Technology Assessment

Technology Assessment Program

Skin Substitutes for Treating Chronic Wounds

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Skin Substitutes for Treating Chronic Wounds

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ECRI Institute EPC

David L. Snyder, Ph.D.

Nancy Sullivan, B.A.

Karen M. Schoelles, M.D., S.M., F.A.C.P.

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None of the investigators has any affiliations or financial involvement related to the material presented in this report.

Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

Vickie R. Driver, M.S., D.P.M., F.A.C.F.A.S.
Associate Professor of Surgery
Director, Clinical Research Limb Preservation, Wound Healing
Director, Research Fellowship and International Scholars Program
Boston University Medical Campus and Boston University School of Medicine
Boston, Massachusetts

Mary E. Ritchey, Ph.D.
Associate Division Director
FDA/CDRH/Office of Surveillance and Biometrics
Food and Drug Administration
Silver Spring, MD

Skin Substitute Products Considered in This Report:

Products derived from human donor tissue, minimally processed:

- AlloDerm Regenerative Tissue Matrix
- Allopatch HD™
- Alloskin™
- Cymetra® Micronized AlloDerm
- Dermacell® and Arthroflex®
- Flex HD®
- GammaGraft®
- Graftjacket® Regenerative Tissue Matrix
- Matrix HD™
- Memoderm™
- Puros® Dermis
- Repliform®
- TheraSkin®

Products derived from living human and/or animal tissues and cells:

- Apligraf®/Graftskin
- Dermagraft®

Acellular animal-derived products:

- ACell UBM Hydrated Wound Dressing
- ACell UBM Lyophilized Wound Dressing
- Aongen™ Collagen Matrix
- Atlas Wound Matrix
- Avagen Wound Dressing
- Collagen Sponge (Innocoll)
- Collagen Wound Dressing (Oasis Research)
- Collaguard®
- CollaSorb™
- CollaWound™
- Collexa®
- Collieva®
- Coreleader Colla-Pad
- Dermadapt™ Wound Dressing
- DressSkin
- E-Z Derm
- EndoForm Dermal Template™
- Excellagen
- FortaDerm™ Wound Dressing
- HA Absorbent Wound Dressing
- Helicoll
- Integra™/Bilayer Matrix Wound Dressing
- Integra™ Flowable Wound Matrix
- LTM Wound Dressing

MatriStem
MatriStem® Wound Matrix
Matrix Collagen Wound Dressing
Medline Collagen Wound Dressing
Oasis®
Primatrix™
Primatrix™ Dermal Repair Scaffold
SIS Wound Dressing II
SS Matrix™
Stimulen™ Collagen
TheraForm™ Standard/Sheet
Unite® Biomatrix
Unite™ Biomatrix

Biosynthetic products:
Hyalomatrix® (Laserskin®)
Hyalomatrix®
Jaloskin®
Suprathel®
Talymed®

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Executive Summary

Background

The Center for Medicare Management at the Centers for Medicare and Medicaid Services (CMS) requested this report from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the ECRI Institute Evidence-based Practice Center (EPC) (Contract Number: HHSA 290-2007-10063).

A wide variety of wound care products are available for clinicians to choose from when treating chronic wounds. Many of these products are said to mimic or substitute for some aspect of the skin's structure and function to promote healing and wound closure. The materials used to produce these products may be derived from human or animal tissue and may undergo extensive or minimal processing to make the finished product. The extent of processing and the source of the material used in the product also determines what regulatory pathway may be required before the product can be marketed. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. For this report, we have not created a definition for a skin substitute product. Instead we used the products listed under CMS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those products indicated for chronic wounds. We note that FDA does not refer to any product or class of products as "skin substitutes," and we are not proposing an official classification system.

In addition to identification of the products, a second objective of this review was to begin to characterize the state of the evidence base on skin substitutes as wound care products. To address this objective, we sought to determine the number of RCTs of these products and to assess the efficacy of skin substitutes under the conditions presented in the trials. Systematically reviewing and analyzing all the clinical research on skin substitutes is beyond the scope of this report.

This report specifically examined the use of skin substitutes for treating the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (including venous ulcers and arterial ulcers). Treatment of burn wounds with skin substitutes is outside the scope of this report.

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 a basal layer of constantly dividing keratinocytes that lies next to the dermis. The dermis is composed mostly of collagen fibers and some elastic fibers produced by fibroblasts that, along with water and large proteoglycan molecules, make up the extracellular matrix. This layer of the skin provides mechanical strength and a substrate for water and nutrient diffusion; it contains blood vessels, nerves, and cells involved in immune function, growth, and repair. The dermis also contains sweat glands, oil glands, and hair follicles. The subcutaneous layer is composed of adipocytes that form a thick layer of adipose tissue.[1]

Wounds are breaches in the structure of the skin that compromise skin function. Chronic wounds have not completed the healing process (restoring tissue loss and skin function) in the expected time frame, usually within 30 days;[2] have not responded to initial treatment; or persist

despite appropriate care.[3] These wounds usually do not close without interventions. Diabetic foot ulcers, venous leg ulcers, and pressure ulcers are the chronic wounds most often treated with skin substitute products.

Skin substitutes were developed as an alternative to skin grafts for burn patients. Autologous tissue grafting is an invasive and painful procedure, and the extent of damaged skin is often too large to be covered by autologous tissue graft alone. However, skin substitutes are now primarily used in treating chronic wounds rather than for burns, in part because chronic wounds are far more common than burn wounds.[4]

A true "skin substitute" would act like an autologous skin graft in adhering to the wound bed while providing the physiological and mechanical functions of normal skin.[4] The skin substitutes included in this report contain various combinations of cellular and acellular components intended to stimulate the host to regenerate lost tissue and replace the wound with functional skin. Presumably, successful healing during management with these products would also require maintenance of a moist wound environment and other procedures thought to promote healing. These include removal of exudate and necrotic tissue, infection control, nutritional support, pressure avoidance (e.g., off-loading for diabetic foot ulcers and pressure ulcers), and edema control (e.g., compression for venous leg ulcers).[5]

Dieckmann et al. have suggested that skin substitutes can be divided into two broad categories: biomaterial and cellular.[5] Biomaterial skin substitutes do not contain cells (acellular) and are derived from natural or synthetic sources. Natural sources include human cadaver skin processed to remove the cellular components and retain the structural proteins of the dermis and collagen matrix obtained from bovine and porcine sources. Synthetic sources include various degradable polymers such as polylactide and polyglycolide. Whether natural or synthetic, the biomaterial provides an extracellular matrix that allows for infiltration of surrounding cells. Cellular skin substitutes are distinguished by their origin: xenogeneic (from nonhuman species), autologous (from the patient), and allogenic (from another human). Keratinocytes and fibroblasts obtained from these sources are cultured in vitro to produce the cellular material used to make the substitute. However, the division of skin substitutes into either biomaterial or cellular is not completely accurate because the two are combined in several wound care products (see Table 2).

FDA regulates products commonly referred to as "skin substitutes" under one of four categories, depending on the product's origin and composition: human-derived products regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps); human- and human/animal-derived products regulated through premarket approval (PMA) or as a Humanitarian Use Device (HUD) obtained through a humanitarian device exemption (HDE); or as animal-derived products and synthetic products regulated under the 510(k) process.[6-8]

Human tissue can be obtained from human donors, processed, and used exactly in the same role in the recipient (e.g., skin for skin, tendon for tendon, bone for bone). These uses are regulated as human tissue intended for transplantation (HCT/Ps) as long as the proposed clinical use and manufacturing methods are consistent with definitions of "Homologous Use" and "Minimal Manipulation" cited in 21 CFR (Code of Federal Regulations) 1271. Human tissue and cells may also be used as a source of cells for culturing to produce cellular-derived material for wound healing. These products may be regulated under the Biologics License Application (BLA) (under the Federal Public Health Service [PHS] Act) or PMA/HDE (under the Federal Food, Drug and Cosmetic [FD&C] Act), depending on their composition and primary mode of action.

Many medical products intended for use in treating wounds are derived from animals. Porcine and ovine tissues and skin are processed into sheets for use as skin substitutes. Bovine fetal tissue is a source of skin cells that are grown in culture to produce skin substitutes. These products may be regulated under the 510(k) process if an appropriate predicate device exists with an equivalent composition and intended use and if the proposed product does not raise any different types of safety or effectiveness questions. When a product does not meet these criteria, it may be reviewed in BLA (PHS Act) or PMA/HDE (FD&C Act) applications, depending on the composition and primary mode of action.

Wound care products regulated under the PMA process are indicated for treating a subset of chronic wounds, those wounds with more than 30 days' duration that have not adequately responded to standard wound care. The 510(k) products are indicated for managing chronic wounds and no restrictions are put on wound duration or prior treatments.

Establishments producing products regulated as HCT/Ps are required to register with FDA and list their HCT/Ps products, but they are not required to demonstrate the safety or effectiveness of their HCT/Ps products. Establishments producing devices regulated under the PMA process must submit an application containing the results of scientifically valid clinical investigations demonstrating that the device is effective and safe for its intended purpose before it can be approved for marketing.

To obtain approval for an HUD, an HDE application is submitted to FDA. An HDE is similar in both form and content to a PMA application but is exempt from the effectiveness requirements of a PMA. HDE approval is based on evidence of probable benefit in a disease population occurring at a frequency of fewer than 4,000 patients per year in the United States. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition and that they could not otherwise bring the device to market.

Methods of the Review

The process of systematic review as practiced by AHRQ's EPC Program follows specific prescribed steps:

1. The investigators start with formulated key questions. These questions test hypotheses and are structured using the PICO framework: patients, intervention of interest, comparator, and outcomes. EPCs are encouraged to focus on outcomes that are relevant and important to patients (patient-centered outcomes). The framework is depicted visually in the analytic framework that the EPC Program uses to show the relationship between the key questions and the outcomes used to address these questions (see Figure 1).
2. Inclusion and exclusion criteria for studies to be used in the review are determined based on the specific questions to be addressed. Criteria may vary for each question in the review.

3. Next, an objective and comprehensive search of the medical literature and gray literature (i.e., reports, monographs, and studies produced by government agencies, educational facilities, and corporations that do not appear in the peer-reviewed literature) is conducted. The reference lists of included studies are examined for any studies not identified by electronic searches.
4. Studies are compared with the inclusion criteria developed before examining the evidence, and those included in the review are then critically appraised, noting features of the design and conduct of the studies that create a potential for bias. Risk of bias, in this context, is the extent to which the design and conduct of a single study "protect against all bias in the estimate of treatment effect."[9] Studies with a low risk for bias are typically described as being of "high" quality, whereas those with high risk for bias are described as being of "low" or "poor" quality, and those of "moderate quality" as having intermediate risk for bias. The degree to which a study protects against bias is referred to as "internal validity." Following this appraisal, data are extracted from the included studies and analyzed or summarized as appropriate.

Upon receipt of the work assignment for this review in August 2011, we developed the following Key Questions:

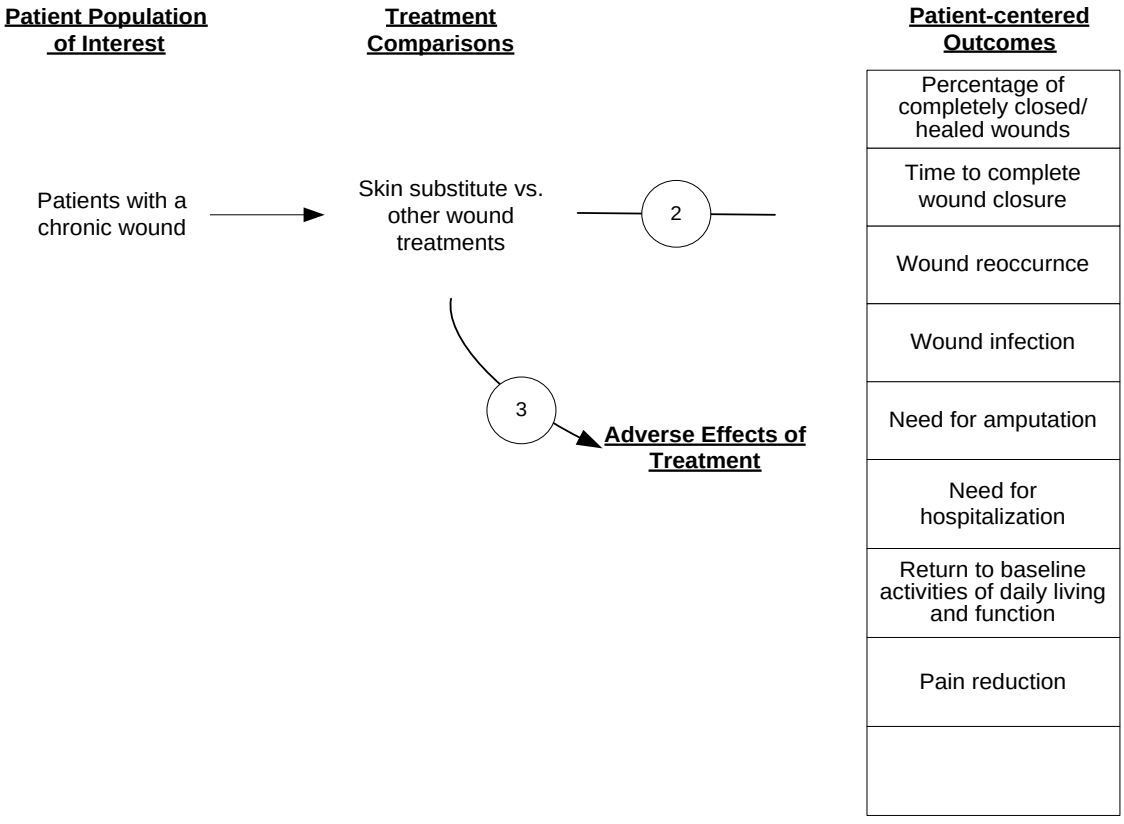
1. What are the U.S. Food and Drug Administration (FDA)-regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361 [21 CFR 1270 & 1271]?
    a. PMA: Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.
    b. 510(k): A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to PMA.
    c. PHS 361 [21 CFR 1270 & 1271]: HCT/Ps (Human cells, tissues, and cellular and tissue-based products). Creates a unified registration and listing system for establishments that manufacture HCT/Ps and establishes donor eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/Ps.
2. For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures:
    a. Percentage of completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing requirements)
    b. Time to complete wound closure
    c. Wound reoccurrence
    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

3. What type and frequency of adverse events are reported in the clinical literature for each of the FDA-regulated skin substitute products?

In addressing the key questions, we sought the specific outcomes depicted in the analytic framework in Figure 1. Key Questions 2 and 3 are represented in the framework by a circled number. Key Question 1 is not related to treatment and outcomes and is not depicted in the figure. According to a guidance document prepared by FDA in 2006, clinical outcomes associated with the use of a wound-treatment product or device can be broadly grouped into two categories: improved wound healing and improved wound care.[10] Several outcomes or endpoints fall into these two categories. According to the FDA document, "complete wound closure of a chronic nonhealing wound is one of the most objective and clinically meaningful wound healing endpoints" and "complete wound closure is defined as skin reepithelialization without drainage or dressing requirements at two consecutive study visits 2 weeks apart."[10] We therefore selected complete wound healing as the primary patient-centered outcome for this report.

Figure 1. Analytic framework



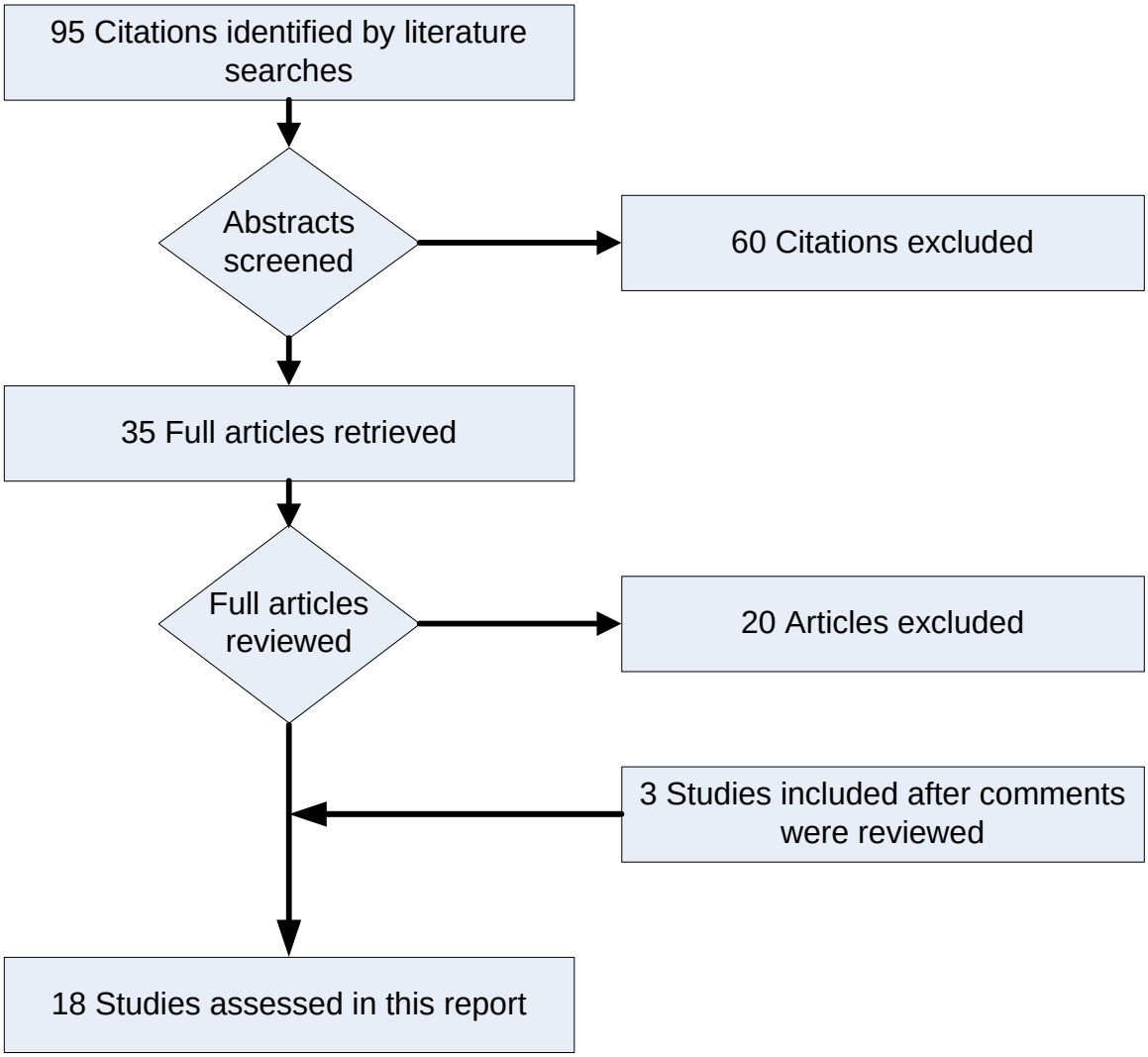
Inclusion criteria were then developed to specify the types of studies appropriate for addressing each of the key questions. These criteria are explained in detail in the "Methods" section of this report but are briefly described here. To address Key Question 1 we started with the list of skin substitute products listed in CMS codes Q4101 to Q4122 and looked to see which FDA product codes the these products were included under. We added similar products with the

same FDA product code. The list of products was then screened to exclude products that were not indicated for chronic wounds. To address Key Questions 2 and 3, we included only randomized controlled trials that enrolled human subjects who had received a diagnosis of a chronic wound (pressure ulcer, diabetic foot ulcer, venous leg ulcer, or arterial leg ulcer) lasting more than 30 days without healing and examined the efficacy of a commercially available skin substitute product regulated by FDA.

Searches were undertaken of 13 electronic bibliographic databases from 1966 to the present for published primary clinical studies and any secondary publications. To supplement the electronic searches, we manually reviewed the reference lists of studies meeting inclusion criteria. Abstracts were reviewed, potential references retrieved, and then full articles were reviewed. Figure 2 is an attrition diagram that provides a visualization of the disposition of materials as they were evaluated for possible inclusion in the report.

Additionally, we searched for ongoing clinical trials using ClinicalTrials.gov and Controlled-trials.com.

Figure 2. Disposition of documents identified by searches



See Table 20 and Table 21 for explanations for exclusions at the abstract and full-article levels.

The most common reasons for exclusion of retrieved articles were the following:

- Study was not a randomized controlled trial.
- Product is not commercially available in the United States.
- Study was a narrative review.
- Publication duplicated an already included study.

Next, an assessment of the potential for bias of the included studies was performed following procedures adopted by EPCs and using a risk-of-bias assessment instrument developed by ECRI Institute specifically for comparative studies of wound care interventions. The overall strength of the evidence base was also judged by following procedures adopted by EPCs and includes assessment of consistency of effect, directness of effect, and precision of the effect estimate.

Evidence for Skin Substitutes

Key Question 1: What are the U.S. Food and Drug Administration (FDA)-regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361[21 CFR 1270 & 1271]?

Definitions:

a. PMA: Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.

b. 510(k): A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to PMA.

c. PHS 361 [21 CFR 1270 & 1271]: HCT/Ps. Creates a unified registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps and establishes donor eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/Ps.

This section of the report addresses which skin substitute products are currently regulated by FDA for use in the United States for treating or managing chronic wounds. This question does not address clinical effectiveness or efficacy. Our searches identified several products that are intended as skin substitutes but may also be used for other medical purposes. Our search results, contained in the following tables, are likely not comprehensive, and other products may fit this report's collection of a skin substitutes that were not identified by our searches. Based on the FDA regulations that govern each product we identified and the origin and composition of the products, skin substitutes can be organized into four groups: human-derived products regulated as HCT/Ps (see Table 1), human- and human/animal-derived products regulated through PMA or humanitarian device exemption (HDE) (see Table 2), animal-derived products regulated under the 510(k) process (see Table 3), and synthetic products regulated under the 510(k) process (see Table 4). Our searches identified 57 skin substitute products.

Table 2 indicates that skin substitute products using human fibroblasts and keratinocytes (derived from neonatal foreskins) and combined with other acellular components are regulated under the PMA process and receive the FDA product code MGR (dressing, wound and burn, interactive). For these products, the term "treatment" is used in the indications for use with chronic wounds. Each of the PMA entries in Table 2 is actually a combination of living human cells and another component (bovine collagen in Apligraf® and polyglactin mesh in Dermagraft®). FDA considers these to be combination products (i.e., combinations of device and biological components into a single entity) and regulates them as medical devices. Besides providing a biologic wound covering, these products also contain human cells capable of producing human growth factors and cytokines that may stimulate angiogenesis, tissue expansion, and re-epithelialization.[5] Thus, these products may interact with the wound bed and assist in the wound healing process. The indications for use of these products are also more specific compared with products regulated under the 510(k) process. The wounds must be noninfected, greater than one month in duration, and unresponsive to conventional treatment.

Table 3 and Table 4 indicate that skin substitute products considered Class II devices and regulated under the 510(k) process are included in FDA product codes KGN (dressing, wound, collagen), FRO (dressing, wound, drug), and MGP (dressing, wound and burn, occlusive) and use the term "management" of wounds in the indications for use on chronic wounds. These products use animal tissue collagen or synthetic material to create an extracellular matrix that acts as a wound covering and scaffold for tissue invasion and regrowth. They do not contain human cells and, therefore, do not have a natural source of growth factors or cytokines involved in initiating the wound healing process. The actual extent to which any one growth factor or cytokine is essential for wound repair has not been determined.[5]

We did identify one exception to the above scheme. EndoForm Dermal Template derived from ovine forestomach, and included in FDA product code KGN, is an exception to the use of the term "management" of wounds and instead uses the term "treatment" in the indications for use (see Table 8). The wording of the indications for use of EndoForm is almost identical to the wording used for Integra™, MatriStem, Oasis®, Primatrix™, and Hyalomatrix®, but "treatment" is substituted for "management." The reason for this difference is unclear.

Table 1. Human-derived products regulated solely under 21 CFR 1271 (HCT/Ps)

Product	Manufacturer	Description
AlloDerm Regenerative Tissue Matrix	LifeCell, KCI	Acellular human dermis product
Allopatch HD	Musculoskeletal Transplant Foundation	Acellular human dermis product
Alloskin	AlloSource	Allograft derived from epidermal and dermal cadaveric tissue
Cymetra Micronized AlloDerm	LifeCell, KCI	Injectable form of AlloDerm Regenerative Tissue Matrix
Dermacell	LifeNet Health	Acellular human dermis product
Flex HD	Ethicon and Musculoskeletal Transplant Foundation	Acellular hydrated dermis derived from donated human allograft skin
GammaGraft	Promethean LifeSciences, Inc.	Irradiated cadaveric human skin allograft
Graftjacket	Life Cell, licensed to Wright Medical Technology and KCI	Processed human dermal matrix
Matrix HD	RTI Biologics	Acellular human dermis product

Product	Manufacturer	Description
Memoderm	Memometal Inc.	Acellular human dermis product
Puros Dermis	Zimmer Dental	A natural biological matrix
Repliform	LifeCell and Boston Scientific	Acellular human dermis product
TheraSkin	Soluble Systems	Biologically active cryopreserved human skin allograft with both epidermis and dermis layers

HCT/Ps: Human cells, tissues, and cellular and tissue-based products

Table 2. Human- and human/animal-derived products regulated through the premarket approval (PMA) or humanitarian device exemption (HDE) process

Product and Manufacturer	Product Description	Approval Date	FDA Product Code	FDA Intended Use/Indication for Use
Apligraf/Graftskin - Organogenesis	Apligraf is supplied as a bilayered skin substitute: the epidermal layer is formed by human keratinocytes and has a well differentiated stratum corneum, the dermal layer is composed of human fibroblasts in a bovine type I collagen lattice. Human fibroblasts and keratinocytes were derived from neonatal foreskins.	1998 PMA original 2000 PMA added diabetic ulcers	MGR (dressing, wound and burn, interactive)	"For use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure."
Dermagraft - Advanced Biohealing, Inc. and Smith & Nephew	Cryopreserved human fibroblast-derived dermal substitute on a bioabsorbable polyglactin mesh scaffold. The fibroblasts are obtained from human newborn foreskin tissue.	2001 PMA	MGR (dressing, wound and burn, interactive)	"For use in the treatment of full-thickness diabetic foot ulcers greater than six weeks' duration which extend through the dermis, but without tendon muscle, joint capsule or bone exposure. Dermagraft(r) should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot. Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts. Dermagraft is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution."

MGR is one of the FDA product codes designated for Class III devices

Table 3. Animal-derived products regulated under the 510(k) process

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
ACell UBM Hydrated Wound Dressing – ACell, Incorporated[11]	A wound dressing primarily composed of porcine collagen.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."
ACell UBM Lyophilized Wound Dressing – ACell, Incorporated[12]	A wound dressing primarily composed of porcine collagen.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. The device is intended for one-time use."
Aongen™ Collagen Matrix – Aeon Astron Europe B.V.[13]	A biodegradable material composed of collagen.	2009	KGN (dressing, wound, collagen)	"For the management of wounds including: surgical wounds, trauma wounds, draining wounds, second degree burns, partial and full-thickness wounds, pressure ulcers, venous ulcers, vascular ulcers, diabetic ulcers, and oral wounds and sores."
Atlas Wound Matrix – Wright Medical Technology, Inc.[14]	A sterile, decellularized fenestrated or nonfenestrated processed porcine collagen dermal material.	2009	KGN (dressing, wound, collagen)	For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), draining wounds. The Atlas Wound Matrix is a collagen wound dressing that provides an environment that supports wound healing."
Avagen Wound Dressing – Integra LifeSciences Corp.[15]	A wound dressing comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. The biodegradable matrix provides a scaffold for cellular invasion and capillary growth.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds."

Table 3. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Collagen Sponge – Innocoll Pharmaceuticals[16]	A collagen matrix sponge	2010	KGN (dressing, wound, collagen)	"For the management of wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, partial and full thickness wounds, and superficial injuries."
Collagen Wound Dressing – Oasis Research, LLC[17]	A wound care dressing composed of hydrolyzed bovine collagen.	2000	KGN (dressing, wound, collagen)	"For the management of wounds including full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, second-degree burns, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, dehisced surgical incisions."
Collaguard™ – Innocoll Pharmaceuticals[18]	A clear collagen matrix film	2006	KGN (dressing, wound, collagen)	"For the management of wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, partial and full thickness wounds, and superficial injuries."
CollaSorb™ Collagen Wound Dressing – Hartmann-Conco Inc.[19]	A wound care product composed of native collagen and calcium-alginate.	2009	KGN (dressing, wound, collagen)	"For the management of full and partial thickness wounds including: pressure ulcers, diabetic ulcers, ulcers caused by mixed vascular etiologies, venous ulcers, second degree burns, donor and graft sites, abrasions, dehisced surgical wounds, and traumatic wounds healing by secondary intention."
CollaWound™ dressing – Collamatrix Inc.[20]	A sterile, single use, disposable wound dressing device comprised of insoluble fibrous collagen derived from porcine.	2006	KGN (dressing, wound, collagen)	"For the management of partial and full thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds, first and second degree burns, surgical wounds and superficial injuries."
Collexa® – Innocoll Pharmaceuticals[21]	A collagen matrix sponge	2010	KGN (dressing, wound, collagen)	"For the management of wounds such as: diabetic ulcers, venous ulcers, pressure ulcers, ulcers caused by mixed vascular etiologies, full-thickness and partial-thickness wounds, abrasions, traumatic wounds, first and second degree burns, dehisced surgical wounds, and exuding wounds."
Collieva® – Innocoll Pharmaceuticals[22]	A clear collagen matrix film	2008	KGN (dressing, wound, collagen)	"For the management of wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, partial and full thickness wounds, and superficial injuries."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices.

Table 3. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Coreleader Colla-Pad – Coreleader Biotech Co., Ltd.[23]	A porous matrix consisting of cross-linked bovine collagen.	2011	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds."
Dermadapt™ Wound Dressing – Pegasus Biologics, Inc.[24]	A collagen-based wound dressing described as a decellularized, equine pericardial implant.	2006	KGN (dressing, wound, collagen)	"For the management of moderately to heavy exuding wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), and surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions)."
DressSkin – TEI Biosciences Inc.[25]	A wound dressing composed of hydrolyzed bovine collagen.	2003	KGN (dressing, wound, collagen)	"For the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical wounds—donor sites/grafts, post Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds—abrasions, lacerations, and skin tears; tunneled/undermined wounds; draining wounds."
E-Z Derm - AM Scientifics, Ltd[26]	Biosynthetic wound dressing made from porcine tissue.	1994	KGN (dressing, wound, collagen)	No FDA summary available online
EndoForm Dermal Template™ – Mesynthes[27]	Extracellular matrix derived from ovine forestomach.	2010	KGN (dressing, wound, collagen)	"For single use in the treatment of the following wounds: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices.

