Conforms to anatomy and maintains surface contact."
Amnioexcel®	Integra LifeSciences Corp. acquired Derma Sciences, Plainsboro, NJ, USA	Amnioexcel is dehydrated human amnion-derived tissue allograft with intact extracellular matrix intended for use as a wound covering to aid in closing chronic wounds.	"The membrane forms a protective covering over the wound while providing the key components found in human amnion including an intact ECM, cytokines and other growth factors. It easily integrates into the wound and helps provide the optimal environment to repair, reconstruct and replace wound tissue." Room-temperature stable for 2 years
AmnioFill® Human Placental Tissue Allograft	MiMedx Group, Inc., Marietta, GA, USA	AmnioFill is a nonviable cellular tissue matrix allograft that contains multiple extracellular matrix proteins, growth factors, cytokines, and other specialty proteins present in placental tissue to help enhance healing.	"Human collagen matrix. Contains growth factors that modulate inflammation, reduce scarring, and enhance healing. Versatile tissue form provides a scaffold for ingrowth in acute and chronic wounds. Terminally sterilized for enhanced patient safety. PURION® processed to provide an effective allograft with excellent handling characteristics. 5 year shelf life stored at ambient conditions."

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
AmnioFix® Amnion/Chorion Membrane Allograft	MiMedx Group	AmnioFix is a bioactive tissue matrix allograft composed of dehydrated human amnion/chorion membrane (dHACM) that preserves and contains multiple extracellular matrix proteins, growth factors, cytokines, and other specialty proteins. AmnioFix is intended to reduce scar tissue formation, modulate inflammation, enhance surgical wound healing, and act as a barrier membrane.	"Acts as a barrier membrane. Reduces scar tissue formation. Modulates inflammation. Enhances healing. Terminally sterilized for enhanced patient safety. PURION® processed to provide an effective allograft with excellent handling characteristics. 5 year shelf life stored at ambient conditions."
Amniomatrix® Human Amniotic Suspension Allograft	Integra LifeSciences acquired Derma Sciences	Amniomatrix is a cryopreserved suspension allograft derived from the amniotic membrane and components of the amniotic fluid. It is cryopreserved using the patented CryoPrime™ processing method that preserves the structural properties of the collagen, cytokines, growth factors, ECM, and viable cellular materials. Amniomatrix is intended to help supplement the recipient's tissue and aid in the closing of chronic wounds.	"The liquid based suspension is especially suited to help repair wounds where membrane products might not be as effective (i.e. tunneling or deep wounds)." Should be stored at -60°C or below.
Artacent® Wound	Tides Medical, Lafayette, LA, USA	Wound-specific, dual-layer amniotic tissue graft designed for enhanced efficacy and ease-of-use. Intended for chronic wounds.	"Artacent Wound is the only wound-specific amniotic patch that can be applied with either side facing the wound. Amniotic tissues are safe, natural biologic barriers, with native membranes supplying a wide array of growth factors. The unique design of Artacent Wound allows for easy manipulation and repositioning, making it a flexible, dependable option for a variety of wound covering applications." Dehydrated, storage at room temperature, shelf life greater than 2 years.
BioDFactor® Viable Tissue Matrix	Integra LifeSciences, originally BioD, LLC	BioDFactor Viable Tissue Matrix is a flowable tissue allograft derived from morselized amniotic tissue and components of the amniotic fluid.	"BioDFactor® Viable Tissue Matrix is a cryopreserved allograft derived from the human placental tissues. It has been developed for use as a wound covering in the treatment of localized tissue defects or areas of inflammation. Placental tissues are a rich source of collagen, elastin, fibronectin, and growth factors to support tissue repair and regeneration. Additionally, amniotic tissue has anti-adhesive and anti-microbial properties important in the treatment of soft tissue injuries." Maintain the product at -65°C or colder until immediately prior to use, 2 year shelf life
Biodfence®	Integra LifeSciences, originally BioD, LLC	BioDFence® G3 and BioDDryFlex® are membrane allografts derived from the human placental tissues for use as a tissue barrier that covers and protects the underlying tissues. BioDFence G3 is a multilayer amnion and chorion allograft providing enhanced handling characteristics. BioDDryFlex is a single-layer amniotic allograft for applications in which bulk may not be optimal.	Website does not list any specific benefits for chronic wounds. Ambient temperature storage, terminally sterilized with a 5-year shelf life.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Biovance® Amniotic Membrane Allograft	Alliqua Biomedical, Langhorne, PA, USA	Biovance is a decellularized, dehydrated human amniotic membrane (DDHAM) with a preserved natural epithelial basement membrane and an intact ECM structure with its biochemical components. The epithelial basement membrane and ECM of this allograft provide a natural scaffold that allows cellular attachment or infiltration and growth factor storage. Biovance provides a protective cover and supports the body's wound healing processes. Biovance is an allograft intended for use as a biological membrane covering that provides the ECM while supporting the repair of damaged tissue. It is intended for chronic wounds.	"The easy-to-use human amniotic membrane allograft with 5-year off-the-shelf convenience ease of application and wound visualization. The progenerative power of the amniotic membrane supports the body's natural ability to restore tissue to a pre-wound state. The natural function of the amniotic membrane brings protection and support to the wound it covers. BIOVANCE contains natural substances found in amniotic membrane tissue that support the body's ability to heal."
Cellesta Amniotic Membrane	Ventris Medical, Newport Beach, CA, USA	Cellesta Amniotic Membrane is a placental allograft product. The single-layered allografts are affixed to a poly mesh backing and can be sutured, glued, or laid over the desired tissue. Only the poly mesh is removed; either side of the graft may be applied to the target tissue. This natural human tissue scaffold with relevant, inherent characteristics can be used for therapeutic solutions.	"Cellesta is a natural human tissue scaffold that protects and cushions, just as it does in utero. Made up of growth factors, hyaluronic acid, cytokines, amino acids, and extracellular matrix proteins, it makes an attractive wound material." Store at ambient temperature.
Cygnus® Amnion Patch Allografts	Vivex Biomedical, Atlanta, GA, USA	Cygnus is applied as an anatomic barrier that helps provide mechanical protection while supporting healing with endogenous growth factors. The Cygnus proprietary process preserves the natural healing properties of amniotic tissue, maintaining inherent levels of key extracellular matrix molecules, growth factors, and cytokines.	"Requires no up-front preparation, and hydrates rapidly in the surgical site • Stored at ambient temperature with a 5-year shelf-life. • Orientation stickers and notch in the upper left hand corner allow placement of the patch epithelial side up and stromal side down. • E-Beam sterilization provides sterility assurance level (SAL) of 10-6."
Dermavest® and Plurivest® Human Placental Connective Tissue Matrix	Aedicell, Inc., Honeoye Falls, NY, USA	"Dermavest Human Placental Tissue Matrix (HPTM) is comprised of donated human placental tissue (placenta disc, amnion/chorion and umbilical cord) that has been particularized, processed to remove cells, cellular material and contamination, freeze-dried to remove moisture, pressed into a sheet then E-beam irradiated at a minimum 17.5 kGy with a validated sterilization process."	"Dermavest provides a scaffold to replace damaged or inadequate integumental tissue." Store at room temperature. 3-year shelf life.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
EpiCord®	MiMedx	"EpiCord is a dehydrated, non-viable cellular umbilical cord allograft.… EpiCord is processed using the PURION® PLUS process, a unique approach that provides an easy to use allograft stored at ambient conditions."	"EpiCord provides a protective environment for the healing process. Provides a connective tissue matrix to replace or supplement damaged or inadequate integumental tissue. 5 year shelf life stored at ambient conditions."
Epifix®	MiMedx	Epifix is a dehydrated human amnion/chorion membrane (dHACM) allograft. EpiFix is a bioactive tissue matrix allograft composed of dHACM that preserves and contains multiple ECM proteins, growth factors, cytokines, and other specialty proteins. Promoted to treat diabetic foot ulcers and venous leg ulcers.	• "Acts as a barrier membrane. • Reduces scar tissue formation. • Modulates inflammation. • Enhances healing. • Terminally sterilized for enhanced patient safety. • Purion processed to provide an effective allograft with excellent handling characteristics. • 5 year shelf life stored at ambient conditions."
FlowerAmnioPatch™ and FlowerAmnioFlo™	Flower Orthopedics, Horsham, PA, USA	FlowerAmnioPatch is a dual-layer amniotic membrane allograft and FlowerAmnioFlo is a flowable amnion tissue allograft.	• "FlowerAmnioPatch is a Ready-for-Surgery™, dual-layer amniotic membrane allograft with excellent handling characteristics. • Safe, natural covering that improves wound healing. • Reduces inflammation. • Adhesion barrier. • Reduces scarring at surgical site. • Decreases post-operative pain." • Stored at room temperature.
Genesis Amniotic Membrane	Genesis Biologics, Anaheim, CA	Genesis Amniotic Membrane is derived from human placenta.	Since amnion contains natural growth factors, cytokines, and hyaluronic acid, there are no steroidal side effects. Application of Genesis Amniotic Fluid scaffold helps in the composition of wound healing. Genesis Amniotic Membrane lowers inflammation and diminishes scar tissue.
Integra® BioFix® Amniotic Membrane Allograft	Integra LifeSciences	Integra BioFix and Integra BioFix Plus (BioFix) are sterile, human tissue allografts derived from allogeneic dehydrated and decellularized amniotic membrane. BioFix is intended for use as a wound covering for surgical sites, voids, and tissue defects.	"BioFix Amniotic Allografts are carefully processed using HydraTek® technology, a proprietary process designed to preserve the natural structure and biological properties of the tissue, to provide ideal graft handling, strength, and performance." "Features & Benefits: • Omnidirectional Placement–Membranes can be implanted on either side to provide an effective covering and gliding surface over the tissue. • Foundation for Regeneration–The Extracellular Matrix contains collagen and other fibrous proteins that provide a structural scaffold to support cellular migration. Naturally occurring growth factors, fibronectin, integrins, laminins, and hyaluronic acid play a key role in cell proliferation, differentiation, and adherence to the scaffold." Store at ambient temperature.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Integra BioFix Flow Placental Tissue Matrix Allograft	Integra LifeSciences	Integra BioFix Flow is a sterile, human tissue allograft derived from decellularized particulate human placental connective tissue matrix. It is intended for use as a connective tissue matrix.	"Features & Benefits: • Off-the-Shelf Storage–BioFix Flow can be stored at an ambient temperature for 5 years. • Reduces Inflammation, Scarring, and Pain–Amniotic tissues may reduce inflammation, fibrous tissue growth, and potential scar tissue formation. • Flexible Application–BioFix Flow is ready to implant and precisely targets defects using a range of needle gauges for ease of implantation."
Interfyl™ Human Connective Tissue Matrix	Alliqua Biomedical, Langhorne, PA, USA	Interfyl is connective tissue matrix filler derived from the placenta of a healthy, full-term pregnancy. Available in flowable and particulate formulations.	"Support tissue regeneration in complex surgical spaces." "An adaptable filler of decellularized connective tissue matrix: • Able to completely fill irregular spaces or soft tissue voids resulting from trauma, surgery, or aging. • Allows for cell adherence and growth during tissue repair. • Consists of natural human structural and biochemical extracellular matrix components. • Adapts to local mechanical forces. • Provides structural support while maintaining elasticity." Store in its original packaging in a clean, dry environment at an ambient room temperature.
Neox® Wound Allografts	Amniox Medical, Inc., Miami, FL, USA	Neox Wound Matrix is human umbilical cord and amniotic membrane preserved to maintain the innate physical and biological properties of these tissues. Neox Wound Allograft is indicated for use as a wound covering for dermal ulcers and defects.	"The regenerative healing properties of Umbilical Cord and Amniotic Membrane delivered in a 1 mm thick allograft for superior handling and fixation, preserved using our patented Cryotek® process." Shelf life is two years from date of manufacture. Can be stored in a standard refrigerator or freezer at specified temperatures and specified times.
NuShield®	Organogenesis, Inc., Canton, MA, USA	NuShield is a dehydrated placental allograft designed to protect and support healing in a variety of wound sizes and types.	"Organogenesis' proprietary BioLoc™ processing method results in less manipulation than other dehydrated amniotic allografts. This process preserves the native structure of the amnion and chorion membranes, and maintains the spongy/intermediate layer, which is an abundant source of proteoglycans, glycoproteins and hyaluronic acid. Through this process, NuShield is also optimized to provide excellent strength, flexibility, and handling." Five-year shelf life