Table 3. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Excellagen – Tissue Repair Company[28]	A wound care device composed of formulated, 2.6% (26 mg/mL) fibrillar bovine dermal collagen (Type I).	2011	KGN (dressing, wound, collagen)	"For the management of wounds including partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds."
FortaDerm™ Wound Dressing – Organogenesis, Inc.[29]	A single-layer fenestrated sheet of porcine intestinal collagen.	2001	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post laser surgery, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds."
HA Absorbent Wound Dressing – ConvaTec, A Division of E.R. Squibb and Sons, Inc.[30]	An absorbent fibrous fleece (F) or rope (R), entirely composed of HYAFF 11p75™, a benzyl ester of hyaluronic acid.	1999	KGN (dressing, wound, collagen)	"For over-the-counter use, HA Absorbent Wound Dressing-F may be used for wounds such as: abrasions, lacerations, minor cuts and first degree burns. Under the supervision of a healthcare professional, HA Absorbent Wound Dressing-F may be used for wounds such as: leg ulcers, pressure ulcers (stages I-IV), and diabetic ulcers, surgical wounds (post-operative, donor sites, dermatological), second degree burns; management of wounds that are prone to bleeding such as wounds that have been mechanically or surgically débrided, donor sites, and traumatic wounds. HA Absorbent Wound Dressing-R is indicated for use in the management of deep exuding wounds, sinuses, and fistulae."
Helicoll – ENCOLL Corp.[31]	A translucent, off-white, semi-occlusive, self-adhering and ready to use pre-sterilized Type-1 Collagen Sheet.	2004	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears), and surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric), wound dehiscence."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices.

Table 3. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Integra™/Bilayer Matrix Wound Dressing - Integra Lifesciences Corp.[32]	Bilayered matrix composed of a porous layer of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer.	2002	FRO (dressing, wound, drug)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic and vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds."
Integra™ Flowable Wound Matrix[33]	A wound care device comprised of granulated cross-linked bovine tendon collagen and glycosaminoglycan.	2007	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds."
LTM Wound Dressing – LifeCell Corp.[34]	A terminally sterilized sheet of the processed porcine dermal matrix	2008	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post laser surgery, podiatric wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns and skin tears), draining wounds, and other bleeding surface wounds."
MatriStem - ACell, Inc.[35]	Extracellular matrix product derived from porcine urinary bladder tissue.	2009	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds."
MatriStem® Wound Matrix – ACell, Inc.[36]	A sterile, porcine-derived, naturally-occurring lyophilized extracellular matrix sheet.	2011	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunnel/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices.

Table 3. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Matrix Collagen Wound Dressing – Collagen Matrix, Inc.[37]	An opaque, absorbent, collagen membrane matrix intended for topical use.	2004	KGN (dressing, wound, collagen)	"For the management of moderately to heavily exudating wounds and to control minor bleeding. Collagen Topical Wound Dressing may be used for the management of exudating wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, acute wounds (for example trauma and surgical wounds), and partial thickness burns."
Medline Collagen Wound Dressing – Medline Industries, Inc.[38]	Not available in 510(k) clearance information.	2006	KGN (dressing, wound, collagen)	"For the management of wounds including: full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, partial and full thickness burns, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, and dehisced surgical incisions. These dressings may be cut to size and may be layered for the management of deep wounds."
Oasis® - Cook Biotech, Inc.[39]	Extracellular matrix derived from porcine small intestinal submucosa	2006	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled, undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds."
Primatrix™ – TEI Biosciences Inc.[40]	Acellular dermal tissue matrix.	2008	KGN (dressing, wound, collagen)	"For the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical wounds–donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds–abrasions, lacerations, and skin tears; tunneled/undermined wounds; and draining wounds."
Primatrix™ Dermal Repair Scaffold - TEI Biosciences[41]	Extracellular matrix dermal substitute derived from fetal bovine dermis collagen.	2006	KGN (dressing, wound, collagen)	"For the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds; draining wounds."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices.

Table 3. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
SIS Wound Dressing II – Cook Biotech, Incorporated[42]	A wound dressing primarily composed of porcine collagen.	2000	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."
SS Matrix™ – Cook Biotech Incorporated[43]	A matrix product primarily composed of porcine collagen.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."
Stimulen™ Collagen – Southwest Technologies, Inc.[44]	A sterile primary single use dressing comprised of soluble modified bovine collagen base.	2004	KGN (dressing, wou nd, collagen)	"For the management of wounds including full and partial thickness wounds, pressure ulcers (stages I-IV), venous stasis ulcers, diabetic ulcers, partial thickness burns, acute wounds, abrasions, traumatic wounds healing by secondary intention, donor sites and other surface wounds."
TheraForm™ Standard/Sheet – Sewon Cellontech Co., Ltd.[45]	An absorbable collagen membrane derived from porcine.	2009	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."
Unite® Biomatrix – Synovis Orthopedic and Woundcare, Inc.[46]	A decellularized equine pericardial extracellular matrix (xenograft)	2011	KGN (dressing, wound, collagen)	"For the management of moderately to severely exudating wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness [second-degree] burns, skin tears), surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions)."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices.

Table 3. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Unite™ Biomatrix – Pegasus Biologics, Inc.[47]	A collagen-based wound dressing consisting of decellularized, equine pericardium.	2007	KGN (dressing, wound, collagen)	"For the local management of moderately to heavy exuding wounds including: partial and full thickness wounds, draining wounds, pressures sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions)."

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KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices.

Table 4. Biosynthetic products regulated under the 510(k) process

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Hyalomatrix KC Wound Dressing (Laserskin) - Anika Therapeutics[48]	Hyalomatrix is a bilayered wound dressing composed of a nonwoven pad made of a benzyl esters of hyaluronic acid (HYAFF) and a semipermeable silicone membrane.	2001	MGP (dressing, wound and burn, occlusive)	"For the management of wounds in the granulation phase such as pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, wounds and burns treated with meshed grafts. It is intended for use as a temporary coverage for wounds and burns to aid in the natural healing process."
Hyalomatrix Wound Dressing - Anika Therapeutics S.r.l.[49]	Hyalomatrix is a bilayered wound dressing composed of a nonwoven pad made of HYAFF 11 (a benzyl ester of hyaluronic acid) and a semipermeable silicone membrane.	2007	FRO (dressing, wound, drug)	"For the management of wounds including: partial and full-thickness wounds; second-degree burns; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery , post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds."
Jaloskin - Anika Therapeutics S.r.l.[50]	Jaloskin is a semipermeable, transparent film dressing, composed of HYAFF 11 (a benzyl ester of hyaluronic acid) only	2010	FRO (dressing, wound, drug)	"For the management of superficial moderately exuding wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, skin tears) and first and second degree bums."
Suprathel - Polymedics Innovations[51]	Synthetic, biocompatible, and absorbable skin substitute made from polymers of lactic acid.	2009	FRO (dressing, wound, drug)	"For temporary coverage of non-infected skin defects, such as superficial wounds, under sterile conditions. The dressing is intended to maintain a moist wound healing environment. A moist wound healing environment allows autolytic débridement. The Suprathel Wound and Burn Dressing is used in the management of: Partial and full thickness wounds; Pressure (stage I and IV) and venous ulcers; Ulcers caused by mixed vascular etiologies; Venous stasis and diabetic ulcers; 1st and 2nd degree bums; Partial thickness bums; Cuts and abrasions; Acute wounds; Trauma wounds; Surgical wounds; Superficial wounds; Grafted wounds and donor sites."

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Talymed™ – Marine Polymer Technologies, Inc.[52]	A sterile wound matrix comprised of shortened fibers of poly-N-acetylglucosamine, isolated from microalgae.	2010	FRO (dressing, wound, drug)	"For the management of wounds including: diabetic ulcers; venous ulcers; pressure wounds; ulcers caused by mixed vascular etiologies; full thickness and partial thickness wounds; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post laser surgery, and other bleeding surface wounds; abrasions, lacerations; traumatic wounds healing by secondary intention; chronic vascular ulcers; dehisced surgical wounds."

KGN, MGP, and FRO are among the FDA product codes designated for unclassified pre-amendment devices.
HYAFF: Benzyl esters of hyaluronic acid

Key Question 2: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures:

a. Percentage of completely closed/healed wounds
b. Time to complete wound closure
c. Wound reoccurrence
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

Our searches identified 18 randomized controlled trials (RCTs) that met our inclusion criteria (see Table 5). Twelve studies examined diabetic foot ulcers, and six studies examined venous leg ulcers. Only seven skin substitute products were examined in the 18 RCTs. We identified only one study using skin substitutes to treat patients with pressure ulcers, but this study did not meet the inclusion criteria (see Table 20).

Outcomes reported in the included studies were primarily complete wound healing by 12 weeks (13 studies), time to complete wound healing (12 studies), complete wound healing after 12 weeks (9 studies), and wound infection (16 studies). Complete wound healing was defined in these studies as full epithelialization with no drainage, meaning that no exudate or scab was present. However only four of the studies (Edmonds 2009,[53] Landsman et al. 2008,[54] Krishnamoorthy et al. 2003,[55] and Marston et al. 2003[56]) reported reassessment of wound healing within 2 weeks of wound closure. Eight studies used various followup methods that included biweekly, monthly, or every 3 month wound reassessment till the end of the study. Wound recurrence after 12 weeks was reported in seven studies. Six studies do not mention reassessment or planned followup to assessment the durability of wound closure. Other outcomes listed in Key Question 2 were not as frequently reported, and measures of function and activities of daily living were not reported in any study.

One of the 18 RCTs was considered to have an unclear risk of bias primarily because of poor reporting of methods (see Table 22 to Table 26), which limited the assessment. Eight studies were considered to have low risk of bias, and nine were considered to have moderate risk of bias. None of the studies reported blinding of wound assessment. Other areas of concern for study design and conduct were poor reporting of comorbidities and wound severity prior the start of treatment. Only seven of the 18 studies included in this report mention the use of a run-in period prior to enrolling patients in the study and only two studies reported wound severity prior to starting treatment.

The strength of the evidence base for evaluating complete wound healing of diabetic foot ulcers at 12 weeks was graded as low for the comparisons of Graftjacket vs. moist wound

products, the comparison of Apligraf vs. a nonadherent dressing and for Graftskin vs. saline-moistened gauze. Each of these studies represented a multicenter trial with a low risk of bias for the outcome of complete wound healing. The outcome measure was direct and the results were precise. Although the evidence for the comparison of Dermagraft vs. saline-moistened gauze came from 3 studies including 530 patients and had a precise result of a direct outcome, we judged the strength of the evidence to be only low because the studies had a moderate risk of bias. The strength of the evidence for other comparisons for diabetic foot ulcers were graded insufficient, primarily because the overall risk of bias was moderate and/or the reported treatment effect (percentage increase in completely healed wounds) was imprecise.

Only two comparisons were judged to have low strength of evidence for complete wound healing of venous or mixed ulcers at 12 weeks. One compared Apligraf and compression to compression, and one compared Oasis Wound Matrix with compression to compression. In each case, the included study was a multicenter trial, had a low risk of bias and reported a precise and direct result. The other comparisons were from studies with moderate risk of bias and imprecise results; these were judged to have an insufficient strength of evidence grade.

A grade of low means we have low confidence that the evidence reflects the true effect of skin substitutes on complete wound healing, and we believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. A grade of insufficient indicates that the available evidence does not support a conclusion regarding the comparison.

The applicability of the evidence is another important issue with the studies included in this report. The patients examined in these studies were of generally good health, under good glycemic control, and had adequate blood flow to the wound area to assist in the healing process. Among study design and other patient information of interest to this report, prior wound treatments were not reported in any of the studies and comorbidities were poorly reported. Because patients enrolled in these studies are in generally good health and free of infected wounds, medications that would impede wound healing, clinically significant medical conditions, significant peripheral vascular disease, malnutrition, and uncontrolled diabetes the applicability of the evidence to patients who are in poorer overall health is unclear.

Only 7 of the 57 skin substitute products identified for this report were examined in RCTs. Wound healing data from one group of skin substitutes cannot be extrapolated to other groups because of the difference in composition and healing properties. Similarly, data from studies of diabetic foot ulcers cannot be extrapolated to venous leg ulcers because of the differences in etiology and pathophysiology. Therefore, clinical evidence from RCTs demonstrating the efficacy of skin substitute products for treating chronic wounds is very limited.

In 12 of the included studies, treatment efficacy was judged by the number of wounds healed after 12 weeks of treatment. Two studies reported on wound healing at fewer than 12 weeks, one at 8 weeks,[57] and one at 11 weeks.[58] The remaining studies measured wound healing at 16 weeks,[59,60] 20 weeks,[61] 32 weeks,[62] and 6 months[63] (see Table 49 to Table 53). Recurrence rates varied widely across studies but were comparable between groups within studies. Other outcomes not directly related to wound healing, such as amputation, hospitalization, return to function, and pain relief, were poorly reported.

Table 5. List of included randomized controlled trials

Study	Comparison	Wound Type
DiDomenico et al. 2011[64]	Apligraf vs. TheraSkin	DFU
Edmonds 2009[53]	Apligraf vs. nonadherent dressing	DFU
Falanga et al. 1998[63]	Apligraf with compression vs. compression therapy	Leg, Venous
Krishnamoorthy et al. 2003[55]	Dermagraft plus multilayered compression bandage therapy (Profore™) vs. multilayered compression therapy	Leg, Venous
Marston et al. 2003[56]	Dermagraft vs. saline-moistened gauze	DFU
Naughton et al. 1997[62]	Dermagraft vs. saline-moistened gauze	DFU
Gentzkow et al. 1996[65]	Dermagraft vs. saline-moistened gauze	DFU
Reyzelman et al. 2009[66]	Graftjacket acellular matrix vs. moist wound therapy with alginates, foams, hydrocolloids, or hydrogels	DFU
Brigido 2006[59]	Graftjacket acellular matrix vs. weekly debridement, Curasol wound hydrogel and gauze dressing	DFU
Veves et al. 2001[67]	Graftskin vs. saline-moistened gauze alone	DFU
Uccioli et al. 2011[68]	Hyalograft 3D autograft/LasersSkin vs. nonadherent paraffin gauze	DFU
Caravaggi et al. 2003[58]	Hyalograft 3D autograft/LaserSkin vs. nonadherent paraffin gauze	DFU
Romanelli et al. 2010[57]	Oasis Wound Matrix vs. a petrolatum-impregnated gauze	Leg, Mixed
Landsman et al. 2008[54]	Oasis Wound Matrix vs. Dermagraft	DFU
Romanelli et al. 2007[60]	Oasis Wound Matrix vs. Hyaloskin (contains hyaluronan)	Leg, Mixed
Mostow et al. 2005[69]	Oasis Wound Matrix with compression vs. compression alone	Leg, Venous
Niezgoda et al. 2005[70]	Oasis Wound Matrix vs. Regranex Gel (contains platelet-derived growth factor)	DFU
Kelechi et al. 2011[61]	Talymed poly-N-acetyl glucosamine (pGlcNAc) with compression vs. nonadherent absorptive primary dressing with compression	Leg, Venous

DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
Leg: Vascular leg ulcer
SOC: Standard of care

Key Question 3: What type and frequency of adverse events are reported in the clinical literature for each of the FDA-regulated skin substitute products?

Cellulitis and osteomyelitis were reported in several studies. Many of the studies report adverse events but do not specify what they are.

Conclusion

Our searches identified 57 skin substitute products (as identified in this report) available in the United States that are used to manage or treat chronic wounds and are regulated by FDA. Based on the FDA regulations that govern each product we identified and on the origin and

composite of the products, skin substitutes can be organized into four groups: human-derived products regulated as HCT/Ps, human- and human/animal-derived products regulated through PMA or HDE, animal-derived products regulated under the 510(k) process, and synthetic products regulated under the 510(k) process. Human tissue can be obtained from human donors, processed, and used in exactly the same role in the recipient, such as a dermal replacement to be placed in a wound as a skin substitute (regulated as HCT/Ps). These products may be regulated under the Biologics License Application (BLA) (under the PHS Act) or PMA/HDE (under the FD&C Act), depending on their composition and primary mode of action. Other skin substitutes are derived only from animal tissue or biosynthetic materials and are regulated under the 510(k) process.

One of this report's goals was to begin to characterize the state of the evidence on skin substitutes as wound care products for chronic wounds. For this report, we sought to determine the number of RCTs of these products and to assess the efficacy of skin substitutes in the trials. The following key points were noted about the strength of this evidence and its applicability:

- Eighteen RCTs examining only seven of the skin substitute products identified for this report met the inclusion criteria. Twelve of the studies examined diabetic foot ulcers, and six studies examined vascular leg ulcers.
- No studies of pressure ulcers met our inclusion criteria; only one RCT of pressure ulcers was identified.
- Of the included studies, none had a high risk of bias and one had an unclear risk of bias, while the others were divided between low (eight studies) and moderate (nine studies) risk of bias.
- No studies reported blinding of the person assessing wound healing
- 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 strength of the evidence base for evaluating complete wound healing of diabetic foot ulcers at 12 weeks was graded as low for the comparisons of Graftjacket vs. moist wound products, the comparison of Apligraf vs. a nonadherent dressing, for Graftskin vs. saline-moistened gauze, and for Dermagraft vs. saline-moistened gauze. The strength of the evidence for other comparisons for diabetic foot ulcers were graded insufficient, primarily because the overall risk of bias was moderate and/or the reported treatment effect (percentage increase in completely healed wounds) was imprecise. A grade of low means we have low confidence that the evidence reflects the true effect of the skin substitute on complete wound healing as compared to another intervention, and we believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Two comparisons were judged to have low strength of evidence for complete wound healing of venous or mixed ulcers at 12 weeks - one comparing Apligraf and compression to compression, and one comparing Oasis Wound Matrix with compression to compression. In each case, the included study was a multicenter trial, had a low risk of bias and reported a precise and direct result. The other comparisons were from studies with moderate risk of bias and imprecise results; these were judged to have an insufficient strength of evidence grade.

- Data on wound recurrence was reported in only seven studies where followup was between 6 and 14 months. Recurrence rates varied widely across studies but were comparable between groups within studies.
- Only generally healthy patients were enrolled in studies. Patients with infected wounds, who used medications that could impede wound healing, had clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes were excluded.
- No clinical efficacy data from RCTs are available for the large majority of the skin substitute products identified in this report.
- Overall applicability of the evidence base is limited to a small number of skin substitutes examining diabetic foot ulcers and vascular leg ulcers and to patients in generally good health.
- Various features of study design and conduct as pointed out in this report could be improved in future wound care studies to ensure better study quality and low potential for bias.

Our evaluation of the clinical literature indicates that studies comparing the efficacy of skin substitutes to alternative wound care approaches are limited in number, apply mainly to generally healthy patients, and examine only a small portion of the skin substitute products available in the United States.

The results of the available studies cannot be extended to other skin substitute products because of differences in active components in the various products. Additionally, the results from studies of diabetic foot ulcers do not extrapolate to studies of vascular leg ulcers or pressure ulcers because of differences in wound pathophysiology and etiology. The studies that are available are also not generalizable to the broader patient population that is not as healthy as the patients in these studies. Also missing from this evidence base were studies that compared the various types of skin substitute products. Only two of the 18 studies compared two skin substitute products (Oasis versus Hyaloskin and Apligraf versus TheraSkin). How a human dermal substitute such as Graftjacket compares with a human derived skin substitute such as Dermagraft when treating a diabetic foot ulcer or a vascular leg ulcer is unknown. Such comparisons could be useful to clinicians trying to decide which wound treatment products to use. 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.

Abbreviations and Acronyms

ABI	Ankle brachial index
AHRQ	Agency for Healthcare Research and Quality
CFR	Code of Federal Regulations
CMS	U.S. Centers for Medicare and Medicaid Services
DFU	Diabetic foot ulcer
FDA	U.S. Food and Drug Administration
HCT/Ps	Human cells, tissues, and cellular and tissue-based products
HDE	Humanitarian device exemption

HUD	Humanitarian Use Device
HYAFF	Benzyl ester of hyaluronic acid
PHS	Public Health Service
PMA	Premarket Approval
RCT	Randomized controlled trial
SOC	Standard of care

Background

The Center for Medicare Management at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the ECRI Institute Evidence-based Practice Center (EPC) under Contract Number: HHSA 290-2007-10063.

A wide variety of wound care products are available for clinicians to choose from when treating chronic wounds. Many of these products are said to mimic or substitute for some aspect of the skin's structure and function to promote healing and wound closure. The materials used to produce these products may be derived from human or animal tissue and may undergo extensive or minimal processing to make the finished product. The extent of processing and the source of the material used in the product also determines what regulatory pathway may be required before the product can be marketed. CMS requested this report on the types of wound care products that are commonly referred to as "skin substitutes" and on the regulatory pathways required for the different types of products. For this report, we have not created a definition for a skin substitute product. Instead we used the products listed under CMS codes Q4101 to Q4122 as a starting point and looked for similar products listed in the U.S. Food and Drug Administration (FDA) product codes to generate a list of products. We included only those products indicated for chronic wounds. We note that FDA does not refer to any product or class of products as "skin substitutes," and we are not proposing an official classification system.

In addition to identification of the products, a second objective of this review was to begin to characterize the state of the evidence base on skin substitutes as wound care products. To address this objective, we sought to determine the number of RCTs of these products and to assess the efficacy of skin substitutes under the conditions presented in the trials. Systematically reviewing and analyzing all the clinical research on skin substitutes is beyond the scope of this report.

This report specifically examined the use of skin substitutes for treating the following chronic wound types: diabetic foot ulcers, pressure ulcers, and vascular ulcers (including venous ulcers and arterial ulcers). Treatment of burn wounds with skin substitutes is outside the scope of this report.

Normal Healthy Skin

As the interface between the environment and body, the skin has several distinct functions. It protects the underlying tissues from abrasions, the 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 to control the flow of blood 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 a basal layer of constantly dividing keratinocytes that lies next to the dermis. 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. This layer of the skin provides

mechanical strength and a substrate for water and nutrient diffusion; it contains blood vessels, nerves, and cells involved in immune function, growth, and repair. The dermis also contains sweat glands, oil glands, and hair follicles. The subcutaneous layer is composed of adipocytes that form a thick layer of adipose tissue.[1]

Chronic Wounds

Wounds are breaches in the structure of the skin that compromise skin function. Superficial wounds such as abrasions affect mainly the epidermis and are quickly healed by growth of new keratinocytes to cover the damaged skin. Partial-thickness skin loss involves the epidermis and dermis and requires more extensive healing, especially if the wound is large. Full-thickness skin loss involves penetration through the epidermis and dermis into the subcutaneous tissue and may expose muscle and bone.

Chronic wounds have not completed the process of healing (restoring tissue loss and restoring skin function) in the expected time frame, usually within 30 days;[2] have not responded to initial treatment; or persist despite appropriate care.[3] These wounds usually do not close without interventions and are sometimes resistant to healing interventions. Diabetic foot ulcers, pressure ulcers or "bed sores," vascular ulcers, and complications of surgically created sternal wounds commonly become chronic wounds because their etiologies impede healing, and they persist without proper medical care. For this review, we consider chronic wounds to be wounds present for more than 30 days and acute wounds to be those present for fewer than 30 days. Diabetic foot ulcers, venous leg ulcers, and pressure ulcers are the chronic wounds most often treated with a skin substitute.

Chronic wounds of the lower extremity (from hips to feet) affect about 6 million people in the United States, especially the elderly.[3]

Diabetic Foot Ulcers

Patients with diabetes often develop foot ulcers due to atherosclerosis that impedes blood flow to the extremities and peripheral neuropathy that prevents the sensation of discomfort associated with mechanical stress on or injury to the feet. Each of these complications of diabetes increases the probability of ulcer formation on pressure-bearing areas of the feet. Neuropathy is present in 60 percent to 70 percent of patients with diabetic foot ulcers, with 15 percent to 20 percent of patients having a combination of neuropathy and vascular problems. Patients with diabetic neuropathy are often not aware of repeated mechanical trauma, and ulcers commonly form under the foot. An estimated 16 million Americans are known to have diabetes. Among patients with diabetes, 15 percent develop a foot ulcer, and 12 percent to 24 percent of individuals with a foot ulcer require amputation.[71]

Diabetic foot ulcers may be classified using the Wagner Classification System.[72] This system is based mainly on wound depth and consists of six wound grades. Grade 0 foot ulcers have intact skin with bony deformities or dry keratinized skin that increases the potential for ulceration, grade 1 involves ulceration of the dermis, grade 2 has ulceration involving tendons and joints, grade 3 extends to the bone and causes osteomyelitis, grade 4 shows localized gangrene, and grade 5 has gangrene involving a major portion of the foot.[73] Improved foot care will often help in healing foot ulcers caused by diabetic neuropathy, but ischemic foot ulcers are often difficult to heal unless the underlying vascular problems are corrected.[71,74]

The major health consequences of diabetic foot ulcers are wound infections, osteomyelitis, and subsequent amputation. Individuals with severe diabetic foot ulcers may be at risk of dying due to concomitant arteriosclerotic disease involving the coronary or renal arteries. Managing diabetic foot ulcers requires appropriate therapeutic footwear, a wound dressing that provides a moist environment, débridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present, and evaluation and correction of peripheral arterial insufficiency.[71,75]

Pressure Ulcers

Pressure ulcers, also called "decubitus ulcers," "bed sores," or "pressure sores," are defined as lesions caused by unrelieved pressure or shear resulting in damage of underlying tissue.[76] These wounds often occur over bony prominences. Prolonged pressure causes ischemia, which leads to tissue necrosis that typically first occurs in the tissue closest to the bone. Ischemic cell death produces inflammation that results in blood clotting, platelet aggregation, immune complex formation, and the accumulation of inflammatory cells. Patients who are chairbound or bedridden are at increased risk for developing pressure ulcers. The following factors further increase their risk of pressure ulcer development: advanced age, impaired ability to reposition themselves, friction, decreased sensory perception, impaired nutrition, and excessive exposure to moisture (i.e., incontinence, excessive perspiration, wound drainage).[77] The exact incidence and prevalence of pressure ulcers are unclear. Reports of pressure ulcer incidence vary widely, from 0.4 percent to 38.0 percent in acute care, from 2.2 percent to 24.0 percent in long-term care, and from 0 percent to 17 percent in home care.[78]

Pressure ulcers are classified in stages according to the degree of tissue damage. Stage 1 pressure ulcers are distinguished by non-blanchable redness of intact skin, stage 2 by superficial skin loss (partial-thickness skin loss of the epidermis and dermis), stage 3 by subcutaneous tissue loss (full-thickness skin loss penetrating through the epidermis and dermis into the subcutaneous tissue), and stage 4 by tissue loss that extends into the underlying muscle, tendon, or bone.[77] The health consequences of pressure ulcers include local infection, sepsis, osteomyelitis, and pain.[79] Local infection of pressure wounds is common and is usually controlled by débridement and antibiotics. Osteomyelitis is a risk in pressure ulcer patients because these ulcers develop over bony prominences.

Treatment of pressure ulcers centers on the following interventions: managing tissue load (i.e., pressure, friction, shearing), nutritional support, ulcer care, and managing bacterial colonization and infection.[77] Usual care for pressure ulcers depends on the ulcer stage and usually includes pressure relief and skin protection to prevent progression of the ulcer to advanced stages, débridement of necrotic tissue in stage 3 and 4 ulcers, wound cleansing, and dressings that promote a moist wound environment and absorb exudate.

Vascular Leg Ulcers

Vascular leg ulcers are the result of chronic venous insufficiency (venous leg ulcers, 80 percent to 95 percent of vascular ulcers), or arterial insufficiency (arterial leg ulcers, 5 percent to 10 percent). Between 10 percent and 35 percent of the U.S. population has some type of venous disease, and lower extremity skin ulcers are reported in 1 percent to 22 percent of individuals older than age 60.[80]

The underlying problem in venous leg ulcers is venous hypertension in the deep and superficial venous system caused by incompetent valves and the incomplete removal of blood from the venous system. The disorder may be due to a previous blood clot that destroys the valves, a comorbid medical problem (arterial disease), or a hereditary absence of the valves in the venous system. The venous hypertension dilates capillaries and increases capillary filtration, causing edema followed by subcutaneous tissue destruction and ulcer formation. Wounds caused by venous insufficiency are hard to heal and often recur.[80]

Venous leg ulcers, if left untreated, may remain for years and lead to depression, anxiety, reduced activity, and a reduction in the patient's quality of life.[81,82] Pain may be experienced by as many as 80 percent of venous leg ulcer patients.[83] Edema of the leg is frequently associated with venous leg ulcers. The edema may be the result of the venous insufficiency, inflammation, compromised lymphatic system associated with the wound, or systemic disorders such as heart failure.[84] Contact dermatitis is also common in patients with venous leg ulcers, and allergic reactions to wound dressings, topical ointments, and bandage material may hinder wound healing.