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
PalinGen® Membrane & Hydromembrane	Amnio Technology LLC, Phoenix, AZ, USA	PalinGen Membrane and Hydromembrane are human allografts processed from healthy placental tissue. Placental tissue and membrane contain collagen substrates, growth factors, and ECM proteins recognized as part of the complex wound healing process.	• "Resorbable. • Chorion free. • Amnion membrane. • Growth Factors. • Cytokines. • Amino Acids. • Extracellular Matrix Proteins. • Hyaluronic Acid. • Available in a variety of sizes. • Sterile. • Room temperature (15° C to 30° C)."
Restorigin™ Amniotic Tissue Patches	Parametrics Medical, Leander, TX, USA	Restorigin Amniotic Tissue Patches is processed amniotic tissue and may be used on chronic wounds.	"Due to its fetal origin, the innate regenerative capability of the tissue supports healing without adhesion or scar formation. Amniotic tissue acts an immune-privileged protective barrier during fetal development. Applied as an anatomical barrier, Restorigin offers mechanical protection while providing a regenerative tissue matrix with specific anti-inflammatory, anti-scarring, and anti-microbial properties. Restorigin's proprietary process preserves the natural regenerative healing properties of the tissue and the growth factors responsible for promoting tissue formation without scarring."
Revita®	StimLabs, LLC, Roswell, GA, USA	Revita is an intact human placental membrane allograft that preserves all layers of the biologic tissue and maintains the physiologic 3D architecture of the natural barrier membrane. Revita provides the complete intact human placental membrane that is the physiologic tissue barrier naturally found in the body. This complete barrier containing amnion, intermediate layer and chorion retains many of the cytokines, growth factors, extracellular components, and cell communication signals the body uses to heal, protect, and grow tissues.	"Using the Clearify™ processing method, Revita preserves all three layers of the amniotic membrane architecture." • "Freeze-dried. • Never delaminated. • Preserves intermediate layer which contains hyaluronic acid and additional proteins." "Revita contains many essential cytokines and growth factors."
WoundEx® Membrane and WoundEx Flow	Skye Biologics, Inc., El Segundo, CA, USA	WoundEx Membrane is a FastActing® dehydrated amniotic membrane skin substitute, available in thin amnion-only WoundEx® 45 and thick chorion-based WoundEx 200. WoundEx Flow is a flowable human placental connective tissue matrix skin substitute. It is provided as a concentrated fluid in the vial and can be extended with saline or anesthetic to provide greater coverage throughout the entire wound.	"WoundEx® Membrane Product Benefits: Provides a native human placental BioActive® ECM, Various sizes minimize graft waste & cost, Adheres to wound bed without fixation, FastActing® Technology improves biologic response." Room temperature storage.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Xwrap® Amniotic Membrane-Derived Allograft	Applied Biologics™, Scottsdale, AZ, USA	Xwrap is a Chorion-Free amniotic membrane wrap, cover or patch.	"Xwrap ECM is a chorion-free, non-crosslinked soft-tissue wound covering which acts as a natural scaffold for cellular migration, attachment, and proliferation. It is a natural alternative to cadaveric or animal-derived products." "Xwrap® ECM is carefully processed to preserve the structural qualities of the amniotic membrane. Amnion is a native source of collagen types III, IV, V, and VII, as well as and fibronectin and laminin. It also contains fibroblasts and growth factors, modulates, cytokine and growth factor levels, and has been shown to have unique properties, including the ability to suppress pain, fibrosis, and bacteria, and to promote wound healing."

ECM=extracellular matrix; kGy=kilogray

Table D-3. Acellular/Dermal replacement from animal tissue source (21 products in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Architect® stabilized collagen matrix	Harbor MedTech, Inc., Irvine, CA, USA	According to the company, Architect is made from a widely available Xenograft commonly used in modern tissue heart valves and many other medical products. This tissue is homogeneous (over 95% type 1 collagen), durable, and porous.	"Architect is the only ECM stabilized by the BriDGE® process which prevents premature degradation by the excess MMPs and other proteases found in chronic wounds. Because Architect® remains intact, its ECM healing properties remain intact, including: Helping to deactivate the inflammatory phase (which results in a reduction of MMPs, elastase, and other proteases). Helping to promote the proliferative/healing phase. Preserving cell signaling factors to trigger and accelerate healing. Providing an intact, durable scaffold for uninterrupted support of cellular growth and regeneration of native tissue." Freeze dried, stored at room temperature, long shelf life (actual length not reported)
Bio-ConneKt® Wound Matrix	MLM Biologics, Inc., Alachua, FL, USA	Bio-ConneKt Wound Matrix is a collagen-based wound dressing for the local management of moderately to heavily exuding wounds. It is composed of reconstituted type I collagen that is stabilized, sterilized to SAL 10^{-6}, and stored at room temperature. Bio-ConneKt Wound Matrix is a sterile, conformable, and porous wound dressing made of reconstituted collagen derived from equine tendon. It is chemically crosslinked to provide resistance to enzymatic degradation. The dressing is provided sterile for single use only.	"bio-ConneKt Wound Matrix is succeeding at chronic wound resolution when other treatments fail. Its unique properties deliver a robust medical solution that handles several complications of the chronic wound environment such as senescent cells, corrupt scaffolding, poor oxygen and blood supply in addition to incessant infection and abnormal inflammatory response."
CollaWound collagen sponge	Collamatrix Co., Ltd., Miaoli County, Taiwan	Collawound collagen sponge website provides no information on the device.	Collawound collagen sponge website provides no information on the device.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Cytal® wound matrix	Acell, Inc., Columbia, MD, USA	Cytal is composed of porcine urinary bladder matrix (UBM). These products maintain an intact epithelial basement membrane. Cytal devices are appropriate for acute wounds and chronic wounds.	ACell's wound management products are medical devices that maintain and support a healing environment by facilitating remodeling of site-appropriate, functional tissue. Store in a clean, dry environment between 15°C-35°C (59°F-95°F) in unopened and undamaged package.
Endoform™ dermal template	Hollister Wound Care, Libertyville, IL, USA	Endoform Dermal Template contains a naturally derived ovine collagen ECM that is terminally sterilized and may be considered more culturally acceptable than other animal-derived sources.	"Broad spectrum MMP reduction • Advanced care accessible to all clinicians. • Cost efficiency through weekly applications." Should be stored between 15ºC/59ºF-40ºC/104ºF in a clean and dry area.
Excellagen®	Taxus Cardium Pharmaceuticals Group, San Diego, CA, USA	Excellagen is collagen gel composed of formulated, 2.6% (26 mg/mL) fibrillar bovine dermal collagen (type 1) that is topically applied directly to the wound surface.	"Excellagen is a flowable, formulated homogenate of purified bovine Type I dermal collagen with collagen's natural 3-dimensional fibrillar structure. Excelllagen promotes chemotaxis, cellular adhesion, migration and proliferation to stimulate granulation tissue formation. Excellagen is indicated for non-healing lower extremity ulcers in diabetic patients, and other dermal wounds and is intended for physician use during debridement procedures, which are used to promote and stimulate wound healing." Refrigerated 35-46°F (2-8°C) storage required
EZ Derm®	Mölnlycke Health Care, Norcross, GA, USA	EZ Derm is a porcine xenograft for partial skin loss injuries or as temporary cover.	"EZ Derm can be used for partial thickness skin loss injuries. EZ Derm can also be used as a temporary cover, or test graft, prior to autografting and as a protective covering over meshed autografts. EZ Derm maintains a protected moist wound environment during the healing process and aids the natural healing of the wound. It assists in controlling early wound exudates and assist in restoring water vapour function and heat loss. EZ Derm allows reepithelialization and growth of granulation tissue and reduces pain and fluid loss. It is a protective barrier by physical means and provide protection of the wound." Stored at room temperature.
Geistlich Derma-Gide™	Geistlich Pharma North America Inc., Princeton, NJ, USA	Geistlich Derma-Gide is a porcine, porous, resorbable, 3D matrix designed specifically for the management of wounds.	Geistlich Derma-Gide is an advanced wound matrix that has been specifically engineered to support angiogenesis and wound closure. Intended to be used for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic venous ulcers, surgical wounds and trauma skin wounds. The device inactivates matrix metalloproteinases (MMP), while supporting migration and proliferation of fibroblasts, keratinocytes and endothelial cells where they are needed.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Helicoll™	EnColl Corp., Fremont, CA, USA	Helicoll is an acellular bovine collagen matrix free of contaminants.	Helicoll reduces wound pain, accelerates the healing rate, reduces scarring, reduces hospital stay, and reduces treatment cost. Shelf life of 3 years at room temperature.
Integra® Matrix Wound Dressing; originally Avagen wound dressing.	Integra LifeSciences Corp., Plainsboro, NJ, USA	Integra Wound Matrix is a wound care device composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth. Integra Wound Matrix provides coverage over exposed bone, tendon, cartilage, and joints.	"A single layer collagen matrix that supports a healing environment for wounds." Room temperature storage with a 24-month shelf life.
MicroMatrix®	ACell, Inc., Columbia, MD, USA	MicroMatrix is composed of a porcine-derived extracellular matrix known as urinary bladder matrix. The device is supplied in a particle form in units up to 1,000 mg and packaged in a glass vial and peel-open pouch. The device is terminally sterilized using electron beam irradiation. ACell's Wound Management Products are medical devices that maintain and support a healing environment by facilitating remodeling of site-appropriate, functional tissue. Composed of naturally occurring urinary bladder matrix (UBM), MicroMatrix maintains an epithelial basement membrane and is appropriate for acute wounds and chronic wounds.	"ACell's Wound Devices: • Contain epithelial basement membrane. • and numerous collagens. • Non-crosslinked wound management scaffold. • Complement standard of care." Store in a clean, dry environment between 15°C-35°C (59°F-95°F)
Miroderm®	Miromatrix Medical, Inc., Eden Prairie, MN, USA	Miroderm is a non-crosslinked acellular wound matrix derived from porcine liver for the management of wounds. 1 surface of Miroderm retains the native liver capsule (an epithelial basement membrane), and the opposite surface is composed of open liver matrix. Originally Miromatrix Wound Matrix.	"The first-and-only wound matrix derived from porcine liver, Miroderm® retains an intact extracellular matrix with unique properties." Stored at room temperature.
Ologen™ Collagen Matrix	Aeon Astron Europe B.V.	Ologen Collagen Matrix is a dry scaffold containing a connected porous structure of 10-300 µm diameter made of cross-linked lyophilized porcine type I atelocollagen (≥90%) and glycosaminoglycans (GAG) (≤10%).	No website is devoted to this product for treating chronic wounds. Stored at room temperature with a shelf life of 36 months.
Kerecis™ Omega3 Wound (originally Merigen wound dressing)	Kerecis, Arlington, VA, USA	Kerecis MariGen Wound Dressing is processed fish dermal matrix composed of fish collagen and is supplied as a sterile, intact, or meshed sheet.	"Kerecis produces tissue-based, skin-substitute products for use in surgery and for treating wounds. Compared to other tissue-transplant products, the Kerecis Omega3 fish skin is cost-effective, offers improved clinical performance, reduces the risk of disease transfer, and has no cultural constraints on usage." Store at 25°C (no more than 40°C).
Oasis® Wound Matrix	Smith & Nephew, Inc., Fort Worth, TX, USA	Oasis Matrix products are naturally derived scaffolds of ECM, composed of porcine small intestinal submucosa (SIS), which help support the body's own wound closure mechanisms.	"Provides pathways for cellular migration and vascular growth." Storage at room temperature with a shelf life of 2 years.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
PriMatrix® Dermal Repair Scaffold	Integra LifeSciences Corp., Plainsboro, NJ, USA	According to the company, PriMatrix Dermal Repair Scaffold is a unique scaffold for the management of wounds. Derived from fetal bovine dermis, the acellular dermal matrix is designed to provide an environment to support cellular repopulation and revascularization processes for wound healing. PriMatrix contains type III collagen found in fetal dermis and believed to be active in developing and healing tissues.	"The PriMatrix proprietary processing technology preserves the beneficial properties of the natural dermal collagen fibers and generates a tissue matrix free of contaminants and artificial chemical crosslinks. When applied to the patient's wound PriMatrix rapidly fills with blood, binding both cells and growth factors. The enriched dermal collagen fibers support cellular repopulation and revascularization processes critical in wound healing." Store at room temperature.
Puracol® and Puracol® Plus Collagen Wound Dressings	Medline Industries, Northfield, IL, USA	Composed of 100% bovine collagen.	"Our Puracol wound dressings (Puracol Plus, Puracol Plus Ag+ and Puracol Ultra Powder) promote natural healing with type I 100% native collagen. Our exclusive, gentle manufacturing technology preserves the collagen's natural structure, resulting in dressings that provide more collagen to a wound for a longer period of time." "Native collagen wound dressings can be used to manage chronic wounds. The addition of collagen to the wound bed may reduce excess MMP activity to promote the wound healing cycle."
PuraPly® Antimicrobial (PuraPly® AM) Wound Matrix (formally called FortaDerm)	Organogenesis, Inc., Canton, MA, USA	PuraPly Antimicrobial Wound Matrix (PuraPly AM) consists of a collagen sheet coated with 0.1% polyhex-methylenebiguanide hydrochloride (PHMB) intended for the management of wounds. PuraPly AM is supplied dry in sheet form. The device is packaged in sterile, sealed single pouches.	"PuraPly AM utilizes a purified native collagen matrix embedded with the antimicrobial [PHMB], a broad spectrum antimicrobial. It is this combination of native collagen and PHMB that helps manage the reformation of biofilm while supporting healing across a wide variety of wound types, regardless of severity or duration." Stored in a clean, dry location at room temperature.
Talymed®	Marine Polymer Technologies, Inc., Burlington, MA, USA	Talymed advanced matrix is composed of shortened fibers of poly-N-acetyl glucosamine isolated from microalgae.	• "86% of patients experienced complete wound healing. • Non-immunogenic. • Easy to apply. • Store at room temperature for up to 3 years."
TheraForm™ Standard/Sheet Absorbable Collagen Membrane	Sewon Cellontech Co., Seoul, Korea	TheraForm is an absorbable and biocompatible implant to enhance tissue regeneration and can be used with human cell or tissue-specific ingredients. It is a sterile, pliable, porous scaffold made of biocollagen for wound dressing, soft-tissue regeneration scaffold agent, periodontal tissue repair agent, and the control of bleeding.	"Absorbable collagen membrane is a sterile, pliable, porous surgical wound dressing. Standard and Sheet types are ideal wound healing biomatrix."