Treating venous leg ulcers involves cleaning and protecting the wound, facilitating the healing process, and providing hemodynamic support to control the underlying disorder responsible for the ulcer.[80] Wound cleaning can be performed with sterile or nonsterile water or saline and gauze compresses to remove loose slough and eschar from the wound. When necessary, débridement can be performed with application of enzymes or sharp débridement procedures (forceps, scissors, lasers) before applying the dressing and compression bandages. Hemodynamic support is provided by compression bandages that counter the venous hypertension responsible for ulcer development. Compression bandages are a vital part of treating venous leg ulcers. Therapeutic compression stockings with compression of 30-40 mm Hg will counteract the capillary pressure in the tissues. Restoring blood flow through the skin reduces edema, increases oxygen and carbon dioxide exchange, and increases nutrient flow into the tissues. Compression may be applied using a single-component (a stocking or single type of bandage) or a multi-component system using several layers of material. A systematic review from 2009 examined the evidence for compression treatment of venous leg ulcers. According to the authors, venous ulcers heal more rapidly with compression than without and multi-component systems achieve better healing outcomes than single-component compression.[85]

Arterial ulcers are caused by blood-flow restriction in an artery, resulting in ischemia and ulcer development.[86] Necrotic tissue with minimum exudate is common in this type of ulcer. Treatment is based on restoring perfusion to the affected tissue either through surgery or medication. Compression bandages are not typically used to treat arterial ulcers because they may increase the ischemia and the risk of amputation.[87]

Phases of Normal Wound Healing

Skin wounds heal in three distinct phases: the hemostatic or inflammation phase, the proliferative phase, and the maturation or remodeling phase.[88] The inflammatory phase begins with tissue damage that often results in the release of blood and the formation of a fibrin clot. Platelets release cytokines and growth factors that attract inflammatory cells (neutrophils, eosinophils, and monocytes) and initiate the inflammatory response. The inflammatory phase also initiates cellular and vascular responses that clear dead tissue, bacteria, and foreign material from the wound. Vasodilation and increased capillary permeability around the wound allow

serum proteins and leukocytes to infiltrate the area and begin the healing process. Macrophages appear within 48 hours and aggressively remove dead tissue and bacteria. Activated macrophages secrete cytokines that attract fibroblasts to the wound. The clot forms a temporary shield over the wound and provides a structure through which inflammatory cells, fibroblasts, and vascular endothelial cells move to form granulation tissue. The inflammatory phase lasts about 2–5 days.[74,89-91]

Fibroblasts appear in the wound within 2–3 days and mark the beginning of the fibroblast proliferation phase. This phase may last up to three weeks. Fibroblasts produce and extrude collagen, which then forms into fibers that provide tensile strength to the wound. Fibroblasts also secrete a variety of growth factors that guide the formation of the new extracellular matrix. New blood vessels advance into the wound along with the fibroblasts to satisfy the metabolic needs of collagen formation. The new blood vessels, collagen, and proteoglycan ground substance form the granulation tissue. Granulation tissue fills a deep wound during the early phases of the healing process. Its formation is a key part of wound healing. Myofibroblasts within the granulation tissue contract, pull the wound edges together, and reduce the size of the wound. Re-epithelialization occurs during the fibroblast proliferative phase as epithelial cells (keratinocytes) proliferate and migrate over the granulation tissue. The new epithelial cells provide a barrier to bacteria and prevent fluid loss. In wounds with a large surface, epithelialization is enhanced by a moist environment. Dry wounds with a large dry eschar (commonly referred to as a "scab") impede epithelial cell migration.[74,89-91]

Growth factors and cytokines released into a wound play various roles in orchestrating the chain of events that results in restoration of the skin's barrier function and mechanical integrity. Growth factors are polypeptides that interact with cell receptors to signal migration, proliferation, differentiation, and secretion of proteins such as collagen or additional growth factors. Platelet-derived growth factors (PDGFs) begin the healing process and start the interaction between cells and the extracellular matrix in the wound. Platelets also release transforming growth factor (TGF)-α and TGF-β, which increase cell proliferation. Activated monocytes and macrophages produce additional growth factors that activate angiogenesis. PDGF stimulates fibroblast proliferation and along with TGF-β stimulates fibroblasts to produce collagen, hyaluronic acid, matrix metalloproteinases, and additional proteins that build the extracellular matrix. Growth factors present in the newly formed granulation tissue stimulate the proliferation of keratinocytes at the wound margins. While PDGF and TGF are important elements in the healing process they represent only a small portion of all of the factors involved in wound healing. Vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor, connective tissue growth factor, and other factors have roles in different stages of wound healing. Understanding of the interaction between these growth factors, cells, and the extracellular matrix in chronic wounds is far from complete. Currently, the use of growth factors to promote wound healing has a limited role. Successful use of growth factors will depend on a better understanding of when each growth factor or combination of factors should be used, how to deliver the growth factors to the wound, and what dosages will ensure proper wound healing.[92-94]

By three weeks after injury, collagen synthesis and degradation are in homeostasis, and wound remodeling begins. Maturation of the wound takes place with increasing levels of type I collagen, compared with type III collagen, and thickening of the collagen fibers. The new tissue

formed in the wound progressively increases in tensile strength. This process may continue for up to two years.[74,89-91]

The wound healing process should result in the restoration of skin structure and function. Lazarus et al.[2] has proposed that healed wounds be placed in one of three categories: ideally healed, acceptably healed, and minimally healed. An ideally healed wound has returned to "normal anatomic structure, function, and appearance that includes a fully differentiated and organized dermis and epidermis with intact barrier function." An acceptably healed wound has "epithelialization capable of sustaining functional integrity during activities of daily living." A minimally healed wound has achieved "restoration of epithelial coverage that does not establish a sustained functional result and may recur."[2]

Skin Substitutes

Skin substitutes were developed as an alternative to skin grafts, especially for burn patients. Autologous tissue grafting is an invasive and painful procedure, and often the extent of damaged skin is too large to be covered by autologous tissue graft alone. Tissue engineered skin substitutes and cultured skin cells were developed during the 1980s. Skin substitutes are now primarily used in treating chronic wounds rather than for burns, in part because chronic wounds are far more common than burn wounds.[4]

A true "skin substitute" would act like an autologous skin graft in adhering to the wound bed while providing the physiological and mechanical functions of normal skin.[4] The skin substitutes included in this report contain various combinations of cellular and acellular components intended to stimulate the host to regenerate lost tissue and replace the wound with functional skin. Presumably, successful healing during management with these products would also require maintenance of a moist wound environment and other procedures thought to promote healing. These include removal of exudate and necrotic tissue, infection control, nutritional support, pressure avoidance (e.g., off-loading for diabetic foot ulcers and pressure ulcers) and edema control (e.g., compression for venous leg ulcers).[5]

Dieckmann et al. have suggested that skin substitutes can be divided into two broad categories: biomaterial and cellular.[5] Biomaterial skin substitutes do not contain cells (acellular) and are derived from natural or synthetic sources. Natural sources include human cadaveric skin processed to remove the cellular components and retain the structural proteins of the dermis and collagen matrix obtained from bovine and porcine sources. Synthetic sources include degradable polymers such as polylactide and polyglycolide. Whether natural or synthetic, the biomaterial provides an extracellular matrix that allows for infiltration of surrounding cells. Cellular skin substitutes are distinguished by their origin: xenogeneic (from nonhuman species), autologous (from the patient), and allogenic (from another human). Keratinocytes and fibroblasts obtained from these sources are cultured in vitro to produce the cellular material used to make the substitute. However, the classification of skin substitutes into either biomaterial or cellular is not completely accurate since the two are combined into several wound care products (see Table 7).

Usual Care for Chronic Wounds

Several requirements are necessary for proper and rapid healing of an open wound. During healing, either the edges of the wound seal back together (healing by "primary intention") or granulation tissue must form to fill the wound bed (healing by "secondary intention"). Most

importantly, the wound must remain moist because new epidermal cells will only travel across moist surfaces. Bacterial infection must be controlled and any fluids should be removed from the wound site while appropriate moisture is maintained. Additionally, contributing factors to wound occurrence should be eliminated or minimized if elimination is not possible. Bedridden patients may need special support surfaces and protein-calorie malnutrition and vitamin deficiencies should be corrected. Inadequate blood flow to the site of the wound should be corrected if possible, and drugs known to impede wound healing should be adjusted.[89]

Usual care for established chronic wounds incorporates common principles mentioned above that apply to managing all wound types. Clinicians remove necrotic tissue through débridement (achieved through sharp débridement using forceps and scissors, autolytic débridement by endogenous enzymes present in the wound, or application of exogenous enzymes in commercially available wound care products), maintain moisture balance by selecting the proper wound dressing to control exudate, and take measures to prevent or treat wound infections and to correct ischemia in the wound area. For venous leg ulcers, some form of compression is part of usual care. For diabetic foot ulcers, some form of off-loading is part of usual care. However, the methods for achieving each of these wound management principles varies among clinical practice guidelines and clinical studies.[10,95]

Wound dressings used as usual care show considerable variability among clinical studies. A systematic review commissioned by the AHRQ Technology Assessment Program found that among 43 RCTs examining the treatment of diabetic foot ulcers, 51 percent used saline wet-to-dry dressing as the control while 14 percent used a hydrocolloid dressing. The number of dressing changes per day also varied. Among 66 RCTs of venous leg ulcers, saline wet-to-dry was the control dressing in only 3 studies while an occlusive dressing such as hydrocolloid was used in 25 studies. Other control dressings used in the venous leg ulcers studies included the Unna boot, dry gauze, Vaseline gauze, or ointment. Venous ulcer dressings were changed less frequently than diabetic foot dressings, most often once or twice weekly.[95]

Chronic wounds are often treated with saline-moistened cotton gauze (wet-to-moist). Gauze dressings are moderately absorptive, easily available, and inexpensive. Saline-moistened gauze dressings can maintain a moist wound environment provided they are kept continuously moist until the dressing is removed. Therefore, wet-to-moist gauze dressings require close maintenance and added nursing time. The removal of a wet-to-moist dressing that has been allowed to dry may reinjure the wound by removing granulation tissue and lead to delayed wound healing. The removal of dried gauze dressings also causes the patient considerable pain, impedes healing, and increases the risk of infection. While gauze dressings are much less expensive per dressing than modern synthetic dressings, the increase in labor costs and ancillary supplies such as gloves and biohazardous waste disposal increase the total cost of care. The drawbacks of saline-moistened gauze dressings have been reviewed elsewhere.[96]

The phrase “standard of care” was commonly used in the studies included in this report in reference to the wound care used in the control group or the base wound care to which a skin substitute was added (see Appendix C for descriptions of control group wound care). However, as described above, “usual care” or “standard of care” does not describe an agreed-upon set of procedures to be used when treating chronic wounds. In the evidence tables describing the wound care received in each study in this report, we have separated the description into three parts: the skin substitute, the control dressing, and the ancillary wound treatment. The Ancillary Wound Treatment column describes the usual care or standard care received by all patients.

Skin Grafts

Skin grafts are used in treating venous leg ulcers,[97] diabetic foot ulcers, and burn wounds.[65,97] Skin grafts are believed to assist wound healing by providing dermal collagen, growth factors, and biological occlusion and protection of the wound. Skin grafts are usually taken from a portion of intact skin of the same individual (autograft), but may be obtained by human skin donors (allograft). Skin grafts may be used in later stages of wound healing after the wound has established sufficient granulation tissue to support the graft. A recent Cochrane Review points out that insufficient evidence from RCTs was available to indicate whether skin grafting increased venous ulcer healing.[98]

Wound Dressings

Dressings are selected based on the characteristics of the wound at any given point during the healing process.[89] Wounds that produce exudate need an absorptive dressing (hydrocolloid, foam, alginate, hydrofiber) and dry wounds need a dressing that provides hydration (hydrogel). The type of dressing used will change as the wound goes through the phases of healing. Wound dressings that inhibit the loss of water vapor from the wound, thereby creating a moist environment, promote wound healing. Moist wound environments promote epithelialization and healing. Besides creating a moist wound environment, ideal dressings perform the following functions: remove excess exudates and toxic components, allow gaseous exchange, provide thermal insulation, and protect against secondary infection. A wide variety of wound dressings is available.[99-102] Some of the unique features of each are described below.

The following dressings may be used on chronic or acute wounds depending on the nature of the wound.

- Low or nonadherent dressings are inexpensive and allow wound exudate to pass through into a secondary dressing while helping to maintain a moist wound environment. These dressings are specially designed to reduce adherence to the wound bed. Nonadherent dressings are made from open weave cloth soaked in paraffin, textiles, or multilayered or perforated plastic films. This type of dressing is suitable for flat, shallow wounds with low exudate such as a venous leg ulcer.
- Hydrocolloid dressings are composed of adhesive, absorbent, and elastomeric components. Carboxymethylcellulose is the most common absorptive ingredient. They are permeable to moisture vapor, but not to water. Additionally, they facilitate autolytic débridement, are self-adhesive, mold well, provide light-to-moderate exudate absorption, and can be left in place for several days, minimizing skin trauma and disruption of the healing process. They are intended for use on light-to-moderate exuding, acute or chronic partial- or full-thickness wounds but are not intended for use on infected wounds. Upon sustained contact with wound fluid, the hydrocolloid forms a gel.
- Foam dressings vary widely in composition and construction. They consist of a polymer, often polyurethane, with small, open cells that are able to hold fluids. Some varieties of foam dressings have a waterproof film covering the top surface and may or may not have an adhesive coating on the wound contact side or border. Foams are permeable to water and gas, and are able to absorb light to heavy exudate. This type of dressing is frequently used under compression stockings in patients with venous leg ulcers.

- Film dressings consist of a single, thin transparent sheet of polyurethane coated on one side with an adhesive. The sheet is permeable to gases and water vapor but impermeable to wound fluids. Film dressings retain moisture, are impermeable to bacteria and other contaminants, allow wound observation, and do not require a secondary dressing. Excessive fluid buildup may break the adhesive seal and allow leakage. Film dressings are intended for superficial wounds with little exudate and are commonly used as a secondary dressing to attach a primary absorbent dressing. The dressing may remain in place for up to seven days if excessive fluid does not accumulate. Film dressings have been used extensively to treat split-thickness graft donor sites.
- Alginate dressings are made from calcium or calcium-sodium salts of natural polysaccharides derived from brown seaweed. When the alginate material comes into contact with sodium-rich wound exudates, an ion exchange takes place and produces a hydrophilic gel. This hydrophilic gel is capable of absorbing up to 20 times its weight and does not adhere to the wound. This dressing can remain in place for about seven days if enough exudate is present to prevent drying. This category of dressing is best suited for moist, moderate-to-heavy exuding wounds. Alginate dressings require a secondary dressing, such as a film dressing, to hold them in place and to prevent the alginate from drying out.
- Hydrofiber dressing is composed of sodium carboxymethylcellulose fibers.[103] The fibers maintain a moist wound environment by absorbing large amounts of exudate and forming a gel. This dressing is not intended for lightly exuding wounds. A secondary dressing is required.
- Hydrogel sheets are three-dimensional networks of cross-linked hydrophilic polymers. Their high water content provides moisture to the wound, but these dressings can absorb small-to-large amounts of fluid, depending on their composition. Depending on wound exudate levels, hydrogels may require more frequent dressing changes, every 1–3 days, compared with other synthetic dressings. Hydrogel sheets can be used on most wound types but may not be effective on heavily exuding wounds. The gel may also contain additional ingredients such as collagens, alginate, or complex carbohydrates. Amorphous hydrogels can donate moisture to a dry wound with eschar and facilitate autolytic débridement in necrotic wounds. A second dressing may be used to retain the gel in shallow wounds.

Growth Factors

Growth factors have the potential to be important options when treating wounds. Becaplermin (Regranex gel, Ortho-McNeil Pharmaceutical, Inc., Titusville, NJ, USA) contains human recombinant PDGF and has been approved by FDA for treating diabetic neuropathic ulcers with adequate peripheral circulation.[104] Four randomized controlled trials have demonstrated that becaplermin is more effective than placebo in promoting diabetic foot ulcer healing. In these studies becaplermin had a complete healing rate of 50 percent with a mean of 14 weeks to healing compared with 36 percent at 20 weeks for placebo. However, becaplermin's clinical experience outside these RCTs has not been as positive. In everyday clinical situations the healing rates have been reported to be closer to 33 percent for becaplermin and 26 percent for controls. The high cost of the drug coupled with the less-than-expected healing rates may explain why becaplermin has not been more widely used.

U.S. Food and Drug Administration Regulations Governing Skin Substitute Products

The U.S. Food and Drug Administration (FDA) does not refer to any product or class of products as "skin substitutes." However, products commonly described as "skin substitutes" are regulated by FDA under one of the four categories described below depending on the origin and composition of the product.

Human Cells, Tissues, and Cellular and Tissue-Based Products

Cells and tissues taken from human donors and transplanted to a recipient are regulated under PHS 361 [21 CFR 1270 & 1271]. This regulation describes the rules concerning the use of HCT/Ps for human medical purposes. The final rule, 21 CFR Part 1271, became effective on April 4, 2001, for human tissues intended for transplantation that are regulated under section 361 of the PHS Act and 21 CFR Part 1270. HCT/Ps are regulated by the Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Establishments producing HCT/Ps must register with FDA and list their HCT/Ps. HCT/Ps establishments are not required to demonstrate the safety or effectiveness of their products and FDA does not evaluate the safety or effectiveness of these products.

As defined in 21 CFR Part 1271, HCT/Ps "means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue." Cells, tissues, and organs derived from animals other than humans are not considered HCT/Ps. HCT/Ps are minimally manipulated and are intended for homologous use only, meaning they are used for "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/Ps that performs the same basic function or functions in the recipient as in the donor." According to the regulations an "HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous use; is for allogeneic use in a first-degree or second-degree blood relative; or is for reproductive use."[105]

Premarket Approval

Premarket approval (PMA) by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. FDA has three regulatory classes for medical devices, based on the degree of control necessary to assure that the devices are safe and effective. A Class III device "supports or sustains human life, are of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury. Insufficient information exists on a Class III device so that performance standards (Class II) or general controls (Class I) cannot provide reasonable assurance that the device is safe and effective for its intended use." Before Class III devices can be marketed, they must have an

approved PMA application. “Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.”[7]

According to FDA documents a “Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device.” The application must contain “valid clinical information and scientific analysis on sound scientific reasoning” with “sufficient valid scientific evidence” to allow FDA to determine that the device is “safe and effective for its intended use(s).” PMAs are typically reviewed by an FDA advisory committee that provides FDA with recommendations on whether to approve the application.[7] Therefore, wound care products regulated under the PMA process will require evidence that they promote wound healing before they are approved for marketing.

510(k) Submissions

According to FDA documents a “510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent (SE), to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. A legally marketed device, as described in 21 CFR 807.92(a)(3), is a device that was legally marketed prior to May 28, 1976 (preamendments device), for which a PMA is not required, or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process. The legally marketed device(s) to which equivalence is drawn is commonly known as the ‘predicate.’ Although devices recently cleared under 510(k) are often selected as the predicate to which equivalence is claimed, any legally marketed device may be used as a predicate.”[8]

Unlike PMA, 510(k) confers reasonable assurance of safety and effectiveness via demonstration of substantial equivalence to a legally marketed device that does not require premarket approval. Substantial equivalence means that the new device is as safe and effective as the predicate device(s). Section 510(k) requires the manufacturer of a new device to submit a premarket notification report containing information that allows FDA to determine whether the new device is “substantially equivalent”' to a legally marketed device that does not require premarket approval. Unless exempted from premarket notification requirements, the new device may not be marketed, under section 510(k), unless it receives a substantial equivalence order from FDA or an order reclassifying the device into class I or an exempt class II device. According to FDA documents “Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.” Submission of new clinical data showing equivalence is usually not part of the application.[8] Therefore, wound care products regulated under the 510(k) process will not typically require clinical evidence to establish effectiveness in wound healing, as compared with products regulated under the PMA process in which substantial clinical evidence is always required.

Humanitarian Device Exemption

According to FDA documents, “An Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is

manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer`s research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

"To obtain approval for an HUD, a humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market." HDE approval is based on evidence of probable benefit in a disease population occurring at a frequency of less than 4,000 patients per year in the United States.[6]

Methods

The Center for Medicare Management of the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Evidence-based Practice Center: ECRI Institute EPC (Contract Number: HHSA 290-2007-10063). The purpose of this review is to provide information to CMS for consideration in HCPCS coding decisions. The review will facilitate CMS' evaluation of HCPCS coding for skin substitutes by providing CMS with relevant studies and information for consideration of coding changes.

AHRQ's EPC Program partners with private and public organizations to perform scientific reviews of a variety of topics. The process of systematic review as practiced by the EPC Program follows specific prescribed steps:

1. The investigators start with formulated "key" questions. These questions test hypotheses and are structured using the PICO framework: patients, intervention of interest, comparator, and outcomes. EPCs are encouraged to focus on outcomes that are relevant and important to patients (patient-oriented outcomes). The framework is depicted visually in the "analytic framework" that the EPC program uses to show the relationship between the key questions and the outcomes used to address these questions. (See Figure 3.)
2. Inclusion and exclusion criteria for studies to be used in the review are determined based on the specific key questions. Criteria may vary for each question in the review.
3. Next, an objective and comprehensive search of the medical literature and gray literature, (i.e., reports, monographs and studies produced by government agencies, educational facilities and corporations that do not appear in the peer-reviewed literature) is conducted. The reference lists of included studies are examined for any studies not identified by electronic searches.
4. Studies are compared with the inclusion criteria developed before examining the evidence, and those included in the review are then critically appraised, noting features of the design and conduct of the studies that create potential for bias. Risk of bias, in this context, is the extent to which the design and conduct of a single study "protect against all bias in the estimate of treatment effect."[9] Studies with a low potential for bias are typically described as being of "high quality," whereas those with high potential for bias are described as being of "low" or "poor" quality, and those of moderate quality as having intermediate potential for bias. The degree to which a study protects against bias is referred to as "internal validity." Following this appraisal, data are extracted from the included studies and analyzed or summarized as appropriate.

The following is a detailed explanation of the methods followed in this review.

Key Questions

1. What are the U.S. Food and Drug Administration (FDA)-regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361[21 CFR 1270 & 1271]?
    a. PMA: Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.
    b. 510(k): A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to PMA.
    c. PHS 361 [21 CFR 1270 & 1271]: Human cells, tissues, and cellular and tissue-based products. Creates a unified registration and listing system for establishments that manufacture HCT/Ps and establishes donor eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/Ps.
2. For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers), are skin substitutes more effective than other wound care options (usual or standard care, or usual or standard care plus synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures:
    a. Percentage of completely closed/healed wounds (skin closure with complete re-epithelialization without drainage or dressing requirements)
    b. Time to complete wound closure
    c. Wound reoccurrence
    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
3. What type and frequency of adverse events are reported in the clinical literature for each of the FDA-regulated skin substitute products?

Analytic Framework

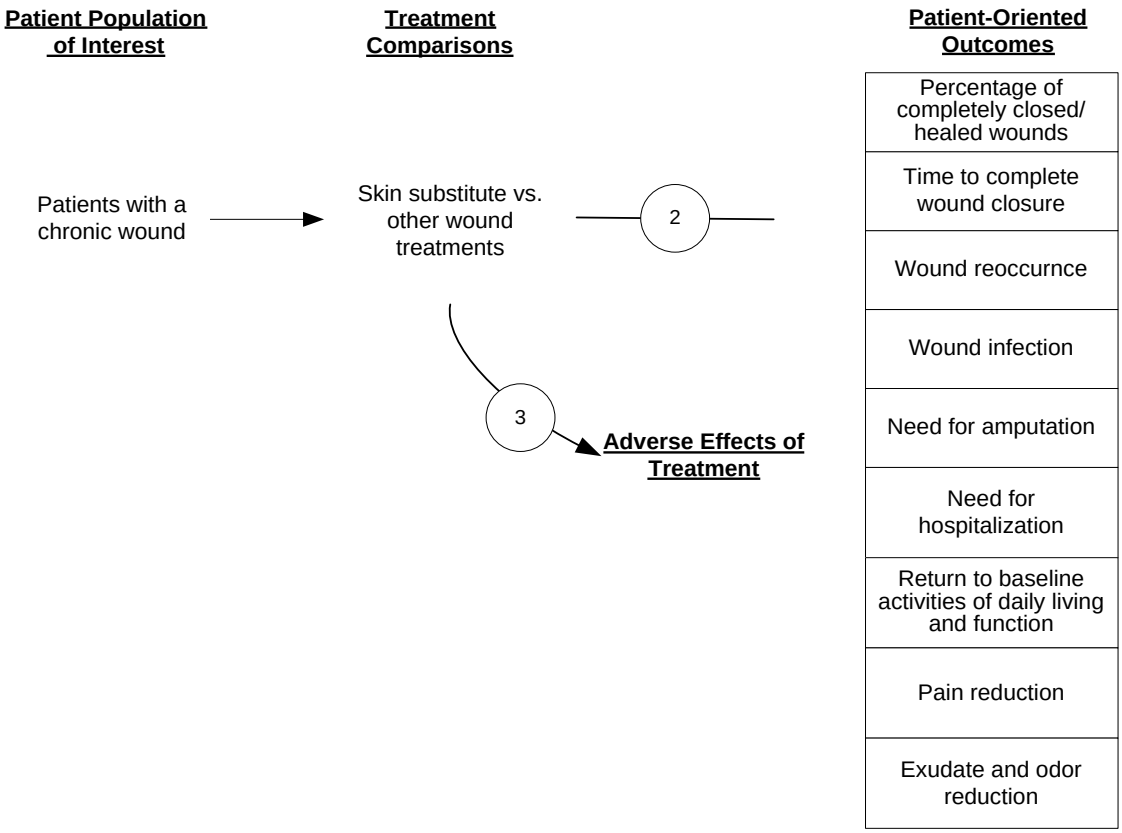
The analytic framework below (Figure 3) graphically depicts the events that individuals with chronic wounds experience as they are treated with a skin substitute. This figure portrays the pathway of events that patients experience, starting from when they are first identified (the far left of the figure), to the treatments they receive, and to patient-oriented outcomes. As such, patients in the population of interest are identified and "enter" the pathway at the left of the figure. Key Questions 2 and 3 are represented in the framework by a circled number. Key Question 1 is not related to treatment and outcomes and is not depicted in the figure.

According to a guidance document prepared by FDA in 2006, clinical outcomes associated with the use of a wound-treatment product or device can be broadly grouped into two categories—improved wound healing and improved wound care.[10] A number of outcomes or endpoints fall into these two categories. According to the FDA document, "complete wound closure of a chronic nonhealing wound is one of the most objective and clinically meaningful wound healing endpoints" and "complete wound closure is defined as skin reepithelialization without drainage or dressing requirements at two consecutive study visits 2 weeks apart."[10] Wound closure as an outcome measure has also been emphasized in several other wound care publications.[2,106,107]We therefore selected complete wound healing as the primary patient-centered outcome for this report. We did not require that studies report confirmation of wound closure at two consecutive visits 2 weeks apart for inclusion in this report but tabled information on wound reassessment along with other study design and conduct information in Table 27 to Table 31. A single assessment of wound closure at a single followup period would only allow for determination of minimal healing as described by Lazarus et al.[2] We are therefore also interested in noting how many studies used reassessment of wound closure and at what time periods.

FDA regards the parameter of partial wound healing as insufficient as a primary endpoint "because the clinical benefit of incremental wound size changes has not been established."[10] We therefore did not consider this a primary outcome for this report.

Improvements in wound care can potentially reduce the occurrence of conditions, such as infection, that can interfere with proper wound healing.[10] Thus, measuring the impact of skin substitutes on the occurrence or healing of infections, as well as its impact on the incidence of other problems, such as sepsis, edema, or amputation, is important.

Figure 3. Analytic framework



Inclusion Criteria

We used the following criteria to determine which studies identified by our searches would be included in our analysis. These criteria were developed before any review of the clinical literature. Inclusion and exclusion criteria were developed to specify the types of studies appropriate for addressing Key Questions 2 and 3.

Population

1. *Study must have enrolled 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.*

   Studies of animals are outside the scope of this assessment.

2. *Results for patients with different wound etiologies (diabetic ulcers, pressure wounds, leg ulcers) must be reported separately.*

   Percentage healed, time to heal, and the frequency and characteristics of adverse events can be expected to vary depending on the underlying cause of the wound.

Intervention

3. *Study must evaluate the efficacy of a commercially available skin substitute product regulated by FDA.*

Study Design

4. *Studies must be RCTs.*

   Systematically reviewing all of the clinical research for all of these products is beyond the scope of this report. We sought to determine the number of RCTs examining these products and to assess the efficacy of skin substitutes under the conditions examined in these trials. Properly conducted RCTs are considered the best study design for determining the actual efficacy of a medical intervention. The Panel On Wound Care Evidence-based Research (POWER) has suggested that RCTs are the preferred approach for studying biologically based products because these products "are likely to need more sophisticated study designs for acceptability because of issues of unpredictability, possibility of adverse events, and demonstration of efficacy under controlled situations."[108]

5. *Studies must have enrolled at least 10 patients per study arm.*

   The results of smaller studies and especially case reports are often not applicable to the general population.

Outcomes

6. *Study must have reported on at least one of the outcomes listed in Key Question 2.*

7. *The reliability and validity of all instruments measuring relevant outcomes, such as activities of daily and function or pain, must have been addressed in the published literature.*

   However, if a study did not use a validated instrument, the entire study was not necessarily excluded for all outcomes—only its data from instruments in which the psychometric properties were not reported in the published literature were excluded.
8. *For all outcomes, we considered only time points for which at least 50 percent of the enrolled participants contributed data.*

Publication Type

9. *Study must have been published in English.*

   Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our review.
10. *Study was reported as a full-length, peer-reviewed article.*

    Published abstracts and letters alone do not include sufficient details about experimental methods to permit verification and evaluation of study design.[109,110]
11. *When several sequential reports from the same study center were available, we included outcome data from only the largest, most recent or most complete report.*

    However, we used relevant data from earlier and smaller reports if the report presented pertinent data not presented in the larger, more recent report. This criterion prevents double-counting of patients.

Table 20 in Appendix A lists the reasons for exclusion for all excluded studies and retrieved documents.

Search Strategy

To identify relevant information on the benefits and harms of skin substitutes, we employed the following search strategies:

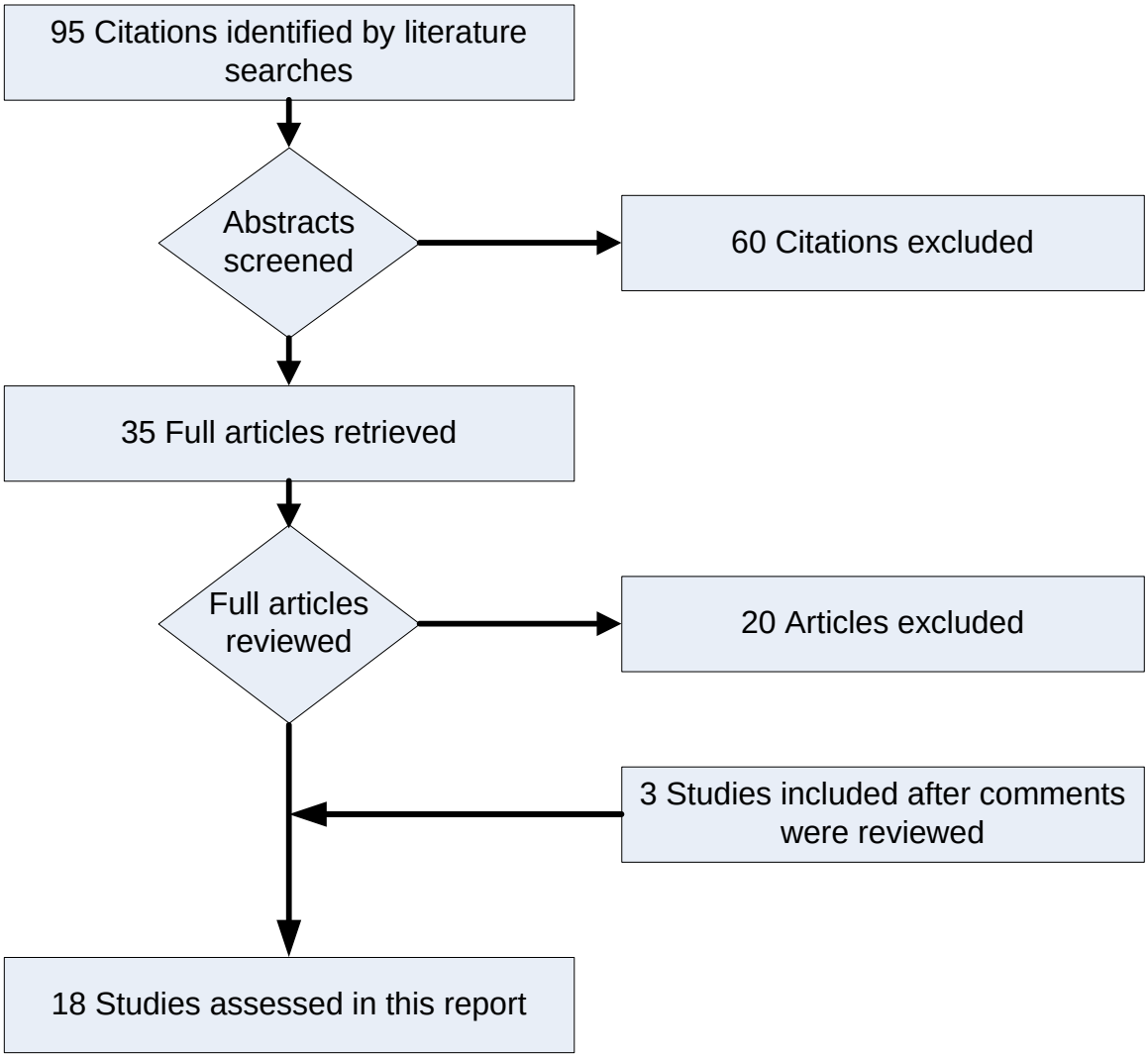
- Systematic search of 13 external and internal electronic databases, including CINAHL, Embase, and Medline from 1950 (Medline)/1980 (Embase)/1982 (CINAHL) to the present for fully published, primary, clinical studies. A detailed search strategy and a full explanation of our electronic database search are presented in Appendix A.
- Systematic search of the following databases unlimited by date for secondary publications (e.g., systematic reviews, Health Technology Assessments): The Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment and Database (HTA).
- Search for additional published and unpublished studies, which included the following steps:
  - Manual search of bibliographies listed in fully published studies
  - Search and written inquiry to regulatory agencies, including FDA and CMS

- Search of www.ClinicalTrials.gov and www.controlled-trials.com for ongoing clinical trials

- Publications were also suggested for inclusion by individuals who commented on the draft report.