ECM=extracellular matrix; MMP= matrix metalloproteinases

Table D-4. Acellular/Dermal replacement from synthetic materials (2 products in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Hyalomatrix® tissue reconstruction matrix	Anika Therapeutics, Bedford, MA, USA	Hyalomatrix is a bilayered, sterile, and flexible advanced wound care device. It is ideally suited for a range of wounds, including pressure ulcers, diabetic foot ulcers, and deep second-degree burns. Hyalomatrix is a nonwoven pad composed of a wound contact layer made of a derivative of hyaluronic acid (HA) in fibrous form with an outer layer composed of a semipermeable silicone membrane. The wound contact layer is biodegradable, and it acts as a 3D scaffold for cellular invasion and capillary growth. The silicone layer controls water vapor loss and provides protective coverage of the wound.	"The Hyalomatrix Advantage: Conveniently conformable to a variety of wound sizes. Minimizes risk of bacterial contamination with protective and flexible covering. Simplifies monitoring–wound can be inspected without matrix removal. Controls water vapor loss with semipermeable layer." Store at room temperature.
Restrata™	Acera Surgical, Inc., St. Louis, MO, USA	Restrata is a fully synthetic electrospun wound dressing composed of randomly oriented nanofibers that create a highly porous scaffold for cellular infiltration and vascularization during wound repair. Its structure was engineered to be similar to that of native extracellular matrix, 1 of the key building blocks of newly forming tissue. The fibers comprising Restrata Wound Matrix are produced from polyglactin 910 and polydioxanone, both bioabsorbable polymers.	Product website not available

Table D-5. Acellular/Dermal replacement from combined natural and synthetic materials (2 products in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Integra® Bilayer Matrix Wound Dressing	Integra LifeSciences Corp., Plainsboro, NJ, USA	Integra Bilayer Wound Matrix is an advanced wound care device composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone layer). Promoted for inpatient use.	"The semi-permeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth." Room temperature with a 24-month shelf life.
Integra® Dermal Regeneration Template and Integra Omnigraft Regeneration Template	Integra LifeSciences	Integra Dermal Regeneration Template (Integra Template) has 2 layers: a thin outer layer of silicone and a thick inner matrix layer of pure bovine collagen and glycosaminoglycan (GAG). Both collagen and GAG are normal components of human skin. In Integra, the collagen is obtained from bovine tendon collagen, and the glycosaminoglycan is obtained from shark cartilage.	"Silicone layer: Enables immediate wound closure. Controls fluid loss. Provides mechanical protection. Provides a bacterial barrier. Water vapor transmission rate similar to that of normal skin." "3-Dimensional matrix layer: Cross-linked collagen and glycosaminoglycan. Functions as an extracellular matrix. Promotes cellular growth and collagen synthesis. Biodegrades while being replaced by autologous dermal tissue." Room temperature with a 24-month shelf life.

Table D-6. Acellular/Epidermal and Dermal replacement from human placental membrane (1 product in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
AltiPly®	Aziyo Biologics, Silver Spring, MD, USA	Lyophilized Placental Membrane. The growth factor-rich matrix, with an outer basement membrane and epithelial layer, immediately serves as a scaffold for reepithelialization.	"AltiPly is opaque, and thicker than other grafts. The dry graft is flexible and easy to handle. What you can't see is the benefit of our proprietary processing on preserving the quality of the matrix. The growth factor-rich matrix, with an outer basement membrane and epithelial layer, immediately serves as a scaffold for reepithelialization." "Supports wound closure of chronic diabetic foot ulcers (DFU), venous leg ulcers (VLU) and pressure wounds." "Proprietary processing improves growth factor levels over dehydration methods."

Table D-7. Cellular/Dermal replacement from human placental membrane (4 products in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Affinity® Human Amniotic Allograft	Organogenesis, Inc., Canton, MA, USA	Affinity is a fresh amniotic membrane aseptically processed and hypothermically preserved using AlloFresh®, a proprietary storage system. The product is not dehydrated or frozen. Affinity can be applied to chronic wounds, such as diabetic foot ulcers, venous leg ulcers, and pressure ulcers.	"Affinity is the only fresh amniotic membrane that contains: viable cells (including stromal cells, fibroblasts, and epithelial cells), angiogenenic, regenerative and anti-inflammatory growth factors and cytokines, and a native extracellular matrix and multiple important [extracellular matrix] proteins." "Organogenesis' proprietary AlloFresh processing method allows for the fresh, hypothermic storage of the amniotic tissue while retaining its structural integrity, viability, and native benefits." All fresh allografts must be maintained at refrigerated temperature (between 1°C and 10°C) during storage.
FlōGraft® Amniotic Fluid-Derived Allograft	Applied Biologics, Scottsdale, AZ, USA	FlōGraft is chorion-free allograft composed of amnion and amniotic fluid derived from prescreened, live, healthy donors. Amniotic membrane and fluid act as a biologic system that ensures symmetrical structure development and growth, cushions and protects the embryo, has a significant defensive role as a part of the innate immune system, and protects the fetus by maintaining consistent pressure and temperature. FlōGraft retains this protective function as a versatile and manageable liquid allograft and is indicated as an additive in several general surgical applications, including soft-tissue defects, soft-tissue trauma, tendinitis, tendinosis, chronic wounds, and localized inflammation.	FlōGraft is carefully processed to preserve the structural qualities of the amniotic membrane yet allow for the allograft to be implanted using a 22-23 gauge needle. Amnion is a native source of collagen types III, IV, V, and VII, as well as and fibronectin and laminin. It also contains fibroblasts and growth factors, modulates, cytokine, and growth factor levels, and has been shown to have unique properties, including the ability to suppress pain, fibrosis, and bacteria and to promote wound healing. These qualities may provide an ancillary benefit to the primary purpose of FlōGraft human allograft as a soft-tissue defect filler.
Grafix®	Osiris Therapeutics, Inc., Columbia, MD, USA	Grafix (cryopreserved placental membrane) is a cryopreserved amnion or chorion matrix retaining the extracellular matrix, growth factors, and endogenous neonatal mesenchymal stem cells, fibroblasts and epithelial cells of the native tissue.	"Designed for application directly to acute and chronic wounds. Flexible, conforming cover that adheres to complex anatomies." Minimum two year shelf life and should be stored frozen at -80°C.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
GrafixPL Prime	Osiris Therapeutics	GrafixPL Prime (lyopreserved placental membrane) is a lyopreserved amnion matrix retaining the extracellular matrix, growth factors, and endogenous neonatal mesenchymal stem cells, fibroblasts and epithelial cells of the native tissue	"Both cryopreserved and lyopreserved products [Grafix Prime and GrafixPL Prime] retain the viable epithelial cells, fibroblasts, and mesenchymal stem cells found in fresh placental amnion. The extracellular matrix, including collagen, elastin, fibronectin, and laminin, is preserved in the native architecture within both products. The cytokines and growth factors for fresh amnion are preserved in both." Stored at room temperature

Table D-8. Cellular/Dermal replacement from combined natural and synthetic materials (1 product in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Dermagraft®	Organogenesis Inc., Canton, MA, USA	"Dermagraft is a cryopreserved human fibroblast derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold. Dermagraft is manufactured from human fibroblast cells derived from donated newborn foreskin tissue. During the manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a three-dimensional human dermal substitute containing metabolically active, living cells. Dermagraft does not contain macrophages, lymphocytes, blood vessels, or hair follicles."	"Dermagraft helps to restore the compromised DFU [diabetic foot ulcer] dermal bed to facilitate healing by providing a substrate over which the patient's own epithelial cells can migrate to close the wound." Must be stored continuously at -75°C ±10°C.

Table D-9. Cellular/Epidermal and Dermal replacement from human skin (2 products in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
SkinTE™	PolarityTE, Salt Lake City, UT	SkinTE is regenerative full thickness, functional skin. After a small full-thickness tissue sample from a patient is sent to PolarityTE, the construct will be created and returned for application on or in the same patient.	SkinTE is a first-of-its-kind entirely autologous product for skin repair, reconstruction, replacement, supplementation and regeneration. SkinTE has resulted in regenerative full-thickness healing of skin with all its layers (epidermis, dermis and hypodermis) and its appendages (hair follicles, glands, etc.). SkinTE is for the repair, reconstruction and replacement of full-thickness skin. SkinTE can be used by physicians and other medical providers to repair, reconstruct, replace or supplement a patient's damaged or missing skin tissue. It is currently being used by providers for the treatment of acute and chronic wounds.

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Theraskin®	LifeNet Health, Virginia Beach, VA, USA (procurement and processing) Solsys Medical, Newport News, VA, USA (distribution)	According to the manufacturer, TheraSkin is a cryopreserved human, living, split-thickness allograft that contains living cells, growth factors, and an architecturally preserved human ECM scaffold that vascularizes. Around 7-14 days after application, the epidermal cells and any antigenic components are removed, but the dermal scaffold and the matrix is retained. The tissue is safely procured according to industry standards developed by AATB within 24-hours postmortem from an organ donor. The donor criteria for TheraSkin surpass those required by AATB and TheraSkin maintains a proven track record of zero disease transmission. When procured, the allograft is washed with a series of antibiotics and cryopreserved using a proprietary cryopreservation process.	"Application of TheraSkin—a real human skin allograft—can replace damaged skin and can assist in healing most chronic wounds, even wounds that have not progressed for many months and have failed to heal with other therapies." "TheraSkin is a biologically active, cryopreserved human skin allograft, composed of living cells, fibroblasts and keratinocytes, and a fully developed extracellular matrix (ECM) in its epidermal and dermal layers. TheraSkin provides, upon application, a supply of growth factors/cytokines, and a robust collagen scaffold to jumpstart healing in a chronic wound."

AATB=the American Association of Tissue Banks

Table D-10. Cellular/Epidermal and Dermal replacement from combined human and animal sources (1 product in this category)

Product	Manufacturer	Manufacturer's Product Description	Manufacturer Claims
Apligraf®	Organogenesis Inc., Canton, MA, USA	Apligraf is a living cell-based product for chronic venous leg ulcers and diabetic foot ulcers. Apligraf is supplied as a living, bilayered skin substitute. The lower dermal layer combines bovine type 1 collagen and human fibroblasts (dermal cells), which produce additional matrix proteins. The upper epidermal layer is formed by promoting human keratinocytes (epidermal cells) first to multiply and then to differentiate to replicate the architecture of the human epidermis..	"Apligraf plays an active role in healing by providing to the wound living cells, proteins produced by the cells, and collagen, which are important for healing." Should be kept in its tray on the medium in the sealed bag under controlled temperature 68°F-73°F (20°C-23°C) until ready for use

Appendix E. Ongoing Clinical Trials

Table E-1. Ongoing clinical trials

Clinicaltrials.gov Identifier[a]	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT03629236*	Osiris Therapeutics	To evaluate the safety and efficacy of GrafixPL for treating chronic VLUs.	Cellular dermal, natural material–human amniotic/ placental membrane	VLU	January 20, 2021	200	Recruiting	Complete closure of the index ulcer (up to 84 days after baseline visit).
NCT03935386*	Soluble Systems, LLC	To compare the efficacy of using standard compression therapy for chronic VLUs vs. standard compression therapy with the additional use of the application of a human allograft (Theraskin).	Cellular epidermal and dermal, natural material–human	VLU	December 2020	100	Enrolling by invitation	Rate of wound healing, percentage of wounds closed, and change in wound size up to 3 years; number and severity of adverse events.
NCT03626623*	ACell Inc.	To determine whether application of Cytal Wound Matrix 1-Layer intervention to DFUs shows improved wound closure rates vs. SOC.	Acellular dermal, natural materials–animal	DFU	September 2020	150	Not yet recruiting	Incidence of wound closure (100% epithelialization) up to 12 weeks.
NCT03010319*	Integra LifeSciences Corp.	To evaluate the efficacy of PriMatrix Dermal Repair Scaffold in the management of DFUs in subjects with diabetes mellitus vs. SOC.	Acellular dermal, natural material–animal	DFU	June 2020	204	Recruiting	Complete wound closure up to 12 weeks.
NCT03476876*	Baylor College of Medicine with LifeNet Health	To compare outcomes of DermACELL acellular dermal matrix with Integra® Bilayer Matrix Wound Dressing.	Acellular dermal, natural material–human dermis compared with acellular dermal, natural, and synthetic materials	DFU	June 15, 2020	50	Recruiting	Wound size change from baseline to 8 weeks and 16 weeks; time to reach successful granulation from baseline to 16 weeks; incidence from complication from baseline to 16 weeks; change in skin perfusion from baseline to 16 weeks; duration of application.