Figure 4 is an attrition diagram that provides a visualization of the disposition of materials as they were evaluated for possible inclusion in the report.

Figure 4. Disposition of documents identified by searches



The most common reasons for exclusion of retrieved articles (see Table 20) were the following:

- Study was not a randomized controlled trial.
- Product is not commercially available in the United States.
- Study was a narrative review.
- Publication duplicated an already included study.

Identified articles excluded at the abstract level are listed in Table 21.

Study Risk-of-Bias Assessment

After determining which of the publications identified in our searches met our inclusion criteria, we assessed the potential for bias in these studies. Judging study quality by assessing the potential for bias is the first part of grading the strength of an evidence base according to the system used by the EPC program and detailed in the publication by Viswanathan et al.[9] In this system, the risk-of-bias assessment tool is a set of questions that explicitly evaluates the risk of bias. The questions are geared specifically for the field of research being assessed in the review. The potential for bias in each study included in this report was assessed using a risk-of-bias assessment instrument developed by ECRI Institute based on the criteria described by Viswanathan et al.[9] and modified specifically for comparative studies of wound care interventions.

Viswanathan et al.[9] consider "risk of bias to refer to the extent to which a single study's design and conduct protect against all bias in the estimate of effect." Bias is systematic error–as opposed to random error–introduced into a study that leads to an underestimation or an overestimation of the true effect of an intervention.[111,112] In well-constructed studies, biases are minimized by appropriate study design and conduct, and changes in outcomes and differences in outcomes between groups are definitively attributed to the treatment of interest. For these reasons, high-quality studies are those in which study design and conduct eliminate or greatly reduce the potential for bias. The degree to which a study protects against bias is referred to as "internal validity."

The potential for bias in any study may be assessed by asking specific questions about the design and conduct of the study that limits the potential for selection, performance, attrition, and detection biases.[9] Selection bias refers to "systematic differences between baseline characteristics of the groups that arise from self-selection of treatments, physician-directed selection of treatments, or association of treatment assignments with demographic, clinical, or social characteristics."[9] Proper randomization and concealment of allocation are intended to limit selection bias. Performance bias refers to "systematic differences in the care provided to participants and protocol deviation."[9] Differences in care include use of the experimental intervention in the control group and unbalanced use of additional interventions. Attrition bias refers to "systematic differences in the loss of participants from the study and how they were accounted for in the results (e.g., incomplete followup, differential attrition)."[9] Patients who drop out of a study or are lost to followup may be "systematically different from those who remain in the study"[9] and the even distribution of baseline characteristics that was achieved through randomization may be lost if attrition is different between experimental and control groups. Detection bias refers to "systematic differences in outcomes assessment among groups being compared."[9] Detection bias can occur because of inadequate assessor blinding and faulty measurement techniques. "Blinding of outcome assessors, especially with subjective outcome assessments,"[9] and use of "valid and reliable measures"[9] are intended to limit detection bias.

We assessed risk of bias separately for each outcome and each time point in each study. Each time point was assessed separately because longer followup often results in attrition or right-censoring, which may yield patients with characteristics that are different from the originally enrolled patients and also may introduce a systematic difference between the groups being compared. For this report, complete wound healing was the most important outcome to consider and the risk-of-bias assessment of this outcome is reported in Table 22 to Table 26.

We assessed risk-of-bias using the questions listed below. These questions address various areas of study design and conduct that influence the potential for bias in individual studies. The questions were modified to reflect important study design and conduct issues in wound care. Each of these questions was answered as "Yes," "No," or "Not Reported." A "Yes" answer means that the study reported using this particular aspect of study design or conduct. A "No" answer means that the study reported that this particular aspect of study design or conduct was not used. A "Not Reported" answer means the publication did not provide sufficient information to determine whether the study did or did not use this particular aspect of study design or conduct. The questions are phrased so that a "Yes" answer reflects a lower risk-of-bias and a "No" reflects a higher risk-of-bias.

Risk-of-Bias Questions

Selection Bias

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

Detection Bias

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

Performance Bias

7. Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?

Attrition Bias

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

We categorized the risk-of-bias for each outcome/time point in each study as "Low," "Medium," or "High" using the following method:

- Low potential for risk: No more than three "No" answers and Risk-of-Bias Question 7 (ancillary wound treatment) must be answered "Yes."
- Moderate potential for risk: More than three "No" answers and Risk-of-Bias Question 7 (ancillary wound treatment) must be answered "Yes."
- High potential for risk: Risk-of-Bias Question 7 (ancillary wound treatment) is answered "No."
- Studies in which most of the questions can only be answered with "Not Reported" were considered to have an unclear risk-of-bias.

Explanation of Risk-of-Bias Questions

Selection Bias

It is hoped that appropriate methods of randomization ensure that each study participant has the same chance of receiving each intervention.[111,112] Appropriate randomization can be accomplished using computer software or a table of random numbers to assign patients to groups. Allocations by date of birth, date of admission, hospital numbers, or alternating patients are not appropriate randomization methods.

Concealment of group allocation prevents foreknowledge of group assignment in an RCT. This is distinct from patient or assessor blinding. The allocation process should be impervious to any influence by the individual making the allocation. Someone who is not responsible for recruiting participants, such as the hospital pharmacy or a central office should manage the randomization process and generate a random allocation sequence. Allocation using sequentially numbered, opaque, sealed envelopes avoids selection bias when a patient is assigned to treatment.

Differences in wound size, wound duration, or comorbidities between treatment arms have the potential to bias study results and mask true treatment effects. Proper random assignment of enrolled patients should ensure that these parameters are evenly distributed across study arms. Risk-of-Bias Questions 3, 4, and 5 are also tests of the randomization process.

Detection Bias

The FDA guidance document on chronic wound suggests that "blinding of subjects and investigators to the assigned treatment reduces bias and should be employed when feasible."[10] Other organizations interested in improving the quality of evidence in wound management have also suggested that blinding be a part of any study of chronic wounds. POWER considers blinding of "patients, clinical assessment, and analysts where possible" as part of a minimum set of criteria for RCTs.[108] The European Wound Management Association (EWMA) believes that "outcome assessors should be blinded to interventions whenever possible."[106] The Center for Medical Technology Policy (CMTP) also recommends blinding the individual assessing wound healing outcomes.[113] Blinding of patients to wound care treatment is not always possible because of visible differences in the treatment devices, dressings, or wound care routine. Therefore, we did not propose using a question related to blinding of patients as to their treatment. FDA has suggested that "in these situations, blinded assessment by a third-party evaluator should be considered."[10] Blinding of the individuals recording data on complete wound healing, wound size, and other outcomes should be possible and greatly minimizes the potential that results will be affected by the evaluator's expectations.[106] Therefore, the wound assessor should be blinded to patient treatment (Risk-of-Bias Question 6). As mentioned earlier, FDA considers complete wound closure to be "one of the most objective" wound healing endpoints.[10] Objective as opposed to subjective endpoints provide less opportunity for bias and "in general, blinding becomes less important to reduce observer bias as the outcomes become less subjective."[114]

Computerized planimetry uses a digital image and computer software to outline the margins of a wound and determine the enclosed area.[115] The main purpose of computerized planimetry is to accurately assess the surface area of a wound, not to determine if complete wound closure has occurred.[115-118] FDA has suggested that photographic methods should be standardized for lighting, distance, exposure, and camera type.[10] Little et al. have noted the need for accuracy,

validity, reliability, consistency, and reproducibility in wound measurement techniques.[119] As part of this report we have noted the methods used to assess wound size and condition at enrollment and during the course of a study. Because our primary outcome of interest was complete wound healing, we did not consider the use of computerized planimetry a substitute for assessor blinding.

Performance Bias

Performance bias is a "substantial challenge to avoid" when evaluating wound treatments and is prevented when all patients "receive exactly the same treatment with the exception of the study intervention."[106] The FDA guidance document also emphasizes that "good standard care procedures in a wound-treatment product trial are a prerequisite for assessing safety and efficacy of a product."[10] Wound care involves many steps including debridement to remove necrotic tissue from the wound, establishing a moist wound environment, controlling infection, and relieving pain. In any study of wound interventions with a low risk-of-bias, patients in both the experimental and control groups must receive comparable treatments outside of the experimental intervention (Risk-of-Bias Question 7). Such differences in treatment protocols between groups have the potential to introduce confounding factors that may mask the true treatment effect.

We consider identical treatment protocols an essential element in a low potential for risk study of wound treatments. Therefore, in our rating system for this report, we assigned a high risk-of-bias to a study if this criterion was not met or was not reported.

Attrition Bias

Assessment Questions 8 and 9 test whether patient attrition could potentially alter the patient characteristics sufficiently enough to bias study results.

Other Potential Biases

Funding of studies by a device manufacturer either directly or through support or employment of study authors has the potential to bias study results especially if important patient-oriented outcomes are not reported in a publication. However, all of the studies included in this review reported complete wound healing as their primary outcome. Therefore, we have not considered funding source as a potential source of bias in this assessment.

Strength of the Evidence Base

Evidence-based Practice Centers judge the strength of an evidence base using the principles described by Owens et al.[111] Risk-of-bias, consistency, directness, and precision are domains assessed by this process to judge the overall strength of an evidence base. Determining the risk-of-bias in the individual studies in an evidence base (as described above) is the first step in determining the overall strength of an evidence base. An evidence base consisting of studies with a high risk-of-bias implies a low strength of evidence. Consistency looks at "the degree to which reported effect sizes from included studies appear to have the same direction of effect." Directness looks at "whether the evidence links the interventions directly to the health outcomes" and that the most important health outcomes are assessed. The use of intermediate or surrogate outcomes would be considered indirect evidence. Precision is "the degree of certainty surrounding an effect estimate" for each outcome and "a precise estimate should enable decision makers to draw conclusions about whether one treatment is, clinically speaking, inferior,

equivalent (neither inferior not superior) or superior to another. For this report precision was judged by the statistical significance of risk differences for complete wound healing for a given comparison, as any improvement in rates of complete wound healing was considered clinically important. Individual studies with significant differences in rates of complete wound healing were considered precise. When meta-analysis was possible, the estimate was considered precise when the confidence interval was narrow enough to determine the direction of effect.

The overall strength of evidence for each outcome takes into account the assessments made for each of the domains described above and is graded as high, moderate, low, or insufficient. High signifies "high confidence that the evidence reflects the true effect" and no additional research is likely to change the "confidence in the estimate of effect." Moderate signifies "moderate confidence that the evidence reflects the true effect" and future research may change the "confidence in the estimate of effect and may change the estimate." Low signifies that we have limited confidence that the estimate of effect lies close to the true effect for this outcome, the body of evidence has major or numerous deficiencies (or both), and we believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. Applicability is a separate consideration when judging the strength of an evidence base and is determined after the domains discussed above. Applicability is judged from the standpoint of clinical decision makers and how relevant the evidence is to them. The evidence must be evaluated to determine if the patient populations, settings, diseases or conditions, interventions, comparators, and outcomes are most relevant to their decisions. Thus, the evidence is assessed for its ability to reflect "real world" situations. The analytic framework serves to indicate the important patient populations, interventions, comparators, and outcomes important to applicability.

Data Synthesis

This research synthesis is primarily qualitative in nature. We calculated absolute risk differences and relative risks (RR) with 95% confidence intervals for the outcome of complete wound healing at 12 weeks (where possible, or if not, the closest time point provided) for individual studies. We calculated odds ratios (OR) with 95% confidence intervals for individual studies where meta-analyses were possible, and calculated a summary OR using a random effects model. Studies were only combined using meta-analysis when populations and interventions were similar. Statistical heterogeneity was examined using I^2, but the number of studies in the comparisons limited our confidence in measures of heterogeneity. No meta-regressions or subgroup analyses were anticipated or performed given the limited number of studies.

Results

Key Question 1: What are the U.S. Food and Drug Administration (FDA)-regulated skin substitutes that fall under each of the following pathways: PMA, 510(k), PHS 361 [21 CFR 1270 & 1271]?

Definitions:

a. PMA: Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.
b. 510(k): A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to PMA.
c. PHS 361 [21 CFR 1270 & 1271]: Human cells, tissues, and cellular and tissue-based products. Creates a unified registration and listing system for establishments that manufacture HCT/Ps and establishes donor eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/Ps.

This section of the report addresses which skin substitute products are currently regulated by FDA for use within the United States. We note that FDA does not refer to any product or class of products as "skin substitutes," and we are not proposing an official classification system. Key Question 1 does not address clinical effectiveness or efficacy. Our searches identified a number of products that are intended as skin substitutes but may also be used for other medical purposes. Based on FDA regulations that govern each product we identified and the origin and composition of the products, skin substitutes can be organized into four groups: human-derived products regulated as HCT/Ps (see Table 6), human- and human/animal-derived products regulated through PMA or HDE (see Table 7), animal-derived products regulated under the 510(k) process (see Table 8), and synthetic products regulated under the 510(k) process (see Table 9). In total our searches identified 57 skin substitute products.

Human tissue can be obtained from human donors, processed, and used exactly in the same role in the recipient—skin for skin, tendon for tendon, bone for bone. These uses are regulated as human tissue intended for transplantation (HCT/Ps) as long as the proposed clinical use and manufacturing methods are consistent with definitions of "Homologous Use" and "Minimal Manipulation" cited in 21 CFR 1271. Human tissue and cells may also be used as a source of cells for culturing to produce cellular-derived material for wound healing. These products may be regulated under the Biologics License Application (BLA) (under the PHS Act) or PMA/HDE (under the FD&C Act), depending on their composition and primary mode of action.

A number of medical products for treating wounds are derived from animal sources. Porcine and ovine tissues and skin are processed into sheets for use as skin substitutes. Bovine fetal tissue is a source of skin cells that are grown in culture to produce skin substitutes. Wound care products produced from these sources may be regulated under the 510(k) process if there is an appropriate predicate device with an equivalent composition and Intended Use and the proposed product does not raise any different types of safety or effectiveness questions. When a product does not meet these criteria, it may be reviewed in BLA or PMA/HDE applications, depending on the composition and primary mode of action.

Some skin substitute products are made from synthetic material that mimics skin properties. Similar to products derived from animal sources, products derived from synthetic material may be regulated under the 510(k) process if there is an appropriate predicate device with an equivalent composition and Intended Use and the proposed product does not raise any different types of safety or effectiveness questions. When a product does not meet these criteria, it may be reviewed in BLA or PMA/HDE applications, depending on the composition and primary mode of action.

Wound care products regulated under PMA are indicated for treating a subset of chronic wounds, those wounds with a duration greater than 30 days that have not adequately responded to standard wound care. The indications for 510(k) are not as strict. These products are indicated for managing chronic wounds and no restrictions are put on wound duration or prior treatments. Wound dressings cleared under the 510(k) process (or Class I exempt products) are considered to function by providing a moist wound healing environment. Since a moist wound environment is generally considered essential for the proper healing of most wound types these products are commercially distributed with a broad indication for use: "partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds." This wording appears in most of the products regulated under the 510(k) process (see Table 8). When seeking claims beyond providing a moist wound healing environment, a legally marketed predicate device may not exist and clearance through the 510(k) process may not be possible. Therefore, determining whether a PMA or 510(k) application is appropriate is based upon both product composition and claims of product performance.

The information in Table 7 indicates that skin substitute products using human fibroblasts and keratinocytes (derived from neonatal foreskins) and combined with other acellular components are regulated under the PMA process and received FDA product code MGR (dressing, wound and burn, interactive). For these products the term "treatment" is used in the indications for use with chronic wounds. Each of the entries in Table 7 is actually a combination of living human cells and another component (bovine collagen in Apligraf and polyglactin mesh in Dermagraft). FDA considers these Combination Products, a combination of device and biological components into a single entity, and they are regulated as a medical device. Besides providing a biologic wound covering, these products also contain human cells capable of producing human growth factors and cytokines that may stimulate angiogenesis, tissue expansion, and re-epithelialization during the healing process.[5] Thus, these products have the potential to be interactive with the wound bed and assist in the wound healing process.

The information in Table 8 and Table 9 indicates that skin substitute products considered Class II devices and regulated under the 510(k) process are included in FDA product codes KGN (dressing, wound, collagen), FRO (dressing, wound, drug), and MGP (dressing, wound and burn, occlusive) and use the term "management" of wounds in the indications for use on chronic wounds. These products use animal tissue collagen or synthetic material to create an extracellular matrix that acts as a wound covering and scaffold for tissue invasion and regrowth. They do not contain human cells and, therefore, do not have a natural source of growth factors or cytokines involved in initiating the wound healing process. The actual extent to which any one growth factor or cytokine is essential for wound repair has not been determined.[5]

We did identify one exception to the above scheme. EndoForm Dermal Template derived from ovine forestomach, and included in FDA product code KGN, is an exception to the use of

the term “management” of wounds and instead uses the term “treatment” in the indications for use (see Table 8). The wording of the indications for use of EndoForm is almost identical to the wording used for Integra, MatriStem, Oasis, Primatrix, and Hyalomatrix but “treatment” is substituted for “management.” The reason for this difference is unclear.

Human-Derived Products Regulated Solely Under the 21 CFR 1271

AlloDerm® Regenerative Tissue Matrix (LifeCell Corp., a KCI Company)

AlloDerm Regenerative Tissue Matrix is an acellular human dermis product. Donated human skin tissue is supplied by US American Association of Tissue Banks (AATB)-compliant tissue banks and processed into the dermis product. During processing, cells are removed and the product is freeze-dried. The LifeCell Web site promotes AlloDerm for hernia and breast reconstruction. According to packaging instructions for use, “AlloDerm is to be used for repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument.”[120] LifeCell Corp. (Branchburg, NJ, USA) is registered with FDA as an establishment producing HCT/Ps.

Allopatch HD™ (Musculoskeletal Transplant Foundation Sports Medicine)

Allopatch HD is an acellular human dermis designed to provide an extracellular matrix scaffold for tendon augmentation.[121] The Musculoskeletal Transplant Foundation (Edison, NJ, USA) is registered with FDA as an establishment producing HCT/Ps.

Alloskin™ (AlloSource)

Alloskin is a specialty allograft derived from epidermal and dermal cadaveric tissue and designed for wound care. AlloSource (Centennial, CO, USA) has several sites throughout the United States and is registered with FDA as an establishment producing HCT/Ps.[122]

Cymetra® Micronized AlloDerm (LifeCell Corp., a KCI Company)

Cymetra is an injectable form of AlloDerm Regenerative Tissue Matrix. Cymetra is micronized particulate form of AlloDerm that still contains the collagens, elastin, proteins, and proteoglycans that are present in AlloDerm.[123] LifeCell Corp. (Branchburg, NJ, USA) is registered with FDA as an establishment producing HCT/Ps.

DermaCell® (LifeNet Health, Inc.)

DermaCell is a decellularized human dermis allograft designed for reconstruction surgical applications including chronic nonhealing wounds. DermaCell is provided by the Skin and Wound Allograft Institute, which is a wholly owned subsidiary of LifeNet Health. The company believes its MatraCell processing technology creates a readily available, extracellular matrix that then provides a collagen scaffold to support cell ingrowth.[124] LifeNet Health, Inc. (Virginia Beach, VA, USA), is registered with FDA as an establishment producing HCT/Ps.

Flex HD® (Ethicon and Musculoskeletal Transplant Foundation)

Flex HD is an acellular hydrated dermis derived from donated human allograft skin. The skin is processed to remove the epidermis and dermal cells while preserving the acellular matrix of the dermis. The Musculoskeletal Transplant Foundation (MTF) acquires and processes the tissue. MTF has multiple sites throughout the United States.[125] Ethicon sells Flex HD for hernia repair and breast reconstruction.[126] The Musculoskeletal Transplant Foundation (Edison, NJ, USA) is registered with FDA as an establishment producing HCT/Ps.

GammaGraft® (Promethean LifeSciences, Inc.)

GammaGraft is an irradiated cadaveric human skin allograft designed to be a temporary graft for treating wounds including venous stasis ulcers, diabetic foot ulcers, and full-thickness wounds. Irradiating the graft preserves and sterilizes the tissue. The graft is stored in an aluminum foil package and preserved in a penicillin/gentamycin solution. To use GammaGraft the wound area is débrided, the graft is placed and a nonadherent dressing is applied, followed by a gauze dressing.[127] Promethean LifeSciences, Inc. (Pittsburgh, PA, USA), is registered with FDA as an establishment producing HCT/Ps.

Graftjacket® Regenerative Tissue Matrix and Graftjacket® Xpress (Manufactured by LifeCell Corp., Licensed to Wright Medical Technology, Inc., and Licensed to KCI)

Graftjacket Regenerative Tissue Matrix is a processed human dermal matrix designed to provide a scaffold for wound repair. Donated human tissue is treated to remove the epidermis and cellular components, but it retains collagen, elastin, and proteoglycans, and the internal matrix of the dermis remains intact. The tissue is then cryogenically preserved. The company states that removal of the cellular component reduces rejection, retention of dermal proteins allows for revascularization and cellular repopulation, and the preserved tissue matrix reduces inflammation. Graftjacket Xpress is micronized tissue scaffold designed to be used in tunneling ulcers.[128] Wright Medical Technology, Inc. (Arlington, TN, USA), is registered with FDA as an establishment producing HCT/Ps.

Matrix HD™ (RTI Biologics)

Matrix HD is a sterile acellular human dermis designed for reconstructive surgery and for treating chronic skin wounds. RTI Biologics (Alachua, FL, USA) is registered with FDA as an establishment producing HCT/Ps.[129]

Memoderm™ (Memometal, Inc.)

Memoderm is a sterile acellular dermal matrix derived from human allograft skin tissue. Memometal, Inc. (Memphis, TN, USA), is registered with FDA as an establishment producing HCT/Ps.[130]

Puros® Dermis (Zimmer Dental)

Puros Dermis Allograft Tissue Matrix is a natural biological matrix designed for soft tissue augmentation, periodontal/peri-implant soft tissue management, and guided tissue regeneration

procedures. The tissue is treated using the Tutoplast sterilization procedure to kill bacteria, destroy cells, remove prions, and reduce potential tissue rejection. The manufacturer's Web site does not specifically state if Puros Dermis is derived from human tissue, although this may be implied.[131] Puros Dermis does not have 510(k) clearance or premarket approval, suggesting that this is a human-derived tissue product. Zimmer Dental is not registered with FDA as an establishment producing HCT/Ps but Zimmer Spine is registered.

Repliform® (LifeCell Corp./Boston Scientific Corp.)

Repliform Tissue Regeneration Matrix is a human acellular dermis. The donor human skin is processed and then freeze-dried to remove cells while maintaining the collagen, elastin, and proteoglycans. Repliform is processed by LifeCell Corp. and distributed by Boston Scientific Corp. The Boston Scientific Web site promotes Repliform for pelvic floor repair and says it "is intended for the repair or replacement of damaged or inadequate integumental tissue such to repair enteroceles, rectoceles and/or cystoceles and for pelvic floor reinforcement."[132] LifeCell Corp. (Branchburg, NJ, USA) is registered with FDA as an establishment producing HCT/Ps. LifeCell also produces AlloDerm, which seems to be the same product as Repliform.

TheraSkin® (Soluble Systems)

TheraSkin is a biologically active, cryopreserved human skin allograft, composed of living cells, fibroblasts, and keratinocytes and a fully developed extracellular matrix. TheraSkin does not contain any synthetic or animal materials. According to the company Web site, TheraSkin is designed to promote wound healing by providing cellular and extracellular components with growth factors, cytokines, and collagen and to be a natural barrier to infection. TheraSkin may be used in diabetic foot ulcers, venous stasis ulcers, and pressure ulcers. TheraSkin is marketed by Soluble Systems, and tissue is provided by the Skin and Wound Allograft Institute (SWAI), a wholly-owned subsidiary of LifeNet Health, Inc. SWAI (Virginia Beach, VA, USA) is registered with FDA as an establishment producing HCT/Ps.[133]

Human-Derived Products Regulated Through Premarket Approval Process

Apligraf/Graftskin (Organogenesis)

Apligraf is a living, cell-based, bilayered skin substitute designed to treat chronic venous leg ulcers and diabetic foot ulcers. The lower layer contains bovine type 1 collagen and human fibroblasts to form a dermis-like structure that produces additional matrix proteins. Human keratinocytes form an epidermal layer to replicate the structure of the human epidermis. The human keratinocytes and fibroblasts are derived from neonatal foreskins. Apligraf is believed to stimulate the patient's own cells to regenerate tissue and heal the wound through mechanisms that may include the secretion of growth factors, cytokines, and matrix proteins. Apligraf does not contain melanocytes, Langerhans' cells, macrophages, lymphocytes, or tissue structures such as blood vessels, hair follicles, and sweat glands. Apligraf is manufactured by Organogenesis (Canton, MA, USA).[134]

In December 1998, FDA approved Apligraf for marketing under the PMA process for "use with standard therapeutic compression for the treatment of noninfected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not

adequately responded to conventional ulcer therapy." Multiple supplements have been added since the first approval, including an indication for treating diabetic foot ulcers. Several of the supplements involve approval for the use of new human keratinocyte or fibroblast cell strains in the manufacture of Apligraf. Apligraf is included in FDA product code MGR (dressing, wound and burn, interactive).[135]

Dermagraft (Advanced Biohealing, Inc./Smith & Nephew)

Dermagraft is a cryopreserved, human fibroblast-derived dermal substitute containing fibroblasts, extracellular matrix, and a bioabsorbable polyglactin mesh scaffold. The fibroblasts are obtained from human newborn foreskin tissue. The fibroblasts are placed on the scaffold and then proliferate and produce human dermal collagen, matrix proteins, growth factors, and cytokines. The process creates a three-dimensional human dermal substitute with metabolically active human cells. Dermagraft does not contain macrophages, lymphocytes, blood vessels, or hair follicles. It comes frozen as a single sheet (2 by 3 inches) for a single application.[136] In May 2006, Advanced BioHealing purchased the global rights to Dermagraft from Smith & Nephew.

In September 2001, FDA approved Dermagraft for marketing under the PMA process for "use in the treatment of full-thickness diabetic foot ulcers greater than six weeks' duration which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure. Dermagraft® should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot." Dermagraft is included in FDA product code MGR (dressing, wound and burn, interactive). Advanced BioHealing, Inc. (La Jolla, CA, USA), is registered with FDA as an establishment producing HCT/Ps.[137]

Animal-Derived Products Regulated Through the 510(k) Process

The FDA product code KGN contains wound dressings based on collagen. Collagen-based dressings contain purified collagen derived primarily from bovine or porcine sources. The type and concentration of collagen varies depending on the actual dressing. Rather than just providing structural support within a wound, collagen is now believed to play a critical role in all aspects of wound healing. When a wound is first formed, platelets aggregate around exposed collagen. The platelets release a variety of growth factors and cytokines that attract inflammatory cells (macrophages, neutrophils, eosinophils) to the wound. The inflammatory cells degrade collagen and other protein debris in the wound, and at the same time, produce factors that attract and stimulate fibroblast activity. Fibroblasts secrete matrix metalloproteinase (MMP) along with collagen and produce factors that attract additional fibroblasts as well as epithelial cells and vascular endothelial cells into the wound. These cells then produce the granulation tissue that forms the extracellular matrix. The MMPs are responsible for degrading nonviable collagen while the new matrix is forming. However, in chronic wounds, fibroblasts may produce too much MMP and too little of the factors that inhibit MMPs. When this occurs, the MMPs may destroy new, viable collagen and prevent proper wound healing. Collagen-based dressings are believed to aid wound healing by stimulating fibroblast production and have a hydrophilic property that enhances fibroblast movement and inhibition and deactivation of MMPs.[90] FDA product code KGN contains a variety of wound dressings that use collagen in some form as the primary component of the dressing. The following is a description of some of these wound

dressings. Table 8 contains a list of the wound dressings indicated for chronic wounds under product code KGN.

EndoForm (Mesynthes, Ltd.)

EndoForm Dermal Template is an extracellular matrix derived from ovine forestomach. According to the company Web site, "Endoform™ is a proprietary biomaterial containing a rich and complex mix of important biological extracellular matrix (ECM) molecules, including structural (collagens I, III, IV & elastin) and adhesive proteins (fibronectin and laminin), glycosaminoglycans (heparin sulfate and hyaluronic acid) and growth factors (FGF2 & TGFß)."[138]

EndoForm Dermal Template (Mesynthes, Ltd., North Attleboro, MA, USA, and Wellington, New Zealand) was cleared for marketing under the 510(k) process (K092096) in January 2010 for "single use in the treatment of the following wounds: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds." EndoForm Dermal Template is included in FDA product code KGN (dressing, wound, collagen).[27]

E-Z Derm (AM Scientifics, Ltd.)

E-Z Derm is a biosynthetic wound dressing made from porcine tissue chemically treated to cross-link collagen with an aldehyde to add strength and allow storage at room temperature. Because E-Z Derm is composed of porcine tissue, it is considered a porcine xenograft. The shelf life is 18 months. The company Web site promotes E-Z Derm for the temporary coverage of wounds prior to autograft, partial thickness skin loss, to protect meshed autografts, for outpatient skin loss, donor sites, skin ulcerations, and abrasions.[139]

E-Z Derm Biosynthetic Wound Dressing (Brennen Medical, Inc., St. Paul, MN, USA) was cleared for marketing under the 510(k) process in July 1994 (K935189, no summary available). E-Z Derm is included in FDA product code KGN (dressing, wound, collagen).[26]

Integra Bilayer Matrix Wound Dressing (Integra Lifesciences Corp.)

Integra is a bilayered matrix wound dressing composed of a porous layer of cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone) layer. According to the company Web site, the silicone layer allows for controlled water vapor loss and provides a flexible covering for the wound surface. The collagen-glycosaminoglycan matrix is biodegradable and provides a scaffold for cell entry and capillary growth. The silicone membrane is temporary and the collagen-glycosaminoglycan matrix is remodeled as the wound area is repaired. Integra can be stored at room temperature.[140]

In April 2001, FDA approved Integra dermal regeneration template for marketing under the PMA process "for the post excisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient." Bilayer Matrix Wound Dressing (Integra LifeSciences Corp., Plainsboro, NJ, USA) was cleared for marketing under the 510(k) process in August 2002 (K021792) and is indicated "for the management of wounds including:

partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic and vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. This device is intended for one-time use." Integra is included in FDA product code FRO (dressing, wound, drug).[32]

MatriStem (ACell, Inc.)

MatriStem Wound Care Matrix is an extracellular matrix product derived from porcine urinary bladder tissue and designed to be replaced by native tissue in the wound.[141] ACell MatriStem Wound Sheet (ACell, Inc., Columbia, MD, USA) was cleared for marketing under the 510(k) process in October 2009 (K092926) and "is intended for the management of wounds that including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds. The device is intended for one-time use." MatriStem is included in FDA product code KGN (dressing, wound, collagen). MatriStem Wound Care Matrix was cleared for marketing under the 510(k) process in August 2010 (K112409) with MatriStem Wound Sheet as the predicate device and with the same indications.[35]

Oasis Wound Matrix (Cook Biotech, Inc.)