Clinicaltrials.gov Identifier[a]	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT03855514*	Organogenesis	To compare NuShield® plus SOC to SOC alone in subjects with chronic DFUs.	Acellular dermal, natural materials–human amniotic/ placental membrane	DFU	June 30, 2020	125	Recruiting	Time to complete wound closure up to 12 weeks, number of wounds completely closed.
NCT03589586*	LifeNet Health	To evaluate the safety and efficacy of DermACELL in subjects with a single-target chronic VLU.	Acellular dermal, natural material–human dermis	VLU	December 31, 2019	100	Recruiting	Healing rate at 16 weeks–effect of DermACELL on the proportion of chronic VLUs that have achieved 100% reepithelialization without drainage or dressing requirements.
NCT03285698*	Georgetown University with LifeNet Health	To compare clinical outcomes for DermACELL® vs. Integra® Bilayer Wound Matrix.	Acellular dermal, natural materials–human dermis compared with acellular dermal, natural and synthetic materials	Chronic wounds	October 1, 2019	100	Recruiting	Time to heal for split-thickness graft application up to 160 days.
NCT03547635*	Integra LifeSciences	To compare the outcomes associated with use of Amnioexcel Plus Placental Allograft Membrane, a marketed comparator (Apligraf®) and SOC alone in the management of DFUs.	Acellular dermal, natural materials–human amniotic/ placental membrane compared with cellular epidermal and dermal, natural materials–human and animal	DFU	August 31, 2019	114	Enrolling by invitation	Incidence of complete wound closure, as assessed by the investigator at or before week 12 of the treatment phase, which is confirmed closed 2 weeks later.
NCT03708029*	StimLabs	To evaluate the efficacy of Revita full thickness placental allograft in improving wound closure rates and mean closure time in DFUs compared to standard of care.	Acellular dermal, natural materials–human amniotic/ placental membrane	DFU	June 30, 2019	40	Recruiting	Complete wound closure up to 12 weeks.

Clinicaltrials.gov Identifier[a]	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT03502824*	Organogenesis	To demonstrate how PuraPly® Antimicrobial Wound Matrix performs against SOC in Stage II-IV pressure ulcers.	Acellular dermal, natural materials–animal	Pressure ulcer	March 2019	50	Recruiting	Reduction in size of ulcer area between groups up to 24 weeks, improvement in wound bed condition between groups.
NCT02929056*	Greenville Health System with Clemson University and BioDlogics	To evaluate an amniotic membrane (AmnioExCel) dressing and compression therapy vs. SOC alginate dressing and compression to manage venous leg ulcers.	Acellular dermal, natural materials–human amniotic/ placental membrane	Venous leg ulcer	January 2019	40	Enrolling by invitation	Reduction in wound area at 4, 8, and 12 weeks.
NCT03283787*	Acell, Inc.	To evaluate incidence of complete epithelialization in stage 3/4 pressure ulcers using ACell products (primary comparison: MicroMatrix® plus Cytal™ vs. NPWT; secondary comparison: MicroMatrix plus Cytal plus NPWT vs. NPWT).	Acellular dermal, natural materials–animal (both)	Pressure ulcer	December 2018	60	Recruiting	Time to complete wound epithelialization at 12 weeks.
NCT02609594*	SerenaGroup with Musculoskeletal Transplant Foundation	To evaluate the safety and effectiveness of AmnioBand Dehydrated Human Amniotic Membrane plus multi-layer compression therapy (MLCT) vs. MLCT alone to heal venous leg ulcer (also comparing weekly and biweekly applications of AmnioBand).	Acellular dermal, natural materials–human amniotic/ placental membrane	Venous leg ulcer	December 2018	240	Recruiting	Time to complete wound closure at 12 weeks.
NCT02838784*	Tides Medical	To evaluate the efficacy of Artacent™ Human Amniotic Membrane vs. SOC in the treatment of diabetic and vascular lower-extremity ulcers.	Acellular dermal, natural materials–human amniotic/ placental membrane	DFU, venous leg ulcer	December 2018	134	Recruiting	Wound closure and time to wound closure at 12 weeks, ulcer recurrence at 6 months.

Clinicaltrials.gov Identifier[a]	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT02870816*	Professional Education and Research Institute with Musculoskeletal Transplant Foundation	To determine whether amnion membrane grafts are more effective than another tissue engineered skin substitute (not specified).	Acellular dermal, natural material–human amniotic/ placental membrane	DFU	May 2018	60	Recruiting	Complete healing at 6 weeks.
NCT02707406*	Tissue Tech, Inc.	To evaluate the safety, incidence and rate of wound closure with Neox ® Cord 1K, a cryopreserved human umbilical cord allograft, versus SOC.	Acellular dermal, natural materials–human amniotic/ placental membrane	DFU	April 2018	114	Active, not recruiting	Incidence of adverse events up to 16 weeks.
NCT02506452*	Alliqua BioMedical, Inc.	To compare the wound closure outcomes of subjects receiving DFU treatment with a dehydrated decullarized human amniotic membrane allograft (Biovance®) vs. SOC.	Acellular dermal, natural materials–human amniotic/ placental membrane	DFU	December 2017	51	Active, not recruiting	Wound closure at up to 12 weeks following baseline visit defined as 100% reepithelialization without drainage confirmed at 2 weeks following initial observation of closure.
NCT02344329*	University of North Dakota	To compare total contact casting using human amnion allograft (AmnioExcel) vs. total contact casting and SOC to treat DFU.	Acellular dermal, natural materials–human amniotic/ placental membrane	DFU	November 2017	12	Active, not recruiting	Time to closure up to 12 weeks.
NCT03037970*	Lynch Biologics LLC	To investigate the safety and efficacy of Absolve Biologic Wound Matrix vs. placebo. Absolve is a combination of highly purified recombinant human platelet-derived growth factor BB homodimer combined with a biocompatible, collagen resorbable wound dressing.	Not enough product information to determine category	DFU	October 15, 2017	40	Recruiting	Incidence of treatment-emergent adverse events up to week 24; successful wound healing for at least 2 consecutive measurements–first measurement at week 12.

Clinicaltrials.gov Identifier[a]	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT02399826*	Lower Extremity Institute for Research and Therapy with Musculoskeletal Transplant Foundation	To compare the proportion of ulcers completely healed by use of an amniotic membrane graft (AmnioBand) vs. SOC in patients with diabetes with a DFU with adequate arterial perfusion, for wound healing to the affected limb.	Acellular dermal, natural materials–human amniotic/ placental membrane	DFU	January 2017	40	Unknown	Proportion of ulcers completely healed at 6 weeks.

DFU=diabetic foot ulcer; MLCT=multilayer compression therapy; NPWT=negative pressure wound therapy; SOC=standard of care

* Randomized controlled trial

[a] Listing a study on this site does not mean it has been evaluated by the U.S. Federal Government. The safety and scientific validity of a study listed on ClinicalTrials.gov is the responsibility of the study sponsor and investigators.

Table E-2. Completed Clinical Trials Identified in 2012 report

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Purpose	Estimated Enrollment/ Actual Enrollment	Wound Type	Expected Completion Date	2012 Status	2019 Status	Publications	Notes
NCT01676272	Soluble Systems, LLC	To compare a bioengineered skin substitute to a human skin allograft.	100	DFU	April 2013	Enrolling by invitation only	Unknown	N/A	Dermagraft and TheraSkin commercially available in the U.S.
NCT01619670	University Hospital, Basel, Switzerland	To evaluate Apligraf in nonhealing wounds of patients with epidermolysis bullosa.	18/3	Non-healing	June 2014	Currently recruiting	Terminated	N/A	Apligraf commercially available in the U.S.
NCT01729286	Integra LifeSciences Corp.	To assess lower-extremity diabetic (healed) ulcers with PriMatrix.	224/92	DFU	September 2014	Currently recruiting	Terminated	N/A	PriMatrix commercially available in the U.S.
NCT01612806	Integra LifeSciences	To assess PriMatrix and PriMatrix Ag for treating venous leg ulcers.	90/31	VLU	February 2017 actual completion date	Currently recruiting	Terminated (site selection)	N/A	PriMatrix and PriMatrix Ag commercially available in the U.S.

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Purpose	Estimated Enrollment/ Actual Enrollment	Wound Type	Expected Completion Date	2012 Status	2019 Status	Publications	Notes
NCT01270633	Integra LifeSciences	To compare the clinical and economic effectiveness of PriMatrix and SOC in treating DFUs in subjects with controlled DM and without significantly compromised arterial circulation.	25/30	DFU	September 2012 (completed September 2017)	Completed	Terminated (business decision)	None provided	PriMatrix commercially available in the U.S.
NCT00909870	Organogenesis	Patients with venous leg ulcers will be randomly assigned to receive standard therapy (compression) alone or compression plus Dermagraft®.	500/537	VLU	September 2011 (completed August 2011)	Completed	Completed	None provided (Results posted on ClinicalTrials.gov)	Dermagraft commercially available in the U.S.
NCT01450943	VA Office of Research and Development	This study's primary objective is to assess the effectiveness of cellular dermal replacement tissue vs. nonviable extracellular matrix (ECM) for treating nonhealing DFUs. The authors' hypothesis is that these devices are of equal efficacy.	171/169	DFU	October 2014 (completed April 2018)	Currently recruiting	Completed	None provided (No results posted on Clinicaltrials.gov)	Dermagraft and Oasis commercially available in the U.S.
NCT00399308	Shire	This pilot study was designed to test the safety of Celaderm™ in treating venous leg ulcers and to give preliminary information about the efficacy of two different Celaderm dosing regimens.	40/40	VLU	April 2008 (completed on time)	Completed	Completed	None provided (Results posted on Clinicaltrials.gov)	No information on Celaderm on manufacturers website.

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Purpose	Estimated Enrollment/ Actual Enrollment	Wound Type	Expected Completion Date	2012 Status	2019 Status	Publications	Notes
NCT01353495	Wright Medical Technology	Have indolent diabetic ulcers completely healed by the Acellular Porcine Dermal Matrix (APM) in 12 weeks.	40/40	DFU	April 2011 (completed on time)	Completed	Completed	None provided (ClinicalTrials.gov indicates results were twice submitted but returned after Quality Control Review.)	No information on BIOTAPE XMTM on manufacturers website.
NCT00270946	Ortec International	To evaluate the clinical benefits and safety of OrCel plus compression therapy (SOC) vs. compression therapy in treating venous ulcers.	130/NR	VLU	December 2003 (completed on time)	Completed	Completed	None provided (No results posted on ClinicalTrials.gov)	Latest information on Orcel from 2008 (Business Wire announcement).
NCT01327937	Organogenesis	To use microarray technology to identify and characterize the gene expression of multiple relevant genes in biopsies of nonhealing venous ulcers.	30/30	VLU	June 2013	Currently recruiting	Completed	Stone et al. 2017[91]	
NCT01060670	Integra LifeSciences	To evaluate the safety and effectiveness of the Integra® Dermal Regeneration Template for treating DFUs located distal to the malleolus in subjects with DM; neuropathy, and without significantly compromised arterial circulation.	350/545	DFU	October 2013 (completed June 2014)	Currently recruiting	Completed June 2014	Driver et al. 2015[56] included in report	

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Purpose	Estimated Enrollment/ Actual Enrollment	Wound Type	Expected Completion Date	2012 Status	2019 Status	Publications	Notes
NCT01181453	Organogenesis	This study randomly assigned patients with DFUs to receive standard therapy (surgical débridement, saline moistened gauze, and offloading) alone or standard therapy plus Dermagraft®. Dermagraft contains live human fibroblasts grown on an absorbable Vicryl mesh.	314/314	DFUs	March 2000 (completed on time)	Completed	Completed	Marston et al. 2003[68] included in 2012 report	
NCT01181440	Organogenesis	Patients with plantar DFUs will be randomly assigned to receive conventional therapy (débridement, infection control, saline-moistened gauze dressings, and standardized off-weighting) alone or conventional therapy plus Dermagraft.	281/281	DFU	January 1997 (completed on time)	Completed	Completed	2 (Gentzkow et al. 1999,[92] Pollak et al. 1997[93])	
NCT00007280	Roger Williams Medical Center	To evaluate whether a graft of bioengineered skin (BSC) (Apligraf), stimulates the healing process in a person's own skin at the edge of a wound (known as the edge effect).	50/50	Leg/ venous	August 2005 (completed on time)	Completed	Completed	11 Falanga and Sabolinski 1999[94] excluded as subgroup analysis of prior published study (Falanga et al. 1998[74] included in 2012 report); remaining publications were narrative reviews or cell-based studies.	

DFU=diabetic foot ulcer; N/A=not applicable; NR=not reported; PU=pressure ulcer; VLU=venous leg ulcer