Oasis Wound Matrix is an extracellular matrix derived from porcine small intestinal submucosa. According to the company Web site, the intestinal material is absorbed into the wound during the healing process. Oasis is applied to wounds after débridement. The edges of the Oasis sheet extend beyond the wound edges and are secured with tissue sealant, bolsters, dissolvable clips, sutures, or staples. The sheet is rehydrated with sterile saline and covered with a nonadherent, primary wound dressing followed by a secondary dressing to contain exudate. Oasis is reapplied every 7 days or as needed.[142]

Oasis Wound Matrix (Cook Biotech, Inc., West Lafayette, IN, USA) was cleared for marketing under the 510(k) process in July 2006 (K061711) and is indicated "for the management of wounds including: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled, undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds. The device is intended for one-time use." Oasis is included in FDA product code KGN (dressing, wound, collagen).[39]

Primatrix (TEI Biosciences, Inc.)

Primatrix is an animal-derived, extracellular matrix dermal substitute intended to act as a scaffold to allow cell and vascular penetration. According to the company Web site, TEI biological matrix products are derived from fetal bovine dermis collagen. In producing this product, the epidermis, hair, muscle, and fascia are removed. The dermis is then treated to remove cells and infectious agents while preserving biological properties and structures. The product is converted to sheets, freeze dried, and sterilized. When applied to a wound, the product

is rehydrated. The company believes that the high concentration of type III collagen in its product may assist in the wound healing process.[143]

Primatrix Dermal Repair Scaffold (TEI Biosciences, Inc., Boston, MA, USA) was cleared for marketing under the 510(k) process in June 2006 (K061407) and "is intended for the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds; draining wounds." Primatrix is included in FDA product code KGN (dressing, wound, collagen).[41]

Biosynthetic Products Regulated Through the 510(k) Process

Hyalomatrix, Laserskin®, and Jaloskin® (Anika Therapeutics, Inc.)

Hyalomatrix (see Hyalomatrix PA below) is a bilayered wound dressing composed of a nonwoven pad made of a benzyl ester of hyaluronic acid (HYAFF 11) and a semipermeable silicone membrane. The nonwoven pad contacts the wound and, according to the company Web site, "provides a three dimensional matrix for cellular invasion and capillary growth." The silicone membrane "controls water vapor loss, provides a flexible covering for the wound surface, and adds increased tear strength to the device." The HYAFF 11 matrix is biodegradable. The company believes that "when the integration of the HYAFF based material in the newly formed dermal matrix has progressed, a well-vascularized granulation tissue forms. This provides for wound closure via spontaneous re-epithelialization or acts as a suitable dermal layer for skin grafting."[144]

Hyalomatrix KC Wound Dressing (Anika Therapeutics, Inc., Bedford, MA, USA, formerly Fidia Advanced Biopolymers, Abano Terme, Italy) was cleared for marketing under the 510(k) process in July 2001 (K001508) for "the management of wounds in the granulation phase such as pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, wounds and burns treated with meshed grafts. It is intended for use as a temporary coverage for wounds and burns to aid in the natural healing process." Hyalomatrix KC Wound Dressing is included in FDA product code MGP (dressing, wound and burn, occlusive). In the FDA 510(k) database, number K001508 refers to Laserskin Dressing as the device; however, in the 510(k) summary for K001508, the proprietary name is Hyalomatrix KC Wound Dressing and the name Laserskin is not mentioned.[48]

Hyalomatrix PA Wound Dressing (Anika Therapeutics, Inc., Bedford, MA, USA) was cleared for marketing under the 510(k) process in December 2007 (K073251). The company refers to Hyalomatrix PA by its trade name Hyalomatrix. In the 510(k) documents Hyalomatrix is described as a bilayered dressing composed of a nonwoven pad made of HYAFF 11 and a semipermeable silicone membrane. Hyalomatrix "is indicated for the management of wounds including: partial and full-thickness wounds; second-degree burns; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery , post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds. The device is intended for one-time use." Hyalomatrix is included in FDA product code FRO (dressing, wound, drug). The predicate device was "Hyalomatrix KC (Laserskin) Wound Dressing."[49]

Jaloskin (Anika Therapeutics, Inc., Bedford, MA, USA) was cleared for marketing under the 510(k) process in January 2010 (K092257) for "the management of superficial moderately exuding wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, skin tears) and first and second degree bums." Jaloskin is a semipermeable, transparent film dressing, composed of HYAFF 11 only. The hyaluronic acid is derived from bacterial fermentation. Jaloskin is included in FDA product code FRO (dressing, wound, drug).[50]

Anika Therapeutics, Inc. (Bedford, MA, USA), acquired Fidia Advanced Biopolymers S.r.l. (currently Anika Therapeutics S.r.l.) in December 2009. The Anika Therapeutics Web site advertises Hyalomatrix and Jaloskin.

Suprathel® (Polymedics Innovations GmbH)

Suprathel is a synthetic, biocompatible, and absorbable skin substitute made from polymers of lactic acid. The Suprathel membrane is applied once to a clean débrided wound surface and then breaks down during the healing process. According to the company Web site, the products of Suprathel degradation stimulate the healing process by increasing angiogenesis and rebuilding the dermis. The acidification of the wound bed by breakdown products is also supposed to have a bactericidal effect.[145]

Suprathel Wound and Burn Dressing (Polymedics Innovations GmbH, Denkendorf, Germany) was cleared for marketing under the 510(k) process (K090160) in May 2009 for "temporary coverage of noninfected skin defects, such as superficial wounds, under sterile conditions. The dressing is intended to maintain a moist wound healing environment. A moist wound healing environment allows autolytic débridement. The Suprathel Wound and Burn Dressing is used in the management of: Partial and full thickness wounds; Pressure (stage I and IV) and venous ulcers; Ulcers caused by mixed vascular etiologies; venous stasis and diabetic ulcers; 1st and 2nd degree burns; Partial thickness burns; cuts and abrasions; acute wounds; trauma wounds; surgical wounds; superficial wounds; grafted wounds and donor sites." Suprathel is included in FDA product code FRO (dressing, wound, drug).[51]

Talymed (Marine Polymer Technologies, Inc.)

Talymed is a sterile wound matrix comprised of shortened fibers of poly-N-acetylglucosamine, isolated from microalgae. Talymed (MARINE POLYMER TECHNOLOGIES, Danvers, MA, USA) was cleared for marketing under the 510(k) process (K102002) in July 2010 for "the management of wounds including: diabetic ulcers; venous ulcers; pressure wounds; ulcers caused by mixed vascular etiologies; full thickness and partial thickness wounds; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post laser surgery, and other bleeding surface wounds; abrasions, lacerations; traumatic wounds healing by secondary intention; chronic vascular ulcers; dehisced surgical wounds." Talymed is included in FDA product code FRO (dressing, wound, drug).[52]

Products Not Yet Available in the United States for Treating Chronic Wounds

Celaderm (Advanced Biohealing, Inc.)

Advanced BioHealing, Inc., sponsored a clinical trial of Celaderm for treating venous leg ulcers, and information about the trial was available on ClinicalTrials.gov. Celaderm was described as a frozen, cultured, epidermal allograft. Advanced BioHealing, Inc. (La Jolla, CA, USA) is registered with FDA as an establishment producing HCT/Ps. Information on this device was not available on the company or FDA Web sites.[146]

Dermagen (Laboratoires Genévrier, France)

Dermagen is a "sponge composed of collagen and glycosaminoglycans (chondroitins 4 and 6 sulphate), reticulated by ionic bonds with chitosan" under investigation for treating diabetic neuropathic foot ulcers. The study is ongoing with all locations in France but not recruiting participants. Dermagen is made by Laboratoires Genévrier, Antibes, France.[147]

Epicel (Genzyme)

Epicel is a cultured epidermal autograft intended to treat deep dermal or full-thickness burns. According to the product labeling, "Epicel® cultured epidermal autografts (CEA) is an aseptically processed wound dressing composed of the patient's own (autologous) keratinocytes grown ex vivo in the presence of proliferation-arrested, murine (mouse) fibroblasts. Epicel® consists of sheets of proliferative, autologous keratinocytes, ranging from 2 to 8 cell layers thick and is referred to as a cultured epidermal autograft." Epicel is created by co-cultivation of the patient's cells with murine cells and contains residual murine cells. Therefore, FDA considers Epicel a xenotransplantation product.[148]

Epicel (Genzyme Biosurgery, Cambridge, MA, USA) was granted an humanitarian device exemption (HDE) by FDA in October 2007 and is "indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30 percent. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns."[149]

Epidex (Euroderm AG)

Epidex is a skin product generated from keratinocytes from the patient's hair follicles. Epidermal sheets are created with silicone membrane support.[5] Euroderm AG (Baden-Dättwil, Switzerland) seems to be strictly a European company. None of its skin products seem to be sold in the United States and it has no listing with FDA.[150]

Matriderm (Dr. Suwelack Skin and Health Care AG)

Matriderm is a collagen-elastin matrix designed to support dermal regeneration after severe skin injuries. The matrix provides a structure for the invasion of native cells to regenerate the dermis. After placement, Matriderm is covered with a very thin, split-thickness, skin graft. The company Web site promotes Matriderm for treating severe burn injuries.[151]

This product does not seem to be available in the United States and is not listed on the FDA Web site. A company called Suwelack Matrix Systems, Inc., Stony Brook, NY, USA, was established in 2005 but does not have any products listed on the FDA Web site.

OrCel (Forticell Bioscience, Inc.)

OrCel is a bilayered, cellular matrix composed of normal, human, allogeneic, epidermal keratinocytes and dermal fibroblasts. The cells are cultured in two separate layers into a type I bovine collagen sponge. Neonatal human fibroblasts and keratinocytes are obtained from the same donor. According to the company Web site, the matrix is designed to provide a structure for host cell invasion along with a mix of cytokines and growth factors. The matrix is absorbed as the wound heals. Because of the extensive culturing process, the cells do not express the antigens responsible for rejection. The cells produce growth factors. A PMA application with FDA has been filed for treating venous leg ulcers. Studies will test OrCel in treating diabetic foot ulcers. The company Web site indicates that it will promote OrCel for treating chronic and acute wounds. Forticell Bioscience, Inc., is the former Ortec International, Inc.[152]

Composite Cultured Skin (Ortec International, Inc., New York, NY, USA) was granted an HDE by FDA in February 2001 and is "indicated for use in patients with mitten hand deformities due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release of hand contractures (i.e., "mitten" hand deformities)."[153] OrCel has also received PMA approval for treating fresh, clean, split-thickness, donor site wounds in burn patients and may, therefore, be used by physicians off-label on chronic wounds.

PermaDerm (Regenicin)

PermaDerm is under development as a tissue-engineered skin prepared from the patient's own skin cells (autologous). A section of the patient's skin containing both epidermis and dermis is harvested and grown into a graft to cover a large wound area. The process takes 30 days. The product is being developed for burns and chronic wounds. Regenicin (Little Falls, NJ, USA) is working on a PMA application with FDA.[154]

StrataGraft/ExpressGraft (Stratatech Corp.)

StrataGraft for severe burns and ExpressGraft for diabetic foot ulcers and venous leg ulcer are skin substitutes under development at Stratatech Corp. (Madison, WI, USA). According to the company Web site, "Stratatech is a regenerative medicine company focused on the commercialization of novel skin substitute products for therapeutic and research use." StrataGraft is "designed to mimic natural human skin, with both dermal and fully differentiated epidermal layers." ExpressGraft tissues are being developed as "genetically enhanced tissues that produce elevated levels of natural wound healing and anti-microbial factors." These products are not yet commercially available.[155]

Xelma (Mölnlycke Healthcare, Gothenburg, Sweden)

Xelma is an extracellular matrix protein (amelogenins) contained in propylene glycol alginate and water designed to treat wounds, primarily venous leg ulcers. Xelma is applied topically and then covered with a secondary dressing. According to the company Web site, Xelma "temporarily replaces the damaged extracellular matrix proteins" in the wound and

promotes "restoration of the cellular and biochemical balance . . . which will promote granulation tissue formation and normal wound healing."[156] Xelma was not listed on the Mölnlycke Healthcare USA or FDA Web sites.

Table 6. Human-derived products regulated solely under 21 CFR 1271 (HCT/Ps)

Product	Manufacturer	Description
AlloDerm Regenerative Tissue Matrix	LifeCell, KCI	Acellular human dermis product
Allopatch HD	Musculoskeletal Transplant Foundation	Acellular human dermis product
Alloskin	AlloSource	Allograft derived from epidermal and dermal cadaveric tissue
Cymetra Micronized AlloDerm	LifeCell, KCI	Injectable form of AlloDerm Regenerative Tissue Matrix
DermaCell and Arthroflex	LifeNet Health	Acellular human dermis product
Flex HD	Ethicon and Musculoskeletal Transplant Foundation	Acellular hydrated dermis derived from donated human allograft skin
GammaGraft	Promethean LifeSciences, Inc.	Irradiated cadaveric human skin allograft
GraftJacket	LifeCell, licensed to Wright Medical Technology and to KCI	Processed human dermal matrix
Matrix HD	RTI Biologics	Acellular human dermis product
Memoderm	Memometal Inc.	Acellular human dermis product
Puros Dermis	Zimmer Dental	A natural biological matrix
Repliform	LifeCell and Boston Scientific	Acellular human dermis product
Theraskin	Soluble Systems	Biologically active cryopreserved human skin allograft with both epidermis and dermis layers

Table 7. Human- and human/animal-derived products regulated through the premarket approval (PMA) or humanitarian device exemption (HDE) process

Product and Manufacturer	Product Description	Approval Date	FDA Product Code	FDA Intended Use/Indication for Use
Apligraf/ Graftskin – Organogenesis[135]	Living cell based bilayered skin substitute derived from bovine type 1 collagen and human fibroblasts and keratinocytes derived from neonatal foreskins.	1998 PMA original 2000 PMA added diabetic ulcers	MGR (dressing, wound and burn, interactive)	"For use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure. Apligraf is contraindicated for use on clinically infected wounds. Apligraf is contraindicated in patients with known allergies to bovine collagen. Apligraf is contraindicated in patients with a known hypersensitivity to the components of the Apligraf agarose shipping medium."
Dermagraft - Advanced Biohealing, Inc. and Smith & Nephew[137]	Cryopreserved human fibroblast-derived dermal substitute on a bioabsorbable polyglactin mesh scaffold. The fibroblasts are obtained from human newborn foreskin tissue.	2001 PMA	MGR (dressing, wound and burn, interactive)	"For use in the treatment of full-thickness diabetic foot ulcers greater than six weeks' duration which extend through the dermis, but without tendon muscle, joint capsule or bone exposure. Dermagraft(r) should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot. Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts. Dermagraft is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution."

MGR is one of the FDA product codes designated for Class III device

Table 8. Animal-derived products regulated under the 510(k) process

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
ACell UBM Hydrated Wound Dressing – ACell, Incorporated[11]	A wound dressing primarily composed of porcine collagen.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds." The device is intended for one-time use."
ACell UBM Lyophilized Wound Dressing – ACell, Incorporated[12]	A wound dressing primarily composed of porcine collagen.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. The device is intended for one-time use."
Aongen™ Collagen Matrix – Aeon Astron Europe B.V.[13]	A biodegradable material composed of collagen.	2009	KGN (dressing, wound, collagen)	"For the management of wounds including: surgical wounds, trauma wounds, draining wounds, second degree burns, partial and full-thickness wounds, pressure ulcers, venous ulcers, vascular ulcers, diabetic ulcers, and oral wounds and sores."
Atlas Wound Matrix – Wright Medical Technology, Inc.[14]	A sterile, decellularized fenestrated or nonfenestrated processed porcine collagen dermal material.	2009	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), draining wounds. The Atlas Wound Matrix is a collagen wound dressing that provides an environment that supports wound healing."
Avagen Wound Dressing – Integra LifeSciences Corp.[15]	A wound dressing comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. The biodegradable matrix provides a scaffold for cellular invasion and capillary growth.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use."

Table 8. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Collagen Sponge – Innocoll Pharmaceuticals[16]	A collagen matrix sponge	2010	KGN (dressing, wound, collagen)	"For the management of wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, partial and full thickness wounds, and superficial injuries."
Collagen Wound Dressing – Oasis Research, LLC[17]	A wound care dressing composed of hydrolyzed bovine collagen.	2000	KGN (dressing, wound, collagen)	"For the management of wounds including full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, second-degree burns, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, dehisced surgical incisions."
Collaguard™ – Innocoll Pharmaceuticals[18]	A clear collagen matrix film	2006	KGN (dressing, wound, collagen)	"For the management of wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, partial and full thickness wounds, and superficial injuries."
CollaSorb™ Collagen Wound Dressing – Hartmann-Conco Inc.[19]	A wound care product composed of native collagen and calcium-alginate.	2009	KGN (dressing, wound, collagen)	"For the management of full and partial thickness wounds including: pressure ulcers, diabetic ulcers, ulcers caused by mixed vascular etiologies, venous ulcers, second degree burns, donor and graft sites, abrasions, dehisced surgical wounds, and traumatic wounds healing by secondary intention."
CollaWound™ dressing – Collamatrix Inc.[20]	A sterile, single use, disposable wound dressing device comprised of insoluble fibrous collagen derived from porcine.	2006	KGN (dressing, wound, collagen)	"For the management of partial and full thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds, first and second degree burns, surgical wounds and superficial injuries."
Collexa – Innocoll Pharmaceuticals[21]	A collagen matrix sponge	2010	KGN (dressing, wound, collagen)	"For the management of wounds such as: diabetic ulcers, venous ulcers, pressure ulcers, ulcers caused by mixed vascular etiologies, full-thickness and partial-thickness wounds, abrasions, traumatic wounds, first and second degree burns, dehisced surgical wounds, and exuding wounds."
Collieva® – Innocoll Pharmaceuticals[22]	A clear collagen matrix film	2008	KGN (dressing, wound, collagen)	"For the management of wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, partial and full thickness wounds, and superficial injuries."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices

Table 8. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Coreleader Colla-Pad – Coreleader Biotech Co., Ltd.[23]	A porous matrix consisting of cross-linked bovine collagen.	2011	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds."
Dermadapt™ Wound Dressing – Pegasus Biologics, Inc.[24]	A collagen-based wound dressing described as a decellularized, equine pericardial implant.	2006	KGN (dressing, wound, collagen)	"For the local management of moderately to heavy exuding wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), and surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions)."
DressSkin – TEI Biosciences Inc.[25]	A wound dressing composed of hydrolyzed bovine collagen.	2003	KGN (dressing, wound, collagen)	"For the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical wounds—donor sites/grafts, post Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds—abrasions, lacerations, and skin tears; tunneled/undermined wounds; draining wounds."
E-Z Derm - AM Scientifics, Ltd[26]	Biosynthetic wound dressing made from porcine tissue.	1994	KGN (dressing, wound, collagen)	No FDA summary available online
EndoForm Dermal Template– Mesynthes[27]	Extracellular matrix derived from ovine forestomach.	2010	KGN (dressing, wound, collagen)	"For single use in the treatment of the following wounds: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds."
Excellagen – Tissue Repair Company[28]	A wound care device composed of formulated, 2.6% (26 mg/mL) fibrillar bovine dermal collagen (Type I).923	2011	KGN (dressing, wound, collagen)	"For the management of wounds including partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices

Table 8. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
FortaDerm™ Wound Dressing – Organogenesis, Inc.[29]	A single-layer fenestrated sheet of porcine intestinal collagen.	2001	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post laser surgery, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds."
HA Absorbent Wound Dressing – ConvaTec, A Division of E.R. Squibb and Sons, Inc.[30]	An absorbent fibrous fleece (F) or rope (R), entirely composed of HYAFF 11p75™, a benzyl ester of hyaluronic acid.	1999	KGN (dressing, wound, collagen)	"For over-the-counter use, HA Absorbent Wound Dressing-F may be used for wounds such as: abrasions, lacerations, minor cuts and first degree burns. Under the supervision of a healthcare professional, HA Absorbent Wound Dressing-F may be used for wounds such as: leg ulcers, pressure ulcers (stages I-IV), and diabetic ulcers, surgical wounds (post-operative, donor sites, dermatological), second degree burns; management of wounds that are prone to bleeding such as wounds that have been mechanically or surgically débrided, donor sites, and traumatic wounds. HA Absorbent Wound Dressing-R is indicated for use in the management of deep exuding wounds, sinuses, and fistulae."
Helicoll – ENCOLL Corp.[31]	A translucent, off-white, semi-occlusive, self-adhering and ready to use pre-sterilized Type-1 Collagen Sheet.	2004	KGN (dressing, wound, collagen)	"For the topical wound management that includes: partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears), and surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric), wound dehiscence."
Integra/Bilayer Matrix Wound Dressing - Integra Lifesciences Corp.[32]	Bilayered matrix composed of a porous layer of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer.	2002	FRO (dressing, wound, drug)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic and vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices

Table 8. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Integra™ Flowable Wound Matrix[33]	A wound care device comprised of granulated cross-linked bovine tendon collagen and glycosaminoglycan.	2007	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds."
LTM Wound Dressing – LifeCell Corp.[34]	A terminally sterilized sheet of the processed porcine dermal matrix	2008	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post laser surgery, podiatric wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns and skin tears), draining wounds, and other bleeding surface wounds."
MatriStem - ACell, Inc.[35]	Extracellular matrix product derived from porcine urinary bladder tissue.	2009	KGN (dressing, wound, collagen)	"For the management of wounds that including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds."
MatriStem® Wound Matrix – ACell, Inc.[36]	A sterile, porcine-derived, naturally-occurring lyophilized extracellular matrix sheet.	2011	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunnel/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."
Matrix Collagen Wound Dressing – Collagen Matrix, Inc.[37]	An opaque, absorbent, collagen membrane matrix intended for topical use.	2004	KGN (dressing, wound, collagen)	"For the management of moderately to heavily exudating wounds and to control minor bleeding. Collagen Topical Wound Dressing may be used for the management of exudating wounds such as: pressure ulcers, venous stasis ulcers, diabetic ulcers, acute wounds (for example trauma and surgical wounds), and partial thickness burns."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices

Table 8. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Medline Collagen Wound Dressing – Medline Industries, Inc.[38]	Not available in 510(k) clearance information.	2006	KGN (dressing, wound, collagen)	"Medline's Collagen Wound Dressing is indicated for the management of wounds including: full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, partial and full thickness burns, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, and dehisced surgical incisions. These dressings may be cut to size and may be layered for the management of deep wounds."
Oasis - Cook Biotech, Inc.[39]	Extracellular matrix derived from porcine small intestinal submucosa	2006	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled, undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds."
Primatrix – TEI Biosciences Inc.[40]	Acellular dermal tissue matrix.	2008	KGN (dressing, wound, collagen)	"For the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical wounds–donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds–abrasions, lacerations, and skin tears; tunneled/undermined wounds; and draining wounds."
Primatrix™ Dermal Repair Scaffold - TEI Biosciences[41]	Extracellular matrix dermal substitute derived from fetal bovine dermis collagen.	2006	KGN (dressing, wound, collagen)	"For the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds; draining wounds."
SIS Wound Dressing II – Cook Biotech, Incorporated[42]	A wound dressing primarily composed of porcine collagen.	2000	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."

KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices

Table 8. Animal-derived products regulated under the 510(k) process, continued

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
SS Matrix™ – Cook Biotech Incorporated[43]	A matrix product primarily composed of porcine collagen.	2002	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."
Stimulen™ Collagen – Southwest Technologies, Inc.[44]	A sterile primary single use dressing comprised of soluble modified bovine collagen base.	2004	KGN (dressing, wound, collagen)	"For the management of wounds including full and partial thickness wounds, pressure ulcers (stages I-IV), venous stasis ulcers, diabetic ulcers, partial thickness burns, acute wounds, abrasions, traumatic wounds healing by secondary intention, donor sites and other surface wounds."
TheraForm™ Standard/Sheet – Sewon Cellontech Co., Ltd.[45]	An absorbable collagen membrane derived from porcine.	2009	KGN (dressing, wound, collagen)	"For the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."
Unite® Biomatrix – Synovis Orthopedic and Woundcare, Inc.[46]	A decellularized equine pericardial extracellular matrix (xenograft)	2011	KGN (dressing, wound, collagen)	"For the management of moderately to severely exudating wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness [second-degree] burns, skin tears), surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions)."
Unite™ Biomatrix – Pegasus Biologics, Inc.[47]	A collagen-based wound dressing consisting of decellularized, equine pericardium.	2007	KGN (dressing, wound, collagen)	"For the local management of moderately to heavy exuding wounds including: partial and full thickness wounds, draining wounds, pressures sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions)."

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KGN and FRO are among the FDA product codes designated for unclassified pre-amendment devices

Table 9. Biosynthetic products regulated under the 510(k) process

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Hyalomatrix KC Wound Dressing (Laserskin) - Anika Therapeutics[48]	Hyalomatrix is a bilayered wound dressing composed of a nonwoven pad made of a benzyl esters of hyaluronic acid (HYAFF) and a semipermeable silicone membrane.	2001	MGP (dressing, wound and burn, occlusive)	"For the management of wounds in the granulation phase such as pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, wounds and burns treated with meshed grafts. It is intended for use as a temporary coverage for wounds and burns to aid in the natural healing process."
Hyalomatrix Wound Dressing - Anika Therapeutics[49]	Hyalomatrix is a bilayered wound dressing composed of a nonwoven pad made of HYAFF 11 (a benzyl ester of hyaluronic acid) and a semipermeable silicone membrane.	2007	FRO (dressing, wound, drug)	"For the management of wounds including: partial and full-thickness wounds; second-degree burns; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery , post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds."
Jaloskin - Anika Therapeutics[50]	Jaloskin is a semipermeable, transparent film dressing, composed of HYAFF 11 (a benzyl ester of hyaluronic acid) only	2010	FRO (dressing, wound, drug)	"For the management of superficial moderately exuding wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, skin tears) and first and second degree bums."
Suprathel - Polymedics Innovations[51]	Synthetic, biocompatible, and absorbable skin substitute made from polymers of lactic acid.	2009	FRO (dressing, wound, drug)	"For temporary coverage of non-infected skin defects, such as superficial wounds, under sterile conditions. The dressing is intended to maintain a moist wound healing environment. A moist wound healing environment allows autolytic débridement. The Suprathel Wound and Burn Dressing is used in the management of: Partial and full thickness wounds; Pressure (stage I and IV) and venous ulcers; Ulcers caused by mixed vascular etiologies; Venous stasis and diabetic ulcers; 1st and 2nd degree bums; Partial thickness bums; Cuts and abrasions; Acute wounds; Trauma wounds; Surgical wounds; Superficial wounds; Grafted wounds and donor sites."

Product and Manufacturer	Description	Clearance Date	FDA Product Code	FDA Intended Use/Indication for Use
Talymed™– Marine Polymer Technologies, Inc.[52]	A sterile wound matrix comprised of shortened fibers of poly-N-acetylglucosamine, isolated from microalgae.	2010	FRO (dressing, wound, drug	"For the management of wounds including: diabetic ulcers; venous ulcers; pressure wounds; ulcers caused by mixed vascular etiologies; full thickness and partial thickness wounds; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post laser surgery, and other bleeding surface wounds; abrasions, lacerations; traumatic wounds healing by secondary intention; chronic vascular ulcers; dehisced surgical wounds."

KGN, MGP, and FRO are among the FDA product codes designated for unclassified pre-amendment devices.
HYAFF: Benzyl esters of hyaluronic acid

Key Question 2: For patients with chronic wounds (pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers) are skin substitutes more effective than other wound care options (usual care, standard care, synthetic dressings, growth factors, skin grafts, or other treatments used as a comparison) in promoting wound healing for the following outcome measures:

a. Percentage of completely closed/healed wounds
b. Time to complete wound closure
c. Wound reoccurrence
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

Our searches identified 18 RCTs that met our inclusion criteria (see Table 10). Twelve of the studies examined diabetic foot ulcers and six studies examined vascular leg ulcers. Only seven skin substitute products were examined in the RCTs that met our inclusion criteria. We identified only one study using skin substitutes to treat patients with pressure ulcers, but this study did not meet the inclusion criteria (see Table 20). Outcomes reported in these studies were primarily complete wound healing by 12 weeks (13 studies), time to complete wound healing (12 studies), complete wound healing after 12 weeks (9 studies), and wound infection (16 studies) (see Table 11). Complete wound healing was defined in these studies as full epithelialization with no drainage, no exudate or eschar (scab) present (see Table 49 to Table 53). Other outcomes listed in Key Question 2 were not as frequently reported and measures of function and activities of daily living were not reported in any study (see Table 12).

Two studies of Graftjacket (processed human dermal matrix) were the only RCTs examining HCT/Ps. Nine studies (4 for Apligraf and 5 for Dermagraft) examined products derived from humans and regulated through the PMA process (includes 1 study comparing Apligraf with TheraSkin and 1 study comparing Dermagraft with Oasis). Five studies of Oasis wound matrix were the only RCTs examining animal-derived products regulated under the 510(k) process. Three studies of Hyalograft 3D autograft were the only RCTs examining biosynthetic products regulated under the 510(k) process (including 1 study comparing Hyaloskin with Oasis). One RCT examined the efficacy of Talymed (algae-derived). The results obtained from studies of a single product, such as Graftjacket within HCT/Ps, cannot be extrapolated to all products in a group because of differences in product components and healing properties. Therefore, clinical evidence of efficacy obtained from RCTs is not available for most of the skin substitute products discussed in this report.

Table 10. List of included randomized controlled trials

Study	Comparison	Wound Type
DiDomenico et al. 2011[64]	Apligraf vs. TheraSkin	DFU
Edmonds 2009[53]	Apligraf vs. nonadherent dressing	DFU
Falanga et al. 1998[63]	Apligraf with compression vs. compression	Leg, Venous
Krishnamoorthy et al. 2003[55]	Dermagraft plus multilayered compression bandage therapy (Profore™) vs. multilayered compression therapy	Leg, Venous
Marston et al. 2003[56]	Dermagraft vs. saline-moistened gauze	DFU
Naughton et al. 1997[62]	Dermagraft vs. saline-moistened gauze	DFU
Gentzkow et al. 1996[65]	Dermagraft vs. saline-moistened gauze	DFU
Reyzelman et al. 2009[66]	Graftjacket acellular matrix vs. moist wound therapy with alginates, foams, hydrocolloids, or hydrogels	DFU
Brigido 2006[59]	Graftjacket tissue matrix vs. weekly debridement, Curasol wound hydrogel and gauze dressing	DFU
Veves et al. 2001[67]	Graftskin vs. saline-moistened gauze alone	DFU
Uccioli et al. 2011[68]	Hyalograft 3D autograft/Laserskin vs. nonadherent paraffin gauze	DFU
Caravaggi et al. 2003[58]	Hyalograft 3D autograft/Laserskin vs. nonadherent paraffin gauze	DFU
Romanelli et al. 2010[57]	Oasis Wound Matrix vs. a petrolatum-impregnated gauze	Leg, Mixed
Landsman et al. 2008[54]	Oasis Wound Matrix vs. Dermagraft	DFU
Romanelli et al. 2007[60]	Oasis Wound Matrix vs. Hyaloskin (contains hyaluronan)	Leg, Mixed
Mostow et al. 2005[69]	Oasis Wound Matrix with compression vs. compression alone	Leg, Venous
Niezgoda et al. 2005[70]	Oasis Wound Matrix vs. Regranex Gel (contains platelet-derived growth factor)	DFU
Kelechi et al. 2011[61]	Talymed poly-N-acetyl glucosamine (pGlcNAc) with compression vs. nonadherent absorptive primary dressing with compression	Leg, Venous

DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
Leg, Mixed: Venous and arterial leg ulcers
SOC: Standard of care

Table 11. List of wound healing outcomes reported by included studies

Skin Substitutes	References	Complete Wound Healing by 12 Weeks	Complete Wound Healing After 12 Weeks	Time to Complete Wound Healing	Wound Reoccurrence After 12 Weeks	Wound Infection
Apligraf and Graftskin	Edmonds 2009[53]	X	—	X	X	X
	Veves et al. 2001[67]	X	—	X	X	X
	Falanga et al. 1998[63]	—	X	X	X	X
Apligraf and TheraSkin	DiDomenico et al. 2011[64]	X	X (20 weeks)	X	—	X
Dermagraft	Krishnamoorthy et al. 2003[55]	X	—	—	—	X
	Marston et al. 2003[56]	X	—	—	—	X
	Naughton et al. 1997[62]	X	X	X	X	X
	Gentzkow et al. 1996[65]	X	—	X	X	X
Graftjacket	Reyzelman et al. 2009[66]	X	—	X	—	X
	Brigido SA. 2006[59]	—	X	X	—	X
HYAFF (Benzyl esters of hyaluronic acid)	Uccioli et al. 2011[68]	X	X (20 weeks)	X	—	X
	Caravaggi et al. 2003[58]	X (by 11 weeks)	—	X	—	X
Oasis	Romanelli et al. 2010[57]	X (by 8 weeks)	—	X	—	X
	Landsman et al. 2008[54]	X	—	X	—	—
	Romanelli et al. 2007[60]	—	X (16 weeks)	—	—	—
	Mostow et al. 2005[69]	X	X		X	X
	Niezgoda et al. 2005[70]	X	X	X	X	X
Talymed	Kelechi et al. 2011[61]	—	X (20 weeks)	—	—	X

X indicates the study reported this outcome.

Table 12. List of other significant outcomes reported by included studies

Skin Substitutes	References	Need for Amputation	Need for Hospitalization	Measures of Function and Activities of Daily Living	Pain	Exudate	Odor
Apligraf and Graftskin	Edmonds 2009[53]	X				X	
	Veves et al. 2001[67]						
	Falanga et al 1998[63]				X	X	
Apligraf and TheraSkin	DiDomenico et al. 2011[64]		X				
Dermagraft	Krishnamoorthy et al. 2003[55]		X				
	Marston et al. 2003[56]						
	Naughton et al. 1997[62]						
	Gentzkow et al. 1996[65]						
Graftjacket	Reyzelman et al. 2009[66]						
	Brigido SA. 2006[59]						
HYAFF (Benzyl esters of hyaluronic acid)	Uccioli et al. 2011[68]	X					
	Caravaggi et al. 2003[58]						
Oasis	Romanelli et al. 2010[57]				X		
	Landsman et al. 2008[54]						
	Romanelli et al. 2007[60]		X				
	Mostow et al. 2005[69]				X		
	Niezgoda et al. 2005[70]						
Talymed	Kelechi et al. 2011[61]				X		

X indicates the study reported this outcome.

Risk of Bias in the Evidence Base

No RCTs were considered at high risk of bias. However, the RCT by Naughton et al.[62] was considered to have an unclear risk of bias primarily because of poor reporting of methods (most risk-of-bias assessment questions were answered with an NR). The other 17 RCTs were split between low (8 studies) and moderate (9 studies) risk of bias. No study specifically mentions blinding the wound assessor when complete wound healing was determined. Information on wound severity was reported in only two studies. Manufacturer funding did not seem to influence the reporting of key wound healing outcomes in the included RCTs.

Apligraf/Graftskin

All three studies of Apligraf/Graftskin conducted by Organogenesis were considered to have low risk for bias (Edmonds M. 2009,[53] Veves et al. 2001,[67] Falanga et al. 1998[63]). None of the publications reported on comorbidities, so information reported to FDA was used to fill in this information. A fourth study compared Apligraf to TheraSkin (DiDomenico et al. 2011[64]) and was considered to have moderate risk for bias because randomization methods, wound duration, and comorbidities were not reported and the study did not blind wound assessment (see Table 22).

Dermagraft

Three of the four Dermagraft studies were at a moderate risk for bias (see Table 23). Naughton et al.[62] did not report any baseline information by which most of the risk-of-bias assessment questions could be answered and, therefore, was considered to have an unclear risk of bias. In the other studies, randomization method was either not reported or was not appropriate, and wound size, wound duration, and comorbidities were poorly reported.

Graftjacket

One study had a moderate risk of bias for not reporting randomization methods, concealment of group allocation, wound duration, or wound size.[59] Reyzelman et al.[66] was categorized as low risk after information provided by the author indicated use of appropriate randomization methods and concealment of treatment allocation (see Table 24).

Oasis

Four studies of Oasis were considered at moderate risk of bias; one study was considered at low risk of bias. Reporting of comorbidities was absent in all of the studies (see Table 26). Three studies with moderate risk of bias did not report or use appropriate randomization methods or concealment of allocation. In three of the studies, mean wound duration was not reported.

Hyalograft 3D autograft/Laserskin

Two studies evaluating Hyalograft 3D autograft/Laserskin were at a low risk of bias (see Table 25).

Talymed (pGlcNAc)

In this single study reporting comorbidities, appropriate randomization methods and wound duration led to a low risk of bias rating; however, although the investigators were blinded, the study did not report blinding of wound assessment (performed by study nurses)[61] (see Table 25).

Study Design, Patient Enrollment Criteria, Description of Treatment, Patient Characteristics

Information on study design and conduct, patient enrollment criteria, details on treatment, and the characteristics of patients in the studies are contained in Table 27 to Table 48 in Appendix C.

Several important areas of study design and patient information of interest to this report were poorly reported. Prior wound treatments were not reported in any of the studies, and reporting of comorbidities was sparse. Wound severity before enrolling in a study was reported in only two studies.

A run-in period to assess wound healing under standard care before allowing a patient to enter a study has been recommended because some wound healing may be due to improved adherence to standard treatment. FDA recommends excluding patients who demonstrate "substantial healing resulting solely from improved compliance with standard care."[10] The POWER group believes that a "run-in period is a way to normalize or equalize all subjects, making them comparable at the start of the test phase where appropriate."[108] Only 7 of the 18 studies included in this report mention using a run-in period before enrolling patients in the study (see Table 32). Five of the studies used a 2-week run-in period and two studies used a 1-week run-in period.

EWMA[106] has recommended that "a unified outcome approach to wound assessment be established and put into practice. This would allow standardized data assessment across the whole range of clinical research evaluating the efficacy of current and emerging technologies in wound healing." Table 33 describes the methods used at initial wound assessment. A variety of methods were used to determine initial wound size and to measure changes in wound size during the course of a study. Computerized planimetry was used in eight studies, typically in conjunction with photographs and/or tracings. None of the studies mentions training in wound assessment or validation of the methods.

Wound reassessment after initial complete healing is recommended by FDA, POWER, CMTP, and EWMA.[10,106,108,113] The FDA definition for complete wound closure includes a requirement for reappraisal of wound closure at two consecutive study visits 2 weeks apart.[10] FDA also recommends that "trial subjects remain in the study for followup evaluation at least 3 months following complete wound closure." Such a followup period would allow determination of acceptable wound healing rather than minimal wound healing.[2] Four of the studies included in this report reassessed completely healed wounds within 2 weeks of initial wound closure (see Table 32): Edmonds[53], Landsman et al.[54], Krishnamoorthy et al.[55], and Marston et al.[56] Eight studies used various followup methods that included wound reassessment biweekly, monthly, or every 3 months until the end of the study. Six studies did not mention reassessment or planned followup to assess the durability of wound closure.

Patients were generally excluded from studies if their health was suboptimal, they were taking medication that would interfere with wound healing, their wounds were infected, or the blood flow to the affected area was poor. Since Apligraf and Dermagraft are specifically not indicated for infected wounds (see Table 7), studies of these treatments would not include patients with infected wounds at the time of starting treatment with the skin substitute. Several studies also indicated they excluded patients who responded to usual care during screening periods (see studies of Apligraf, Dermagraft, Hyalograft autograft/Laserskin and Oasis described below for details). This procedure ensures that only patients with hard-to-heal chronic wounds are enrolled in the study.

Studies of vascular leg ulcers should enroll only patients with verified venous disease.[157] Of the six studies of vascular ulcers, only Falanga et al. 1998[63] reported using air plethysmography or photoplethysmography to determine venous insufficiency (see Table 34). The other studies did not mention steps taken to verify venous disease. Four studies included only patients with an ankle-brachial pressure index (ABI) above 0.7 to rule out arterial disease. Two studies by Romanelli et al.[57,60] included mixed arterial and venous (A/V) leg ulcers and patients were included if they had an ABI between 0.6 and 0.8. Approximately half of the patients in these studies had mixed A/V leg ulcers. ABI values less than 0.5 indicate poor blood perfusion and predict difficult wound healing.[86]

Some form of ancillary wound treatment was provided to all enrolled patients. This treatment typically included usual care procedures such as debridement, saline-moistened dressings, and a nonweight-bearing regimen. Antibiotics were provided in several studies; two studies cited this as a requirement by current international guidelines.[58,68]

Apligraf/Graftskin

Three of the four studies of Apligraf/Graftskin were sponsored by Organogenesis, Inc., and examined between 72 and 293 patients; two studies were conducted in multiple U.S. centers.[63,67] One study recruited patients in the European Union and Australia.[53] Two studies examining patients with diabetic foot ulcers evaluated efficacy at 12 weeks during a study duration of 6 months,[53,67] and one study examining venous leg ulcers evaluated efficacy at 6 months during a study duration of 12 months.[63] Mean age ranged from 56 to 60 years. Two studies excluded patients who responded to usual care during 7- or a 14-day screening period.[53,67] In the study with the 14-day screening period, the ulcer could not show a greater than 40 percent reduction in size (wound care not reported)[53] and in the study with the 7-day screening period, the wound could not decrease by more than 30 percent while treated with saline-moistened gauze.[67] None of the three studies reported a wound severity score, but they provided information on wound duration and wound size. A maximum of five applications of Apligraf was available in two studies;[63,64] only three applications were permitted in one study.[53] One study did not report wound débridement.[63] Primary dressings used as control treatments in two studies evaluating diabetic foot ulcers were Mepitel nonadherent dressing[53] and saline-moistened Tegapore.[67] One study examining venous leg ulcers used Tegapore nonadherent primary dressing gauze bolster as part of compression therapy.[63]

The fourth study of Apligraf was sponsored by Soluble Systems, the maker of TheraSkin, a cryopreserved, split-thickness, human skin allograft. TheraSkin was compared with Apligraf in a 20-week study.[64] This study enrolled 28 patients with 29 diabetic foot ulcers from a large, multisite, podiatric practice. Average wound size was similar between groups (1.89 cm^2 [Apligraf] vs. 1.82 cm^2 [TheraSkin]). This study did not report wound duration or presence of screening period before study treatments.

Dermagraft

Dermagraft was examined in four studies (3 of diabetic foot ulcers[56,62,65] and 1 of venous leg ulcers[55]). All studies were conducted in multiple settings and were of 12 weeks' duration. The number of patients examined ranged from 50 to 281. Prior to random assignment of subjects, Marston et al.(2003) indicated stratifying patients into two groups based on wound size; however, study results did not reflect these groupings.[56] Krishnamoorthy (2003) and Gentzkow (1996) randomly assigned patients to one of three treatment groups and one control group; the three treatment groups varied by number of Dermagraft applications and weeks applied.[55,65] Krishnamoorthy (2003) reported on presence of deep vein thrombosis per study group.[55] Two of

three studies examining diabetic foot ulcers did not report diabetes type.[62,65] Three studies excluded patients who responded to usual care during screening periods.[55,56,62] In the one study reporting the length of the screening period (14 days), the ulcer could not heal by more than 50 percent while using a multilayered compression bandage.[55] The other two studies did not report the length of the screening period and excluded ulcers that increased or decreased in size by more than 50 percent[56] or showed rapid healing in response to usual care (compression bandages).[62] Multilayered compression therapy was the control treatment in the venous leg ulcer study.[55] Standard of care in the three diabetic wound studies consisted of a nonadherent interface plus saline-moistened gauze in two studies; only saline-moistened gauze was used in the third.[62]

Graftjacket

Graftjacket was examined in two studies. One 12-week study enrolled 86 patients from 11 sites.[66] Mean wound duration (weeks) was similar (23.3 vs. 22.9); however, the mean wound size was greater in the control group (5.1±4.8 versus 3.6±4.3). Brigido et al. (2006), a 16-week study, enrolled 28 patients at one U.S. site.[59] This study reported wound severity (Wagner Grade-2) but did not report wound size or duration.[59] Control wound treatments for Graftjacket studies were weekly debridement and Curasol wound hydrogel[59] in one study, and one of four moist-wound therapies (i.e., alginates, foams, hydrocolloids, hydrogels) based on level of wound exudate in the other.[66] No screening periods to assess wound healing before study treatments were reported in these studies.

Oasis

Oasis Wound Matrix was examined in five studies: three studies of venous leg ulcers[57,60,69] and two studies of diabetic foot ulcers.[54,70] The diabetic foot ulcer studies enrolled 40 and 98 patients. The three studies of venous leg ulcers enrolled between 50 and 120 patients. The studies lasted 8–16 weeks. Two studies were conducted at the same institute.[57,60] One study examining venous leg ulcers excluded patients exhibiting greater than 50 percent reduction in surface area during the screening period while being treated with usual care and compression therapy.[69] Two studies compared two nongauze wound dressings.[54,60] One study (Landsman 2008) randomly assigned patients to Oasis or Dermagraft.[54] This 12-week study included a 1-week run-in period prior to random assignment.[54] Romanelli (2007) randomly assigned patients to Oasis or Hyaloskin.[60] Primary control wound treatments in the remaining studies were described as a petrolatum-impregnated gauze;[57] compression therapy consisting of a nonadherent dressing and a four-layer compression bandaging system;[69] and a daily application of Regranex Gel.[70]

Hyalograft 3D autograft/Laserskin

Hyalograft 3D impregnated with autologous fibroblasts followed by Laserskin impregnated with autologous keratinocytes was examined in two studies of diabetic foot ulcers and compared with nonadherent paraffin gauze.[58,68] One multicenter study enrolled 82 patients from six outpatient centers in Italy; more than 85 percent of the patient population had type 2 diabetes.[58] Three patients were excluded after a 15-day run-in period because the ulcer area decreased to less than 1 cm^2, leaving 79 patients in the intent-to-treat analysis. No significant differences were observed in clinical and wound characteristics; however, mean wound size (dorsal ulcers) was greater for the control group (8.3±9.67 vs. 4.6±5.74). Mean $TcPO_2$ [transcutaneous oxygen] was similar in the two groups (>30 mm Hg). The other multicenter study enrolled 180 patients from seven outpatient centers in Italy; 88 percent of the patient population had type 2 diabetes.[68] Mean ulcer duration was less than 7 months for the total study population. The two study groups were similar with the exception of ulcer area, which was significantly larger in the treatment group (8.8±9.4 vs. 6.7±7.7; p=0.016). Mean $TcPO_2$ [transcutaneous oxygen] was similar

between groups, with 25 patients in the treatment group and 29 in the control group with $TcPO_2$ of 30 mm Hg or less, at high risk of amputation. This study reported using a 2-week screening period with nonadherent paraffin gauze. Seven patients were later excluded because of having an ulcer area of less than 1 cm^2; 13 patients did not return after the baseline visit, leaving 160 patients in the intent-to-treat analysis.

Talymed (pGlcNAc)

Talymed, a poly-N-acetyl glucosamine (pGlcNAc) containing wound dressing, plus standard of care (n=62) was compared with standard care alone (n=20, Group D) for treating venous leg ulcers in a single, 20-week study.[61] The treatment groups were randomized to pGlcNAc once during week 1 (Group A), once every second week (Group B), or once every third week (Group C). Common comorbidities across groups included hypertension (range affected 70 percent to 80 percent), diabetes (54.5 percent to 70.0 percent), class III obesity (range 35 percent to 54 percent), arthritis (30.0 percent to 54.6 percent), and blood clotting disorders (20.0 percent to 40.9 percent). This study did not report using a screening period to assess wound healing before study treatments.

Efficacy of Skin Substitutes

Only seven of the 57 skin substitute products identified for this report were examined in RCTs.

As mentioned in the previous section, patients were generally excluded from studies if their health was suboptimal, they were taking medication that would interfere with wound healing, their wounds were infected, or the blood flow to the affected area was poor. This restriction means that the outcomes reported in these studies address the efficacy (the capacity to produce a desired effect) of skin substitutes rather than the effectiveness (create an effect in real world practice) of skin substitutes.[158] Gartlehner et al. have defined efficacy trials as explanatory trials that "determine whether an intervention produces the expected results under ideal circumstances" and effectiveness trials as pragmatic trials that "measure the degree of beneficial effect under real world clinical settings."[159] Carter et al. have expressed concerns about the applicability of many wound care RCTs to the general population affected by chronic wounds.[160]

Results from one type of skin substitute cannot be extrapolated to other types because of the different properties and components.[10] Neither can results from studies of diabetic foot ulcers be extrapolated to venous leg ulcers because of the differences in etiology and pathophysiology.[10] Therefore, clinical evidence from RCTs demonstrating the efficacy of most skin substitutes in treating chronic wounds is not available.

In 12 of the included studies, treatment efficacy was judged by the number of wounds healed after 12 weeks of treatment. Two studies reported on wound healing at less than 12 weeks, one at 8 weeks,[57] and one at 11 weeks.[58] The remaining studies measured wound healing at 16 weeks,[59,60] 20 weeks,[61] 32 weeks,[62] and 6 months[63] (see Table 49 to Table 53).

Carter[158] has emphasized the need to state the "minimal clinical important difference" indicating that the experimental treatment in a wound care study has a clinical benefit over the control treatment. According to Carter, the minimal clinical important difference should be stated for each outcome and the study should be powered to detect this difference. This guards against merely stating that any statistically significant difference is meaningful when the difference is too small to be clinically important. While any significant difference in the number of patients with complete wound healing, wound reoccurrence, infection, or amputation would be clinically important, our examination of the 18 studies included in this report found that no study

specifically stated a minimal clinical important difference for these or any other outcomes. Only three studies stated an expected difference between treatment and control outcomes when estimating a study's power and sample size (see Table 32). Edmonds et al.[53] expected the treatment to completely heal 50 percent of wounds and the control to heal 32 percent of wounds based on previous pilot studies. Mostow et al.[69] expected a 20 percentage point difference and Caravaggi et al.[58] expected a 40 percentage point difference.

All studies defined healing as full epithelialization of the wound with no drainage. Based on this outcome, the majority of studies reported significantly more healed wounds in the patients treated with skin substitutes. However, the patients enrolled in these studies were in generally good health and free of infected wounds, medications that would impede wound healing, clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes. The extent to which these results can be achieved in actual clinical practice is unclear. Other outcomes not directly related to wound healing, such as amputation, hospitalization, return to function, and pain relief, were poorly reported.

Apligraf/Graftskin

Apligraf/Graftskin is a living cell, bilayered skin substitute derived from bovine type 1 collagen and human fibroblasts and keratinocytes derived from neonatal foreskins. Based on the percentage of wounds closed at 12 weeks, Apligraf/Graftskin was significantly better in all three studies when compared with usual care (see Table 49).[53,63,67] In one of the two studies of diabetic foot ulcers, the control dressings were a nonadherent gauze dressing (Mepitel), covered with a secondary dressing including saline-moistened gauze and dry gauze (healing rate at 12 weeks was 52 percent vs. 26 percent).[53] In the other study, the control was saline-moistened, nonadherent gauze (Tegapore) covered with a layer of saline-moistened gauze followed by dry gauze and a layer of petrolatum gauze (healing rate at 12 weeks was 56 percent vs. 38 percent).[67] The third study compared Apligraf to Tegapore, a gauze bolster, zinc oxide–impregnated, paste bandage (Unna boot), and self-adherent elastic wrap for treating venous leg ulcers.[63] The rate of wounds healed at 6 months was 63 percent for Apligraf and 49 percent for the Unna boot. The median time to wound closure was significantly shorter in the Apligraf group (61 days vs. 181 days).

Dermagraft

Dermagraft is a cryopreserved, human fibroblast-derived dermal substitute. The fibroblasts are obtained from human newborn foreskins. Three of the Dermagraft studies examined diabetic foot ulcers using saline-moistened gauze as the control dressing.[56,62,65] Marston et al. 2003[56] reported better healing at 12 weeks in the Dermagraft group and significantly faster time to complete healing. Naughton et al. 1997[62] reported that more ulcers were healed at 12 weeks in the patients receiving Dermagraft (38.5%) than control (31.7%), but the difference did not reach statistical significance (p=0.14).[62] The third study, Gentzkow et al. 1996,[65] also reported more wounds healed in the Dermagraft group at 12 weeks (50 percent vs. 8 percent). Krishnamoorthy (2003)[55] used Dermagraft to treat venous leg ulcers. Both the Dermagraft group and the control group received compression therapy. The number of wounds healed at 12 weeks (38 percent vs. 15 percent) and median time to wound closure (35 weeks vs. 74 weeks) were better in the Dermagraft group (see Table 50).

Graftjacket

Graftjacket is processed human dermal matrix used as a skin substitute. The two studies of Graftjacket, both of diabetic foot ulcers, did not use simple gauze dressings as the controls. Reyzelman et al. 2009[66] used moist-wound therapy alginates, foams, hydrocolloids, or hydrogels

as control dressings and Brigido 2006[59] used Curasol wound hydrogel and weekly debridement as the control. Both studies reported significantly more wounds closed at 12 weeks (70 percent vs. 46 percent compared with the moist-wound therapy dressings and 86 percent vs. 29 percent compared with Curasol). Both studies also reported a reduced time to wound closure in the Graftjacket groups, but the differences were not significantly different (see Table 51).

Oasis

Oasis is an extracellular matrix derived from porcine small intestinal submucosa. Among the five RCTs using Oasis, three examined venous leg ulcers. A different control dressing was used in each of the three venous leg ulcer studies: petrolatum-impregnated gauze with no compression, Jaloskin containing the extracellular matrix component hyaluronan, and a nonadherent dressing with compression bandages. Healing rates were better in the Oasis-treated patients (at 8 weeks, 80 percent vs. 65 percent compared with petrolatum-impregnated gauze [$p<0.05$];[57] at 16 weeks, 83 percent vs. 46 percent compared with Jaloskin [$p<0.001$];[60] and at 12 weeks, 55 percent (34/62) vs. 34 percent (20/58) compared with a nonadherent dressing with compression bandages [$p=0.02$][69]). Time to wound closure was significantly better only in the study using a nonadherent dressing with compression bandages. The fourth study of Oasis examined diabetic foot ulcers using Regranex Gel (contains platelet-derived growth factor) as the control. At 12 weeks, the Oasis group had more healed plantar ulcers than the Regranex Gel group (49 percent vs. 28 percent), but the result was not quite statistically significant ($p=0.055$).[70] The fifth study examined treatment of diabetic foot ulcers using Oasis or Dermagraft. At 12 weeks, no significant differences were reported between time to closure (35.67±41.47 days with Oasis vs. 40.90±32.32 days with Dermagraft) or percentage of wound closure (76.9 percent with Oasis vs. 84.6 percent with Dermagraft) (see Table 53).[54]

Hyalograft 3D autograft/Laserskin

Hyalomatrix is a bilayered wound dressing composed of a nonwoven pad made of a benzyl ester of hyaluronic acid (HYAFF) and a semipermeable silicone membrane. In the study by Caravaggi et al. 2003,[58] Hyalograft 3D impregnated with autologous fibroblasts followed by Laserskin (similar in construction to Hyalomatrix) with autologous keratinocytes were grafted to diabetic foot ulcers. The control treatment was nonadherent paraffin gauze. Laserskin is described under Key Question 1 of this report under the section on biosynthetic products. After 11 weeks, more wounds (dorsal and plantar) were healed in the Hyalograft/Laserskin group than in the control group, but the difference was not statistically significant (65 percent vs. 50 percent). Dorsal ulcer healing was significantly better in the Hyalograft/Laserskin group (67 percent vs. 31 percent) (see Table 52). In the study by Uccioli et al.,[68] Hyalograft 3D impregnated with autologous fibroblasts followed by Laserskin with autologous keratinocytes were grafted to diabetic foot ulcers. The difference in complete ulcer healing at 12 weeks was not statistically different for patients in the treatment group (19/80, 24 percent) versus the control group (17/80, 21 percent) ($p=0.850$). At 20 weeks, complete ulcer healing was achieved in 50 percent of the treatment group and 43 percent of the control group (log-rank test=0.344) (see Table 52).

Talymed (pGlcNAc)

Talymed is a sterile wound matrix comprised of shortened fibers of poly-N-acetylglucosamine, isolated from microalgae. In the study by Kelechi et al. 2011,[61] Talymed plus standard of care was compared to standard care alone for treating venous leg ulcers. Standard care included a nonadherent absorptive primary dressing and a multilayer compression bandage including a zinc oxide impregnated bandage, padding and a self-adherent

elastic wrap. After 20 weeks, a statistically significant difference at the p=0.005 level was observed for wounds receiving Talymed plus standard care once every other week versus standard care alone (86.4 percent versus 45 percent, intention to treat analysis with last observation carried forward). More wounds were healed in the Talymed group when applied once every three weeks compared to the control group (65 percent vs. 45 percent), but the difference was not statistically significant. Similar wound healing rates (45 percent) were reported for patients receiving one application of Talymed compared to control.

Table 13 shows the results for complete wound healing at 12 weeks (where possible, or for the closest time point reported) as risk differences and as RR with 95% CI (a RR > 1 indicates that the skin substitute being studied resulted in a higher rate of complet wound healing). Two random effects meta-analyses were possible – one for three studies of Dermagraft and one for two studies of Hyalograft 3D autograft/LaserSkin. The meta-analysis of three studies comparing Dermagraft to saline-moistened gauze showed a summary odds ratio of 1.64 (95% CI 1.10 to 2.43) favoring Dermagraft (Figure 5). The other meta-analysis of two studies comparing Hyalograft 3D autograft/Laserskin to nonadherent paraffin gauze found a summary odds ratio of 1.43 (95% CI 0.80 to 2.54), but this finding was not statistically significant (p=0.22) (Figure 6).

While most studies reported the number of wounds healed at 12 weeks or shorter and a few reported on wound healing at later times, only seven studies reported data on wound recurrence (see Table 54). The rates of recurrence were measured most often over 6 months of follow up. No patterns emerged from the limited data available on this outcome.

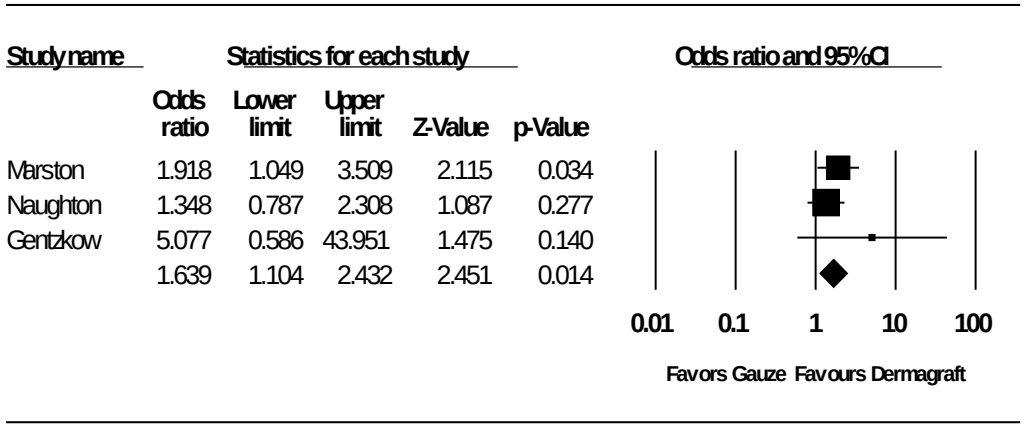
Table 13. Results for complete wound healing

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[64]	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[54]	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[66]	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[59]	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[70]	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[53]	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[56]	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[62]	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[65]	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[67]	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[68]	DFU	Hyalograft 3D autograft/Lasers Skin	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[58]	DFU	Hyalograft 3D autograft/LaserSkin	Nonadherent paraffin gauze	79	Healed at 11 weeks 65% - 50% = 15%	NS (p=0.17)	1.30 (0.88 to 1.93)

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]
Falanga et al. 1998[63]	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)
Krishnamoorthy et al. 2003[55]	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[57]	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[60]	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[69]	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. 2011[61]	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]

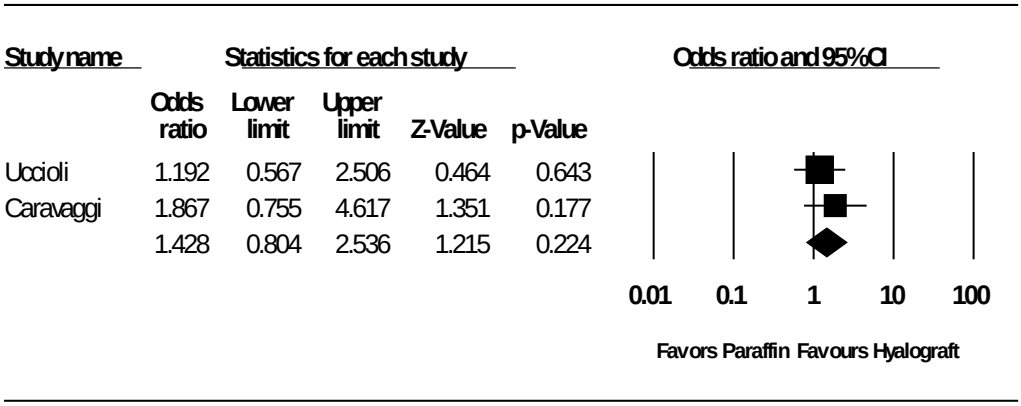
DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
Leg: Vascular leg ulcer
NS: Not Statistically Significant
[a] Calculated by ECRI Institute; p values are for Risk Difference
[b] Calculated for all three active groups combined vs. control. A dose-response was noted with more frequent application 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 that they used "analysis of variance for multiple comparisons," but no variables by which the data might have been adjusted are discussed.
[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).

Figure 5. Complete wound healing at 12 weeks with Dermagraft vs. Saline-moistened gauze for diabetic foot ulcers



Gentzkow - all three Dermagraft groups combined

Figure 6. Complete wound healing at 12 weeks: Hyalograft 3D autograft/LaserSkin vs. nonadherent paraffin gauze for diabetic foot ulcers



Strength of Evidence

Strength of evidence was evaluated based on risk of bias, consistency, directness, and precision. The strength of evidence assessment is described in Table 14 and Table 15.

Table 14. Key Question 2: Strength of evidence grades for complete wound healing with skin substitutes used to treat diabetic foot ulcers

Comparison	# Studies (Total N)	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Rating
Apligraf vs. TheraSkin[64]	1 (28)	MOD	U	D	I % healed at 12 weeks: 41% vs. 67%, NS	?	INSUFFICIENT
Oasis Wound Matrix vs. Dermagraft[54]	1 (26)	MOD	U	D	I % healed at 12 weeks 77% vs. 85%, NS	?	INSUFFICIENT
Graftjacket acellular matrix vs. Moist wound therapy[66]	1 (85)[a]	LOW	U	D	P % healed at 12 weeks: 70% vs. 46%, p=0.03	Graftjacket	LOW
Graftjacket acellular matrix vs. weekly debridement, Curasol wound hydrogel and gauze dressing[59]	1 (28)	MOD	U	D	P % healed at 12 weeks: 57% vs. 7%, p=0.001	Graftjacket	INSUFFICIENT
Oasis Wound Matrix vs. Regranex Gel[70]	1 (98)	MOD	U	D	I % healed at 12 weeks: 49% vs. 28%, NS	?	INSUFFICIENT
Apligraf vs. nonadherent dressing[53]	1 (72)[a]	LOW	U	D	P % healed at 12 weeks: 52% vs. 26%, p=0.03	Apligraf	LOW
Dermagraft vs. saline-moistened gauze[56,62,65]	3 (530)	MOD	C	D	P OR 1.64 (95% CI 1.10 to 2.43)	Dermagraft	LOW
Graftskin vs. saline-moistened gauze[67]	1 (208)[a]	LOW	U	D	P % healed at 12 weeks 56%vs. 38%, p=0.01	Graftskin	LOW
Hyalograft 3D autograft/LaserSkin vs. nonadherent paraffin gauze[58,68]	2 (239)	LOW	C	D	I OR 1.43 (95% CI 0.80 to 2.54)	?	INSUFFICIENT

For consistency, C = consistent, I = inconsistent, U = unknown consistency because there was only one study. For directness, D = direct and I = indirect.
For precision, I = imprecise, P = precise. For the column labeled "Evidence favors," ? denotes inconclusive evidence
Other abbreviations: CI = Confidence interval; Diff = difference, N = number of patients, OR = odds ratio, SOE = strength of evidence
[a] Multicenter study

Table 15. Key Question 2: Strength of evidence grades for complete wound healing with skin substitutes used to treat venous or mixed venous and arterial leg ulcers

Comparison	# Studies (Total N)	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Rating
Apligraf and compression vs. compression[63]	1 (275)[b]	LOW	U	D	P % healed at 12 weeks 53% vs.22%, p<0.001[c]	Apligraf	LOW
Dermagraft plus multilayered compression bandage therapy vs. multilayered compression bandage therapy[55]	1 (52)	MOD	U	D	I % healed at 12 weeks 38% vs. 15%, NS	?	INSUFFICIENT
Oasis Wound Matrix with compression vs. compression alone[69]	1 (120)[b]	LOW	U	D	P % healed at 12 weeks 55% vs. 34%, p=0.02	Oasis Wound Matrix	LOW
Oasis Wound Matrix vs. a petrolatum-impregnated gauze[57a]	1 48)	MOD	U	D	I % healed at 8 weeks 80% vs. 65%, p=0.25[d]	?	INSUFFICIENT
Oasis Wound Matrix vs. Hyaloskin[60a]	1 (54)	MOD	U	D	P % healed at 16 weeks 83% vs. 46%, p=0.001	Oasis Wound Matrix	INSUFFICIENT
Talymed poly-N-acetyl glucosamine (pGlcNAc) with compression vs. nonadherent absorptive primary dressing with compression[61]	1 (82)	LOW	U	D	I % healed at 20 weeks 66% vs. 45%, NS	?	INSUFFICIENT

For consistency, C = consistent, I = inconsistent, U = unknown consistency because there was only one study.
For directness, D = direct and I = indirect.
For precision, I = imprecise, P = precise.
For the column Evidence favors, ? denotes inconclusive evidence
Other abbreviations: NS=nonsignificant
[a] Mixed venous and arterial ulcers
[b] Multicenter study
[c] Complete healing at 12 weeks calculated 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 that they used "analysis of variance for multiple comparisons," but no variables by which the data might have been adjusted are discussed.

The strength of the evidence base for evaluating complete wound healing of diabetic foot ulcers at 12 weeks was graded as low for the comparisons of Graftjacket vs. moist wound products,[66] the comparison of Apligraf vs. a nonadherent dressing,[63] and for Graftskin vs. saline-moistened gauze.[67] Each of these studies represented a multicenter trial with a low risk of bias for the outcome of complete wound healing. The outcome measure was direct and the results were precise. Although the evidence for the comparison of Dermagraft vs. saline-moistened gauze came from 3 studies including 530 patients and had a precise result of a direct outcome, we judged the strength of the evidence to be only low because the studies had a moderate risk of bias.[56,62,65] The strength of the evidence for other comparisons for diabetic foot ulcers were graded insufficient, primarily because the overall risk of bias was moderate and/or the reported treatment effect (percentage increase in completely healed wounds) was imprecise.

Only two comparisons were judged to have low strength of evidence for complete wound healing of venous or mixed ulcers at 12 weeks. One compared Apligraf and compression to compression,[63] and one compared Oasis Wound Matrix with compression to compression.[69] In each case, the included study was a multicenter trial, had a low risk of bias and reported a precise and direct result. The other comparisons were from studies with moderate risk of bias and imprecise results; these were judged to have an insufficient strength of evidence grade.

A grade of low means we have low confidence that the evidence reflects the true effect of skin substitutes on complete wound healing, and we believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. A grade of insufficient indicates that the available evidence does not support a conclusion regarding the comparison. The applicability of the evidence is another important issue with the studies included in this report, and is discussed below.

Applicability

Applicability of the evidence base depends on how well the included studies examine the patient populations, interventions, comparators, and outcomes of interest to clinical decision makers. When evaluating the patient population, consideration is given to whether patients of interest are included in the studies or whether the eligibility criteria has excluded patients with comorbidities or those in poor health. As mentioned above, no studies in the evidence base examined patients with pressure ulcers, so this evidence base does not provide information on this condition. Also mentioned above was the narrow eligibility criteria that eliminated patients in poor health in most studies. Commonly mentioned reasons for exclusion included the following: infected wounds; use of medications that could impede wound healing; clinically significant medical conditions that could impair wound healing; renal, hepatic, neurologic, or immunologic diseases; significant peripheral vascular disease; malnutrition; and uncontrolled diabetes. This restricts the available evidence to a generally healthy patient group.

No studies of the use of skin substitutes to treat pressure ulcers met our inclusion criteria. Our searches identified only one RCT that compared Dermagraft with usual care in treating stage III pressure ulcers, but this study was excluded because fewer than 50 percent of the enrolled participants contributed data on wound healing. The primary study endpoint was the number of patients with completely healed wounds at 24 weeks with a secondary endpoint of wounds healed at 12 weeks. The study enrolled 34 patients, but by week 12, only 16 patients remained in the study and by week 24 the number of patients was 10. Only two patients in each treatment arm had healed wounds by 24 weeks (see Payne et al. 2004 in Table 20). The lack of studies examining the use of skin substitutes for treating pressure ulcers is puzzling, given that

most of the products regulated under the 510(k) process specifically include pressure ulcers as an indication. Publication bias, the failure to publish studies that do not support the efficacy of a new product, may be a possible explanation for the absence of published pressure ulcer studies and could also be present in studies of diabetic foot ulcers and venous leg wounds. Studies may have been conducted but because of poor results compared with usual care, like the Payne et al. study, the study may have been terminated and the results never published. However, our examination of skin substitute studies listed in ClinicalTrials.gov found no completed, terminated, or ongoing studies examining pressure ulcers, indicating that a lack of RCTs in this area may be the explanation.

When considering interventions, only seven of the skin substitutes identified in this report were evaluated in a RCT, meaning that clinical evidence of efficacy from RCTs is not available for the majority of skin substitute products as defined in this report. The skin substitutes derived from human neonatal foreskins and regulated under the PMA process are the best represented group with four studies of Apligraf/Graftskin and four studies of Dermagraft. The animal- or biosynthetic-derived skin substitutes that are regulated under the 510(k) process are represented by five studies of Oasis and one study of Talymed. Two studies of Graftjacket in treating diabetic foot ulcers are the only studies of skin substitutes in the HCT/Ps category.

An evaluation of applicability also considers the comparators and outcomes. In this evidence base, a wide variety of control dressings was used, and in a few of the studies, skin substitute products were actually compared with each other. When considering important wound treatment outcomes, the studies in the evidence base used number of wounds healed in 12 weeks as their primary outcome measure. However, only seven studies reported on wound recurrence, which is another important outcome for determining the efficacy of wound care products.

Taking all these issue of applicability into consideration, overall applicability of the evidence base is limited to a small number of skin substitutes used to treat diabetic foot ulcers and venous leg ulcers, and to patients in generally good health.

Key Question 3: What type and frequency of adverse events are reported in the clinical literature for each of the FDA-regulated skin substitute products?

Adverse events reported in the included RCTs are listed in Table 55 to Table 59. Cellulitis and osteomyelitis were reported in several studies. Many of the studies report adverse events but do not specify what events occurred.

Ongoing Clinical Trials

Our search of ClinicalTrials.gov identified 17 clinical trials with the following status: completed (8), currently recruiting (7), not yet open (1) and unknown (1). Of the eight completed trials, publications were not found for five trials. These trials were completed in 2003 (1), 2008 (1), 2011 (2) and 2012 (1) (see Table 16).

Table 16. Clinical trials

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Purpose	Start Date	Expected Completion Date	Estimated Enrollment	Status	Publications
NCT01676272	Soluble Systems, LLC	To compare a bioengineered skin substitute to a human skin allograft	July 2012	April 2013	100	Enrolling by invitation only	N/A
NCT01619670	University Hospital, Basel, Switzerland	To evaluate Apligraf in nonhealing wounds of patients with epidermolysis bullosa	June 2012	June 2014	18	Currently recruiting	N/A
NCT01729286	TEI Biosciences Inc.	To assess lower extremity diabetic (healed) ulcers with PriMatrix	September 2012	September 2014	224	Currently recruiting	N/A
NCT01612806	TEI Biosciences Inc.	To assess PriMatrix and PriMatrix Ag for the treatment of venous leg ulcers	June 2011	Not reported	90	Currently recruiting	N/A
NCT01623882	Spiracur, Inc.	To assess use of Apligraf and SNaP Pressure Wound Therapy System to treat diabetic and venous stasis lower extremity ulcers	June 2012	December 2015	60	Not yet open	N/A
NCT00521937	Laboratoires Genévrier	To evaluate the healing properties of Dermagen® for treating DFUs.	January 2009	December 2010	388	Unknown	N/A
NCT00909870	Advanced Biohealing, Inc.	Patients with venous leg ulcers will be randomly assigned to receive standard therapy (compression) alone or compression plus Dermagraft(R).	May 2009	September 2011	500	Completed August 2011	None provided
NCT01270633	TEI Biosciences	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.	December 2010	September 2012	25	Completed	None provided

Table 16. Clinical Trials, continued

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Purpose	Start Date	Expected Completion Date	Estimated Enrollment	Status	Publications
NCT01327937	Organogenesis	To use microarray technology to identify and characterize the gene expression of multiple relevant genes in biopsies of nonhealing venous ulcers.	March 2011	June 2013	30	Currently recruiting	N/A
NCT01060670	LifeSciences Corp.	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	April 2010	October 2013	350	Currently recruiting	N/A
NCT01450943	VA Northern California Health Care System	The primary objective of this study is to assess the effectiveness of cellular dermal replacement tissue vs. nonviable extracellular matrix (ECM) for treating nonhealing DFUs. Our hypothesis is that these devices are of equal efficacy.	October 2011	October 2014	171	Currently recruiting	N/A
NCT00399308	Advanced Biohealing, Inc.	This pilot study was designed to test the safety of Celaderm(TM) in treating venous leg ulcers and to give preliminary information about the efficacy of two different Celaderm(TM) dosing regimens.	January 2007	April 2008	40	Completed	None provided
NCT01181453	Advanced Biohealing, Inc.	This study randomly assigns patients with DFUs to receive standard therapy (surgical débridement, saline moistened gauze and offloading) alone or standard therapy plus Dermagraft(R). Dermagraft is a device containing live human fibroblasts grown on an absorbable Vicryl mesh.	December 1998	March 2000	314	Completed	1 Marston et al.[56] included in report

Table 16. Clinical Trials, continued

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Purpose	Start Date	Expected Completion Date	Estimated Enrollment	Status	Publications
NCT01181440	Advanced Biohealing, Inc.	Patients with plantar DFUs will be randomized to receive conventional therapy (débridement, infection control, saline-moistened gauze dressings, and standardized off-weighting) alone or conventional therapy plus Dermagraft(R).	September 1994	January 1997	281	Completed	2
NCT00007280	National Institute of Arthritis and Musculoskeletal and Skin Diseases	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).	October 2000	August 2005	50	Completed	11 Falanga 1999[161] excluded as subgroup analysis of prior published study (Falanga 1998[63] included); remaining publications were narrative reviews or cell-based studies
NCT01353495	Wright Medical Technology	Have indolent diabetic ulcers completely healed by the Acellular Porcine Dermal Matrix (APM) in 12 weeks.	April 2010	April 2011	40	Completed	None provided
NCT00270946	Ortec International	To evaluate the clinical benefits and safety of OrCel plus compression therapy (SOC) vs. compression therapy in treating venous ulcers.	April 2002	December 2003	130	Completed	None provided

N/A: Not applicable

Discussion and Conclusions

Our searches identified 57 skin substitute products (as defined in this report) available in the United States that are used to manage or treat chronic wounds and regulated by FDA. Based on FDA regulations that govern each product we identified and on the origin and composite of the products, skin substitutes can be organized into four groups: human-derived products regulated as HCT/Ps, human- and human/animal-derived products regulated through PMA or humanitarian device exemption (HDE), animal-derived products regulated under the 510(k) process, and synthetic products regulated under the 510(k) process. Human tissue can be obtained from human donors, processed, and used exactly in the same role in the recipient, such as a dermal replacement to be placed in a wound as a skin substitute (regulated as HCT/Ps). Human tissue and cells may also be used as a source of cells for culturing to produce cellular-derived material for wound healing. These products may be regulated under the BLA or PMA/HDE processes, depending on their composition and primary mode of action. Other skin substitutes are derived only from animal tissue or biosynthetic materials and are regulated under the 510(k) process.

The skin substitutes listed in this report cover a wide variety of components, from cellular to acellular, that may provide important elements in treating or managing chronic wounds. The products regulated under the 510(k) process were generally acellular and contained collagen as the primary component. These products are indicated for managing partial- to full-thickness wounds including pressure ulcers, venous ulcers, and diabetic ulcers and may be used as first-line treatments. In contrast, products such as Apligraf and Dermagraft, regulated under PMA, that contain a human cellular component combined with a acellular component are indicated for chronic wounds that have not healed for more than 30 days. Therefore, the wounds treated by Apligraf or Dermagraft have not responded to other treatments such as gauze or to the products regulated under the 510(k) process. Because of the requirements placed on the PMA process, products such as Apligraf and Dermagraft also have more clinical evidence from RCTs supporting their efficacy compared with products regulated under the 510(k) process. Products using the 510(k) process rely on similarity to predicate products to support their efficacy.

We identified some products not regulated through the PMA process that were examined in RCTs. These included TheraSkin (compared with Apligraf), Graftjacket (compared with various wound dressings), Hyalograft 3D/Laserskin (compared with gauze), Oasis Wound Matrix (compared with gauze and other wound dressings), and Talymed (compared with gauze). When assessing risk of bias of the RCTs included in this report and the strength of the evidence base, no special consideration was given to whether a product was regulated under PMA or 510(k).

One of the goals of this report was to begin to characterize the state of the evidence base on skin substitutes as wound care products for chronic wounds. For this report, we sought to determine the number of RCTs of these products and to assess the ability of skin substitutes to promote wound healing in these trials. Eighteen RCTs, examining only seven of the skin substitute products identified for this report, met the inclusion criteria. Twelve of the studies examined diabetic foot ulcers and six studies examined venous and/or arterial leg ulcers. No studies of pressure ulcers met our inclusion criteria; only one RCT of pressure ulcers was identified.

Very few of the skin substitute products identified in this report have been examined in RCTs. Comparisons with other alternatives to usual wound care were also limited. Saline-moistened gauze or nonadherent paraffin gauze was the most used comparison in trials examining the treatment of diabetic foot ulcers.

Various organizations interested in wound care have made recommendations for the proper design and conduct of studies evaluating wound treatments.[10,106,108,113] These recommendations

coupled with recommendations on how to assess risk of bias in a study are the basis for the questions used to assess study quality in this report. Blinding of the individuals assessing wound outcomes was suggested by all of these organizations. Our review of the methods used in the studies included in this report indicates that no study actually blinded wound assessors to treatment assignment. While complete wound closure is an objective outcome with less need for blinding, other less objective outcomes such as time to 50 percent wound closure or rate of wound reduction should be assessed in a blinded fashion. While we judged eight studies to have low potential for bias and nine studies to have moderate potential for bias when assessing complete wound closure, the assessment of other wound outcomes would likely have higher potential for bias. Various features of study design and conduct as pointed out in this report could be improved in future wound care studies to ensure better study quality and low potential for bias.

The strength of the evidence base for evaluating complete wound healing of diabetic foot ulcers at 12 weeks was graded as low for the comparisons of Graftjacket vs. moist wound products,[66] the comparison of Apligraf vs. a nonadherent dressing,[63] and for Graftskin vs. saline-moistened gauze.[67] Each of these studies represented a multicenter trial with a low risk of bias for the outcome of complete wound healing. The outcome measure was direct and the results were precise. Although the evidence for the comparison of Dermagraft vs. saline-moistened gauze came from 3 studies including 530 patients and had a precise result of a direct outcome, we judged the strength of the evidence to be only low because the studies had a moderate risk of bias.[56,62,65] The strength of the evidence for other comparisons for diabetic foot ulcers were graded insufficient, primarily because the overall risk of bias was moderate and/or the reported treatment effect (percentage increase in completely healed wounds) was imprecise.

Only two comparisons were judged to have low strength of evidence for complete wound healing of venous or mixed ulcers at 12 weeks. One compared Apligraf and compression to compression,[63] and one compared Oasis Wound Matrix with compression to compression.[69] In each case, the included study was a multicenter trial, had a low risk of bias and reported a precise and direct result. The other comparisons were from studies with moderate risk of bias and imprecise results; these were judged to have an insufficient strength of evidence grade.

A grade of low means we have low confidence that the evidence reflects the true effect of skin substitutes on complete wound healing, and we believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. A grade of insufficient indicates that the available evidence does not support a conclusion regarding the comparison.

Applicability of the evidence base to address important questions about the effectiveness of skin substitutes for treating chronic wounds in typical populations was limited. The overall applicability of the evidence base is limited to a small number of skin substitute products examining diabetic foot ulcers and venous and/or arterial leg ulcers and to patients in generally good health. Although these results are consistent in showing a benefit when using skin substitutes and suggest that skin substitutes could be used in treating diabetic foot ulcers and venous leg ulcers, the patients enrolled in these studies were in generally good health and free of infected wounds, medications that would impede wound healing, clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes. The results of these studies may not easily translate to everyday clinical situations. The expected population with chronic wounds is likely to have these conditions; therefore, the results reported in studies without these patients may not extrapolate well. The applicability of the findings to sicker patients may be limited.

The results of the available studies cannot be extended to other skin substitute products because of differences in active components in the various products. Additionally, the results from studies of diabetic foot ulcers do not extrapolate to studies of venous or arterial leg ulcers because of differences in pathophysiology and etiology. Therefore, no clinical efficacy data from RCTs are available for the large majority of the skin substitute products identified in this report. The studies that are available may not be generalizable to a broader patient population that is not as healthy as the patients in these studies.

Also missing from this evidence base were studies that compared the various types of skin substitute products. Only two of the 18 studies compared two skin substitute products (Oasis versus Hyaloskin and Apligraf versus TheraSkin). How a human dermal substitute such as Graftjacket compares with a human derived skin substitute such as Dermagraft when treating a diabetic foot ulcer or a vascular leg ulcer is unknown. Such comparisons could be useful to clinicians trying to decide which wound treatment products to use. 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.

References

1. Chern PL, Baum CL, Arpey CJ. Biologic dressings: current applications and limitations in dermatologic surgery. Dermatol Surg 2009 Jun;35(6):891-906. PMID: 19397669

2. Lazarus GS, Cooper DM, Knighton DR, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol 1994 Apr;130(4):489-93. PMID: 8166487

3. American Society of Plastic Surgeons. Evidence-based clinical practice guideline: chronic wounds of the lower extremity. Arlington Heights (IL): American Society of Plastic Surgeons; 2007 May. 21 p. Also available: http://www.guideline.gov.

4. Eisenbud D, Huang NF, Luke S, et al. Skin substitutes and wound healing: current status and challenges. Wounds 2004;16(1):2-17. Also available: http://www.medscape.com/viewarticle/470251_print.

5. Dieckmann C, Renner R, Milkova L, et al. Regenerative medicine in dermatology: biomaterials, tissue engineering, stem cells, gene transfer and beyond. Exp Dermatol 2010 Aug;19(8):697-706. PMID: 20545761

6. Humanitarian device exemption. [internet]. Rockville (MD): U.S. Food and Drug Administration (FDA); 2010 Aug 30 [accessed 2011 Nov 30]. [2 p]. Available: http://www.fda.gov.

7. PMA approvals. [internet]. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 Jun 18 [accessed 2011 Nov 30]. [3 p]. Available: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm.

8. Center for Devices and Radiological Health (CDRH). Premarket notification (510k). [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2010 Sep 3 [accessed 2011 Nov 30]. [4 p]. Available: http://www.fda.gov.

9. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews [AHRQ Publication No. 12-EGC047-EF]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2012 Mar. 33 p. Also available: http://www.effectivehealthcare.ahrq.gov.

10. Center for Biologics Evaluation and Research (CBER). Guidance for industry: chronic cutaneous ulcer and burn wounds — developing products for treatment. Rockville (MD): U.S. Food and Drug Administration, Center for Drug Evaluation and Research; 2006 Jun. 22 p. Also available: http://www.fda.gov/cder/guidance/index.htm#clinical%20medicine.

11. ACell, Incorporated. 510(k) summary for ACell UBM hydrated wound dressing. K022854. Rockville (MD): U.S. Food and Drug Administration (FDA); 2002 Dec 30. 5 p. Also available: http://www.fda.gov.

12. ACell, Incorporated. 510(k) Summary for Acell UBM lyophilized wound dressing. K021637. Rockville (MD): U.S. Food and Drug Administration (FDA); 2002 Dec 19. 5 p. Also available: http://www.fda.gov.

13. Aeon Astron Europe B.V. 510(k) summary for Aongen collagen matrix. K080868. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 May 14. 5 p. Also available: http://www.fda.gov.

14. Wright Medical Technology, Inc. 510(k) summary for Atlas wound matrix. K090954. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 Jul 30. 5 p. Also available: http://www.fda.gov.

15. Integra LifeSciences Corporation. 510(k) summary for Avagen wound dressing. K022127. Rockville (MD): U.S. Food and Drug Administration (FDA); 2002 Sep 10. 4 p. Also available: http://www.fda.gov.

16. Innocoll Pharmaceuticals. 510(k) summary for collagen sponge. K092805. Rockville (MD): U.S. Food and Drug Administration (FDA); 2010 Feb 16. 5 p. Also available: http://www.fda.gov.

17. OASIS Research, LLC. 510(k) summary for collagen wound dressing. K002443. Rockville (MD): U.S. Food and Drug Administration (FDA); 2000 Oct 18. 5 p. Also available: http://www.fda.gov.

18. Innocoll Pharmaceuticals. 510(k) summary for CollaGUARD. K061746. Rockville (MD): U.S. Food and Drug Administration (FDA); 2006 Oct 2. 5 p. Also available: http://www.fda.gov.

19. Hartmann-Conco, Inc. 510(k) summary for CollaSorb collagen wound dressing. K091338. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 Aug 26. 5 p. Also available: http://www.fda.gov.

20. Collamatrix, Inc. 510(k) summary for CollaWound dressing. K061474. Rockville (MD): U.S. Food and Drug Administration (FDA); 2006 Jul 5. 5 p. Also available: http://www.fda.gov.

21. Innocoll Pharmaceuticals. 510(k) summary for Collexa. K100574. Rockville (MD): U.S. Food and Drug Administration (FDA); 2010 Oct 4. 5 p. Also available: http://www.fda.gov.

22. Innocoll Pharmaceuticals. 510(k) summary for Collieva. K081782. Rockville (MD): U.S. Food and Drug Administration (FDA); 2008 Sep 30. 5 p. Also available: http://www.fda.gov.

23. Coreleader Biotech Co., Ltd. 510(k) summary for Coreleader Colla-Pad. K102946. Rockville (MD): U.S. Food and Drug Administration (FDA); 2011 May 20. 5 p. Also available: http://www.fda.gov.

24. Pegasus Biologics, Inc. 510(k) summary for DermADAPT wound dressing. K061494. Rockville (MD): U.S. Food and Drug Administration (FDA); 2006 Sep 21. 5 p. Also available: http://www.fda.gov.

25. TEI Biosciences, Inc. 510(k) summary for DressSkin. K023778. Rockville (MD): U.S. Food and Drug Administration (FDA); 2003 Sep 29. 5 p. Also available: http://www.fda.gov.

26. Brennen Medical, Inc. 510(k) summary E-Z Derm biosynthetic wound dressing. K935189. [internet]. Rockville (MD): U.S. Food and Drug Administration (FDA); 1994 Jul 11 [accessed 2011 Nov 30]. [1 p]. Available: http://www.fda.gov.

27. Mesynthes, Ltd. 510(k) summary for Endoform dermal template. K092096. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 Jul 10. 5 p. Also available: http://www.fda.gov.

28. Tissue Repair Company. 510(k) summary for Excellagen. K110318. Rockville (MD): U.S. Food and Drug Administration (FDA); 2011 Oct 3. 6 p. Also available: http://www.fda.gov.

29. Organogenesis, Inc. 510(k) summary for FortaDerm wound dressing. K011026. Rockville (MD): U.S. Food and Drug Administration (FDA); 2001 Jun 13. 4 p. Also available: http://www.fda.gov.

30. ConvaTec, a division of E.R. Squibb and Sons, Inc. 510(k) summary of safety and effectiveness for HA absorbent wound dressing. K984388. Rockville (MD): U.S. Food and Drug Administration (FDA); 1999 Mar 3. 5 p. Available: http://www.fda.gov.

31. ENCOLL Corp. 510(k) summary for Helicoll. K040314. Rockville (MD): U.S. Food and Drug Administration (FDA); 2004 Aug 12. 6 p. Also available: http://www.fda.gov.

32. Integra LifeSciences Corporation. 510(k) summary for bilayer matrix wound dressing. K021792. Rockville (MD): U.S. Food and Drug Administration (FDA); 2002 Aug 14. 4 p. Available: http://www.fda.gov.

33. Integra LifeSciences Corporation. 510(k) summary for Integra flowable wound matrix. K072113. Rockville (MD): U.S. Food and Drug Administration (FDA); 2007 Oct 10. 4 p. Also available: http://www.fda.gov.

34. LifeCell Corporation. 510(k) summary for LTM wound dressing. K082103. Rockville (MD): U.S. Food and Drug Administration (FDA); 2008 Oct 8. 6 p. Also available: http://www.fda.gov.

35. ACell, Inc. 510(k) summary for ACell MatriStem wound sheet. K092926. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 Oct 28. 4 p. Available: http://www.fda.gov.

36. ACell. 510(k) summary for MatriStem wound matrix. K112409. Rockville (MD): U.S. Food and Drug Administration (FDA); 2011 Aug 29. 4 p. Also available: http://www.fda.gov.

37. Collagen Matrix, Inc. 510(k) summary for collagen topical wound dressing. K040558. Rockville (MD): U.S. Food and Drug Administration (FDA); 2004 Mar 17. 5 p. Also available: http://www.fda.gov.

38. Melkerson MN. (Director, Division of General, Restorative and Neurological Devices, Office of Device Evaluation, Center for Devices and Radiological Health, U.S. Food and Drug Administration). Section 510(k) premarket notification of intent to market Medline collagen wound dressing. Medline Industries, Inc. K060456. 2006 Jun 19. 3 p.

39. Cook Biotech, Inc. Special 510(k) summary for Oasis wound matrix. K061711. Rockville (MD): U.S. Food and Drug Administration (FDA); 2006 Jul 18. 4 p. Available: http://www.fda.gov.

40. TEI Biosciences, Inc. 510(k) summary for PriMatrix. K083440. Rockville (MD): U.S. Food and Drug Administration (FDA); 2008 Dec 12. 5 p. Also available: http://www.fda.gov.

41. TEI Biosciences, Inc. 510(k) summary for PriMatrix. K061407. Rockville (MD): U.S. Food and Drug Administration (FDA); 2006 Jun 29. 5 p. Available: http://www.fda.gov.

42. Cook Biotech, Incorporated. 510(k) summary for SIS Wound Dressing II. K993948. Rockville (MD): U.S. Food and Drug Administration (FDA); 2000 Jan 6. 4 p. Also available: http://www.fda.gov.

43. Cook Biotech Incorporated. 510(k) Summary for SS Matrix. K020732. Rockville (MD): U.S. Food and Drug Administration (FDA); 2002 May 30. 4 p. Also available: http://www.fda.gov.

44. Southwest Technologies, Inc. 510(k) summary for Stimulen collagen. K030774. Rockville (MD): U.S. Food and Drug Administration (FDA); 2004 Aug 9. 5 p. Also available: http://www.fda.gov.

45. Sewon Cellontech Co., Ltd. 510(k) summary for TheraForm standard/sheet. K090812. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 Jul 30. 5 p. Also available: http://www.fda.gov.

46. Synovis Orthopedic and Woundcare, Inc. 510(k) summary for Unite Biomatrix. K112399. Rockville (MD): U.S. Food and Drug Administration (FDA); 2011 Sep 7. 5 p. Also available: http://www.fda.gov.

47. Pegasus Biologics, Inc. 510(k) summary for Unite Biomatrix. K071425. Rockville (MD): U.S. Food and Drug Administration (FDA); 2007 Jun 20. 5 p. Also available: http://www.fda.gov.

48. Fidia Advanced Biopolymers. 510(k) summary for Hyalomatrix KD wound dressing. K001508. Rockville (MD): U.S. Food and Drug Administration (FDA); 2001 Apr 23. 4 p. Available: http://www.fda.gov.

49. Anika therapeutics, S.r.l. 510(k) summary for Hyalomatrix. K073251. Rockville (MD): U.S. Food and Drug Administration (FDA); 2011 May 19. 5 p. Also available: http://www.fda.gov.

50. Fidia Advanced Biopolymers S.r.l. 510(k) summary for Jaloskin. K001508. Rockville (MD): U.S. Food and Drug Administration (FDA); 2010 Jan 26. 5 p. Also available: http://www.fda.gov.

51. PolyMedics Innovations, GmbH. 510(k) summary for suprathel wound and burn dressing. K090160. Rockville (MD): U.S. Food and Drug Administration (FDA); 2009 May 7. 6 p. Also available: http://www.fda.gov.

52. Marine Polymer Technologies, Inc. 510(k) summary for Talymed. K102002. Rockville (MD): U.S. Food and Drug Administration (FDA); 2010 Jul 28. 5 p. Also available: http://www.fda.gov.

53. Edmonds M, European and Australian Apligraf Diabetic Foot Ulcer Study Group. Apligraf in the treatment of neuropathic diabetic foot ulcers. Int J Low Extrem Wounds 2009 Mar;8(1):11-8. PMID: 19189997

54. Landsman A, Roukis TS, DeFronzo DJ, et al. Living cells or collagen matrix: which is more beneficial in the treatment of diabetic foot ulcers? Wounds 2008;20(5):111-6.

55. Krishnamoorthy L, Harding K, Griffiths D, et al. The clinical and histological effects of Dermagraft in the healing of chronic venous leg ulcers. Phlebology 2003;18(1):12-22.

56. Marston WA, Hanft J, Norwood P, et al. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care 2003 Jun;26(6):1701-5. PMID: 12766097

57. Romanelli M, Dini V, Bertone MS. Randomized comparison of OASIS wound matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. Adv Skin Wound Care 2010 Jan;23(1):34-8. PMID: 20101114

58. Caravaggi C, De Giglio R, Pritelli C, et al. HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial. Diabetes Care 2003 Oct 1;26(10):2853-9.

59. Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. Int Wound J 2006 Sep;3(3):181-7. PMID: 16984575

60. Romanelli M, Dini V, Bertone M, et al. OASIS wound matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. Int Wound J 2007 Mar;4(1):3-7. PMID: 17425543

61. Kelechi TJ, Mueller M, Hankin CS, et al. A randomized, investigator-blinded, controlled pilot study to evaluate the safety and efficacy of a poly-N-acetyl glucosamine-derived membrane material in patients with venous leg ulcers. J Am Acad Dermatol 2012 Jun;66(6):e209-15. Epub 2011 May 26. PMID: 21620515

62. Naughton G, Mansbridge J, Gentzkow G. A metabolically active human dermal replacement for the treatment of diabetic foot ulcers. Artif Organs 1997 Nov;21(11):1203-10. PMID: 9384327

63. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human skin equivalent investigators group. Arch Dermatol 1998 Mar;134(3):293-300. PMID: 9521027

64. DiDomenico L, Emch KJ, Landsman AR, et al. A prospective comparison of diabetic foot ulcers treated with either cryopreserved skin allograft or bioengineered skin substitute. Wounds 2011;23(7):184-9. Also available: http://cwccl.patientadvocate.org/articles/DiDomenico%20et%20al.%20Wounds.pdf.

65. Gentzkow GD, Iwasaki SD, Hershon KS, et al. Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes Care 1996 Apr;19(4):350-4. PMID: 8729158

66. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. Int Wound J 2009 Jun;6(3):196-208.

67. Veves A, Falanga V, Armstrong DG, et al. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes Care 2001 Feb;24(2):290-5. PMID: 11213881

68. Uccioli L, Giurato L, Ruotolo V, et al. Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. Int J Low Extrem Wounds 2011 Jun;10(2):80-5. PMID: 21693443

69. Mostow EN, Haraway GD, Dalsing M, et al. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. J Vasc Surg 2005 May;41(5):837-43. PMID: 15886669

70. Niezgoda JA, Van Gils CC, Frykberg RG, et al. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. Adv Skin Wound Care 2005 Jun;18(5 Pt 1):258-66. PMID: 15942317

71. Laing P. Diabetic foot ulcers. Am J Surg 1994 Jan;167(1A):31S-6S. PMID: 8109682

72. Frykberg RG, Armstrong DG, Giurini J, et al. Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. J Foot Ankle Surg 2000;39(5 Suppl):S1-60. PMID: 11280471

73. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. [internet]. North Miami Beach (FL): Wound Care Institute; 1991 [accessed 2005 Sep 7]. [11 p]. Available: http://www.woundcare.org/newsvol2n2/ulcer2.htm.

74. Stadelmann WK, Digenis AG, Tobin GR. Physiology and healing dynamics of chronic cutaneous wounds. Am J Surg 1998 Aug;176(2A Suppl):26S-38S. PMID: 9777970

75. Stillman RM. Diabetic ulcers. [internet]. Omaha (NE): eMedicine.com; 2005 Mar 22 [accessed 2005 Sep 7]. [25 p]. Available: http://www.emedicine.com/med/topic551.htm.

76. de Leon J. Negative pressure wound therapy in pressure ulcer management. Ostomy Wound Manage 2005 Feb;51(2A Suppl):3-8. PMID: 15699557

77. Folkedahl BA, Frantz R. Treatment of pressure ulcers. Iowa City (IA): University of Iowa Gerontological Nursing Interventions Research Center, Research Dissemination Core; 2002 Aug. 30 p.

78. Gupta S, Baharestani M, Baranoski S, et al. Guidelines for managing pressure ulcers with negative pressure wound therapy. Adv Skin Wound Care 2004 Nov-Dec;17(Suppl 2):1-16. PMID: 15716646

79. Smith DM. Pressure ulcers in the nursing home. Ann Intern Med 1995 Sep 15;123(6):433-42. PMID: 7639444

80. Sieggreen MY, Kline RA. Recognizing and managing venous leg ulcers. Adv Skin Wound Care 2004 Jul-Aug;17(6):302-11; quiz 312-3. PMID: 15289718

81. Moffatt CJ, Dorman MC. Recurrence of leg ulcers within a community ulcer service. J Wound Care 1995 Feb;4(2):57-61. PMID: 7600337

82. Barr DM. The Unna's boot as a treatment for venous ulcers. Nurse Pract 1996 Jul;21(7):55-6, 61-4, 71-2, passim. PMID: 8823788

83. Goodfield M. Optimal management of chronic leg ulcers in the elderly. Drugs Aging 1997 May;10(5):341-8. PMID: 9143855

84. Falanga V, Eaglstein WH. A therapeutic approach to venous ulcers. J Am Acad Dermatol 1986 May;14(5 Pt 1):777-84. PMID: 3519695

85. O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers (Review). In: Cochrane Database of Systematic Reviews [internet]. Issue 1. Hoboken (NJ): John Wiley & Sons, Ltd.; 2009 [accessed 2009 May 15]. [Art. No.: CD000265]. Available: DOI: 10.1002/14651858.CD000265.pub2.

86. Gist S, Tio-Matos I, Falzgraf S, et al. Wound care in the geriatric client. Clin Interv Aging 2009;4:269-87. PMID: 19554098

87. Nelson EA, Bradley MD. Dressings and topical agents for arterial leg ulcers. Cochrane Database Syst Rev 2007;(1):CD001836. PMID: 17253465

88. de la Torre JI, Chambers JA. Wound healing, chronic wounds. [internet]. Omaha (NE): eMedicine.com; 2008 Oct 9 [accessed 2009 May 5]. [13 p]. Available: http://emedicine.medscape.com/article/1298452-print.

89. Stillman RM. Wound care. [internet]. Omaha (NE): eMedicine.com; 2008 Aug 19 [accessed 2009 May 18]. [28 p]. Available: http://emedicine.medscape.com/article/194018-print.

90. Brett D. A review of collagen and collagen-based wound dressings. [internet]. St. Petersburg (FL): Smith & Nephew Inc.; 2008 Dec 12 [3 p]. Available: http://www.woundsresearch.com/.

91. Hanna JR, Giacopelli JA. A review of wound healing and wound dressing products. J Foot Ankle Surg 1997 Jan-Feb;36(1):2-14; discussion 79. PMID: 9031020

92. Schultz GS, Davidson JM, Kirsner RS, et al. Dynamic reciprocity in the wound microenvironment. Wound Repair Regen 2011 Mar-Apr;19(2):134-48. PMID: 21362080

93. Krafts KP. Tissue repair: the hidden drama. Organogenesis 2010 Oct-Dec;6(4):225-33. PMID: 21220961

94. Gabriel A. Wound healing and growth factors. In: Medscape Reference [internet]. New York (NY): WebMD LLC; 2011 Aug 22 [accessed 2012 Mar 22]. [7 p]. Available: http://emedicine.medscape.com/article/1298196-overview#showall.

95. Lau J, Tatsioni A, Balk E, et al. Usual care in the management of chronic wounds: a review of the recent literature. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2005 Mar 8. 53 p.

96. Ovington LG. Hanging wet-to-dry dressings out to dry. Adv Wound Care 2002 Mar-Apr;15(2):79-86.

97. ECRI Institute. Occlusive dressings for the treatment of chronic wounds. Plymouth Meeting (PA): ECRI Institute; 2000 Feb. 141 p. (Technology Assessment Report).

98. Jones JE, Nelson EA. Skin grafting for venous leg ulcers. Cochrane Database Syst Rev 2007;(2):CD001737. PMID: 17443510

99. Ovington LG. Advances in wound dressings. Clin Dermatol 2007 Jan-Feb;25(1):33-8. PMID: 17276199

100. Ovington LG. The well-dressed wound: an overview of dressing types. Wounds 1998 Jan-Feb;10(Suppl A):1A-9A.

101. Kannon GA, Garrett AB. Moist wound healing with occlusive dressings a clinical review. Dermatol Surg 1995 Jul;21(7):583-90. PMID: 7606367

102. Jones V, Grey JE, Harding KG. Wound dressings. BMJ 2006 Apr 1;332(7544):777-80. PMID: 16575081

103. Hansson C. Interactive wound dressings a practical guide to their use in older patients. Drugs Aging 1997 Oct;11(4):271-84. PMID: 9342557

104. Papanas N, Maltezos E. Becaplermin gel in the treatment of diabetic neuropathic foot ulcers. Clin Interv Aging 2008;3(2):233-40. PMID: 18686746

105. CFR - Code of Federal Regulations Title 21: Subchapter L--regulations under certain other acts administered by the Food and Drug Administration, Sec. 1271. Human cells, tissues, and cellular and tissue-based products. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2010 Apr 1. 35 p.

106. Gottrup F, Apelqvist J, Price P, et al. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. J Wound Care 2010 Jun;19(6):237-68. PMID: 20551864

107. Gottrup F, Apelqvist J. Present and new techniques and devices in the treatment of DFU: a critical review of evidence. Diabetes Metab Res Rev 2012 Feb;28 Suppl 1:64-71. PMID: 22271726

108. Serena T, Bates-Jensen B, Carter MJ, et al. Consensus principles for wound care research obtained using a Delphi process. Wound Repair Regen 2012 May-Jun;20(3):284-93. PMID: 22564224

109. Narine L, Yee DS, Einarson TR, et al. Quality of abstracts of original research articles in CMAJ in 1989. CMAJ 1991 Feb 15;144(4):449-53. PMID: 1993292

110. Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. JAMA 1999 Mar 24-31;281(12):1110-1. PMID: 10188662

111. Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010 May;63(5):513-23. PMID: 19595577

112. Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration; 2011 Mar. Also available: http://www.cochrane-handbook.org/.

113. Sonnad SS, Goldsack J, Mohr P, et al. Methodological recommendations for comparative effectiveness research on the treatment of chronic wounds. Version 2.0 Final. Baltimore (MD): Center for Medical Technology Policy; 2012 Oct 1. 57 p.

114. Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. Ann Intern Med 2002 Feb 5;136(3):254-9. PMID: 11827510

115. Mayrovitz HN, Soontupe LB. Wound areas by computerized planimetry of digital images: accuracy and reliability. Adv Skin Wound Care 2009 May;22(5):222-9. PMID: 19521289

116. Laplaud AL, Blaizot X, Gaillard C, et al. Wound debridement: comparative reliability of three methods for measuring fibrin percentage in chronic wounds. Wound Repair Regen 2010 Jan-Feb;18(1):13-20. PMID: 20082676

117. Rogers LC, Bevilacqua NJ, Armstrong DG, et al. Digital planimetry results in more accurate wound measurements: a comparison to standard ruler measurements. J Diabetes Sci Technol 2010 Jul;4(4):799-802. PMID: 20663440

118. Oien RF, Hakansson A, Hansen BU, et al. Measuring the size of ulcers by planimetry: a useful method in the clinical setting. J Wound Care 2002 May;11(5):165-8. PMID: 12055939

119. Little C, McDonald J, Jenkins MG, et al. An overview of techniques used to measure wound area and volume. J Wound Care 2009 Jun;18(6):250-3. PMID: 19661849

120. AlloDerm regenerative tissue matrix. [internet]. Branchburg (NJ): LifeCell Corporation; 2011 [accessed 2011 Nov 3]. [1 p]. Available: http://www.lifecell.com/alloderm-regenerative-tissue-matrix/95/.

121. Allopatch HD: acellular human dermis. [internet]. Edison (NJ): MTF Sports Medicine; [accessed 2011 Nov 3]. [1 p]. Available: http://mtfsports.org/allopatch_hd.html.

122. Allograft catalog. Centennial (CO): AlloSource; 2011 Mar. 32 p. Also available: http://www.allosource.org/content/pdf/allografts/allografts.pdf.

123. Cymetra micronized alloderm tissue. [internet]. Branchburg (NJ): LifeCell Corporation; 2011 [accessed 2011 Nov 3]. [1 p]. Available: http://www.lifecell.com/cymetra-micronized-alloderm-tissue/.

124. Skin and Wound Allograft Institute (SWAI) - dermacell. [internet]. Virginia Beach (VA): LifeNet Health; [accessed 2011 Nov 3]. [2 p]. Available: http://www.accesslifenethealth.org/application/skin-and-wound-allograft-institute.

125. FlexHD. [internet]. Edison (NJ): Musculoskeletal Transplant Foundation; [accessed 2011 Nov 3]. [1 p]. Available: http://www.mtf.org/professional/flex_hd.html.

126. FlexHD acellular hydrated dermis family. [internet]. West Somerville (NJ): Ethicon, Inc.; [accessed 2011 Nov 3]. [1 p]. Available: http://www.ethicon360.com/products/flex-hd-acelular-hydrated-dermis-family.

127. GammaGraft. [internet]. Pittsburgh (PA): Promethean LifeSciences, Inc.; [accessed 2011 Nov 3]. [2 p]. Available: http://pl-s.com/gammagraft.html.

128. GraftJacket regenerative tissue matrix - ulcer repair. San Antonio (TX): Kinetic Concepts, Inc.; 10 p. Also available: http://www.kci1.com/cs/Satellite?blobcol=urldata&blobheadername1=Content-type&blobheadername2=Content-disposition&blobheadername3=MDT-Type&blobheadervalue1=application%2Fpdf&blobheadervalue2=inline%3B+filename%3D184%252F69%252FGRAFTJACKET%25C2%25AE%2.

129. Matrix HD. [internet]. Alachua (FL): RTI Biologics, Inc.; [accessed 2011 Nov 3]. [3 p]. Available: http://www.rtix.com/surgeons/implants/sports-medicine/matrix-hd.

130. MemoDerm. [internet]. Memphis (TN): Memometal, Inc.; [accessed 2011 Nov 3]. [2 p]. Available: http://www.mmi-usa.com/memoderm/index.html.

131. Puros dermis allograft tissue matrix. The natural choice for soft tissue augmentation. [internet]. Carlsbad (CA): Zimmer Dental, Inc.; [accessed 2011 Nov 3]. [3 p]. Available: http://www.zimmerdental.com/eblast/september06Dermis.htm.

132. Repliform tissue regeneration matrix. [internet]. Natick (MA): Boston Scientific Corporation; [accessed 2011 Nov 3]. [2 p]. Available: http://www.bostonscientific.com/Device.bsci?page=HCP_Overview&navRelId=1000.1003&method=DevDetailHCP&id=10005411&pageDisclaimer=Disclaimer.ProductPage.

133. TheraSkin. [internet]. Newport News (VA): Soluble Systems; [accessed 2011 Nov 3]. [2 p]. Available: http://www.solublesystems.com/Theraskin.

134. What is Apligraf? [internet]. Canton (MA): Organogenesis Inc.; [accessed 2011 Nov 3]. [1 p]. Available: http://www.apligraf.com/professional/what_is_apligraf/index.html.

135. U.S. Food and Drug Administration (FDA). Approval of the premarket approval application (PMA) for Apligraf. P950032. 1998 May 22. 8 p. Also available: http://www.fda.gov.

136. Dermagraft. [internet]. La Jolla (CA): Advanced Biohealing, Inc.; [accessed 2011 Nov 3]. [2 p]. Available: http://www.dermagraft.com/about/overview/.

137. U.S. Food and Drug Administration (FDA). Approval of the premarket approval application (PMA) for Dermagraft. P000036. 2000 Sep 28. 7 p. Also available: http://www.fda.gov.

138. Endoform platform. [internet]. Lower Hutt (New Zealand): Mesynthes, Ltd; [accessed 2011 Nov 3]. [2 p]. Available: http://www.mesynthes.com/index.php?option=com_content&view=category&layout=blog&id=15&Itemid=17.

139. E-Z Derm: biosynthetic wound dressing. [internet]. Geneva (Switzerland): AM Scientifics, Ltd; [accessed 2011 Nov 3]. [3 p]. Available: http://www.am-scientifics.com/?id=18.

140. Integra product description and benefits. [internet]. Plainsboro (NJ): Integra LifeSciences Corporation; [accessed 2011 Nov 3]. [2 p]. Available: http://www.ilstraining.com/bmwd/bmwd/bmwd_it_01.html.

141. MatriStem wound care matrix. [internet]. Columbia (MD): ACell, Inc; [accessed 2011 Nov 3]. [1 p]. Available: http://www.acell.com/wound_care.php.

142. Oasis wound matrix. [internet]. Healthpoint Biotherapeutics; [accessed 2011 Nov 3]. [1 p]. Available: http://www.oasiswoundmatrix.com/home.

143. PriMatrix. [internet]. Boston: TEI Biosciences; [accessed 2011 Nov 3]. [1 p]. Available: http://www.teibio.com/PriMatrix.aspx.

144. Hyalomatrix. [internet]. Bedford (MA): Anika Therapeutics, Inc; [accessed 2011 Nov 3]. [1 p]. Available: http://www.anikatherapeutics.com/products/dermal/hyalomatrix.html.

145. Suprathel. [internet]. Denkendorf (Germany): PolyMedics Innovations GmbH; [accessed 2011 Nov 3]. [1 p]. Available: http://www.suprathel.de/?L=1.

146. Advanced BioHealing, Inc. An initial evaluation of the safety and activity of celaderm treatment regimens in healing venous leg ulcers. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2011 Nov 3]. [4 p]. Available: http://clinicaltrials.gov/ct2/show/NCT00399308 NLM Identifier: NCT00399308.

147. Laboratories Genevrier. Efficacy and safety study of dermagen vs conventional treatment to treat diabetic neuropathic foot ulcer. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2011 Nov 3]. [4 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT00521937 NLM Identifier: NCT00521937.

148. Epicel - severe burn treatment. [internet]. Cambridge (MA): Genzyme Corporation; [accessed 2011 Nov 3]. [1 p]. Available: http://www.genzyme.com/business/biosurgery/burn/burn_home.asp.

149. U.S. Food and Drug Administration (FDA). Approval of the humanitarian device exemption (HDE) application for the Genzyme Biosurgery Epicel. H990002. 2007 Oct 25. 8 p. Also available: http://www.fda.gov.

150. EpiDex. [internet]. Leipzig (Germany): Euroderm AG; [accessed 2011 Nov 3]. [1 p]. Available: http://www.euroderm-biotech.de/.

151. Matriderm. [internet]. Billerbeck (Germany): Dr. Suwelack Skin & Health Care AG; [accessed 2011 Nov 3]. [2 p]. Available: http://www.skin-healthcare.de/en/tissue_regeneration/MATRIDERM_profil.php.

152. What is OrCel - product description. [internet]. Englewood (CA): Forticell Bioscience, Inc.; [accessed 2011 Nov 3]. [1 p]. Available: http://www.forticellbioscience.com/orcel.html.

153. U.S. Food and Drug Administration (FDA). Approval of the humanitarian device exemption (HDE) application for composite cultured skin. H990013. 2001 Feb 21. 8 p. Also available: http://www.fda.gov.

154. About PermaDerm. [internet]. Little Falls (NJ): Regenicin, Inc.; [accessed 2011 Nov 3]. [1 p]. Available: http://www.regenicin.com/about/about-permaderm.html.

155. StrataGraft skin substitute. [internet]. Madison (WI): Stratatech Corporation; [accessed 2011 Nov 3]. [2 p]. Available: http://www.stratatechcorp.com/about/index.php.

156. Xelma - extracellular matrix protein. [internet]. Gothenburg (Sweden): Molnlycke Health Care; [accessed 2011 Nov 3]. [2 p]. Available: http://www.molnlycke.com/com/Wound-Care-Products/Product-selector---Wound-division/Tabs/Products/Xelma/?activeTab=2.

157. Marston W. (Professor and Chief, Division of Vascular Surgery, Medical Director, UNC Wound Healing Center, University of North Carolina School of Medicine). Personal communication. 2012 Jan 20. 4 p.

158. Carter MJ. Evidence-based medicine: an overview of key concepts. Ostomy Wound Manage 2010 Apr 1;56(4):68-85. PMID: 20424294

159. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. J Clin Epidemiol 2006 Oct;59(10):1040-8. PMID: 16980143

160. Carter MJ, Fife CE, Walker D, et al. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. Adv Skin Wound Care 2009 Jul;22(7):316-24. PMID: 20375969

161. Falanga V, Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers. Wound Repair Regen 1999 Jul-Aug;7(4):201-7. PMID: 10781211

162. Steinberg JS, Edmonds M, Hurley DP Jr, et al. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. J Am Podiatr Med Assoc 2010 Jan-Feb;100(1):73-7. PMID: 20093548

163. Teng YJ, Li YP, Wang JW, et al. Bioengineered skin in diabetic foot ulcers. Diabetes Obes Metab 2010 Apr;12(4):307-15. PMID: 20380651

164. Gibbs S, Blok C, Hoogenband HM, et al. Autologous cultured skin, Tiscover for ambulant treatment of hard-to-heal leg ulcers: a revolutionary approach. Wound Repair Regen 2009 Jul-Aug;17(4):A57.

165. Langer A, Rogowski W. Systematic review of economic evaluations of human cell-derived wound care products for the treatment of venous leg and diabetic foot ulcers. BMC Health Serv Res 2009;9:115. PMID: 19591680

166. Barber C, Watt A, Pham C, et al. Influence of bioengineered skin substitutes on diabetic foot ulcer and venous leg ulcer outcomes. J Wound Care 2008 Dec;17(12):517-27. PMID: 19052516

167. Blozik E, Scherer M. Skin replacement therapies for diabetic foot ulcers: systematic review and meta-analysis. Diabetes Care 2008 Apr;31(4):693-4. PMID: 18162495

168. Cardinal M, Eisenbud DE, Phillips T, et al. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008 Jan;16(1):19-22.

169. Chow I, Lemos EV, Einarson TR. Management and prevention of diabetic foot ulcers and infections: a health economic review. Pharmacoeconomics 2008;26(12):1019-35. PMID: 19014203

170. Vowden P, Romanelli M, Price P. Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers. J Wound Care 2007 May;16(5):189-95. PMID: 17552400

171. O'Donnell TF Jr, Lau J. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. J Vasc Surg 2006 Nov;44(5):1118-25. PMID: 17098555

172. Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics 2004 Jan;27(1 Suppl):s145-9. PMID: 14763548

173. Ehrlich HP. Understanding experimental biology of skin equivalent: from laboratory to clinical use in patients with burns and chronic wounds. Am J Surg 2004 May;187(5A):29S-33S. PMID: 15147989

174. Payne WG, Wright TE, Ochs D, et al. An exploratory study of dermal replacement therapy in the treatment of stage III pressure ulcers. J Appl Res 2004;4(1):12-23.

175. Tausche AK, Skaria M, Bohlen L, et al. An autologous epidermal equivalent tissue-engineered from follicular outer root sheath keratinocytes is as effective as split-thickness skin autograft in recalcitrant vascular leg ulcers. Wound Repair Regen 2003 Jul-Aug;11(4):248-52. PMID: 12846911

176. Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. J Foot Ankle Surg 2002 Sep-Oct;41(5):291-9. PMID: 12400712

177. Falanga VJ. Tissue engineering in wound repair. Adv Skin Wound Care 2000 May-Jun;13(2 Suppl):15-9. PMID: 11074998

178. Harding K, Cutting K, Price P. The cost-effectiveness of wound management protocols of care. Br J Nurs 2000 Nov 8;9(19 Suppl):S6-24. PMID: 12271239

179. Warriner RA 3rd, Cardinal M, on behalf of the TIDE Investigators. Human fibroblast-derived dermal substitute: results from a treatment investigational device exemption (TIDE) study in diabetic foot ulcers. Adv Skin Wound Care 2011 Jul;24(7):306-11. PMID: 21685733

180. Landsman AS, Cook J, Cook E, et al. A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin) on the treatment of diabetic foot ulcers and venous leg ulcers. Foot Ankle Spec 2011 Feb;4(1):29-41. PMID: 21135263

181. Romanelli M, Kaha E, Stege H, et al. Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers: follow-up data. J Wound Care 2008 Jan;17(1):17-8. PMID: 18210952

182. Romanelli M, Dini V, Vowden P, et al. Amelogenin, an extracellular matrix protein, in the treatment of venous leg ulcers and other hard-to-heal wounds: experimental and clinical evidence. Clin Interv Aging 2008;3(2):263-72. PMID: 18686749

183. Hu S, Kirsner RS, Falanga V, et al. Evaluation of Apligraf persistence and basement membrane restoration in donor site wounds: a pilot study. Wound Repair Regen 2006 Jul-Aug;14(4):427-33. PMID: 16939570

184. Vowden P, Romanelli M, Peter R, et al. The effect of amelogenins (Xelma) on hard-to-heal venous leg ulcers. Wound Repair Regen 2006 May-Jun;14(3):240-6. PMID: 16808801

185. Chester DL, Balderson DS, Papini RP. A review of keratinocyte delivery to the wound bed. J Burn Care Rehabil 2004 May;25(3):266-75.

186. Jeschke MG, Rose C, Angele P, et al. Development of new reconstructive techniques: use of Integra in combination with fibrin glue and negative-pressure therapy for reconstruction of acute and chronic wounds. Plast Reconstr Surg 2004 Feb;113(2):525-30. PMID: 14758212

187. Omar AA, Mavor AI, Jones AM, et al. Treatment of venous leg ulcers with Dermagraft. Eur J Vasc Endovasc Surg 2004 Jun;27(6):666-72. PMID: 15121121

188. Saap LJ, Donohue K, Falanga V. Clinical classification of bioengineered skin use and its correlation with healing of diabetic and venous ulcers. Dermatol Surg 2004 Aug;30(8):1095-100. PMID: 15274699

189. Sams HH, Chen J, King LE. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatol Surg 2002 Aug;28(8):698-703. PMID: 12174061

190. Bass MJ, Phillips LG. Pressure sores. Curr Probl Surg 2007 Feb;44(2):101-43.

191. Grey JE, Lowe G, Bale S, et al. The use of cultured dermis in the treatment of diabetic foot ulcers. J Wound Care 1998 Jul;7(7):324-5. PMID: 9791355

192. Fivenson D, Scherschun L. Clinical and economic impact of Apligraf for the treatment of nonhealing venous leg ulcers. Int J Dermatol 2003 Dec;42(12):960-5. PMID: 14636194

193. Kirsner RS, Fastenau J, Falabella A, et al. Clinical and economic outcomes with graftskin for hard-to-heal venous leg ulcers: a single-center experience. Dermatol Surg 2002 Jan;28(1):81-2. PMID: 11991277

194. Brem H, Balledux J, Sukkarieh T, et al. Healing of venous ulcers of long duration with a bilayered living skin substitute: results from a general surgery and dermatology department. Dermatol Surg 2001 Nov;27(11):915-9. PMID: 11737123

195. Dougherty EJ. An evidence-based model comparing the cost-effectiveness of platelet-rich plasma gel to alternative therapies for patients with nonhealing diabetic foot ulcers. Adv Skin Wound Care 2008 Dec;21(12):568-75. PMID: 19065083

196. Karr JC. Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcome between a dermal repair scaffold (PriMatrix) and a bilayered living cell therapy (Apligraf). Adv Skin Wound Care 2011 Mar;24(3):119-25. PMID: 21326023

197. Ortega-Zilic N, Hunziker T, Lauchli S, et al. EpiDex Swiss field trial 2004-2008. Dermatology 2010;221(4):365-72. PMID: 21071921

198. Mizuno H, Miyamoto M, Shimamoto M, et al. Therapeutic angiogenesis by autologous bone marrow cell implantation together with allogeneic cultured dermal substitute for intractable ulcers in critical limb ischaemia. J Plast Reconstr Aesthet Surg 2010 Nov;63(11):1875-82. PMID: 20060793

199. Kirsner RS, Warriner R, Michela M, et al. Advanced biological therapies for diabetic foot ulcers. Arch Dermatol 2010 Aug;146(8):857-62. PMID: 20713816

200. Clerici G, Caminiti M, Curci V, et al. The use of a dermal substitute to preserve maximal foot length in diabetic foot wounds with tendon and bone exposure following urgent surgical debridement for acute infection. Int Wound J 2010 Jun;7(3):176-83. PMID: 20602648

201. Chen X, Chen H, Zhang G. Management of wounds with exposed bone structures using an artificial dermis and skin grafting technique. J Plast Reconstr Aesthet Surg 2010 Jun;63(6):e512-8. PMID: 20004631

202. Brigido SA, Schwartz E, McCarroll R, et al. Use of an acellular flowable dermal replacement scaffold on lower extremity sinus tract wounds: a retrospective series. Foot Ankle Spec 2009 Apr;2(2):67-72. PMID: 19825754

203. Han SK, Kim HS, Kim WK. Efficacy and safety of fresh fibroblast allografts in the treatment of diabetic foot ulcers. Dermatol Surg 2009 Sep;35(9):1342-8. PMID: 19500128

204. Renner R, Harth W, Simon JC. Transplantation of chronic wounds with epidermal sheets derived from autologous hair follicles--the Leipzig experience. Int Wound J 2009 Jun;6(3):226-32. PMID: 19538195

205. Ramelet AA, Hirt-Burri N, Raffoul W, et al. Chronic wound healing by fetal cell therapy may be explained by differential gene profiling observed in fetal versus old skin cells. Exp Gerontol 2009 Mar;44(3):208-18. PMID: 19049860

206. Canonico S, Campitiello F, Della Corte A, et al. The use of a dermal substitute and thin skin grafts in the cure of "complex" leg ulcers. Dermatol Surg 2009 Feb;35(2):195-200. PMID: 19215255

207. Vriens AP, Waaijman T, van den Hoogenband HM, et al. Comparison of autologous full-thickness gingiva and skin substitutes for wound healing. Cell Transplant 2008;17(10-11):1199-209. PMID: 19181214

208. Winters CL, Brigido SA, Liden BA, et al. A multicenter study involving the use of a human acellular dermal regenerative tissue matrix for the treatment of diabetic lower extremity wounds. Adv Skin Wound Care 2008 Aug;21(8):375-81. PMID: 18679086

209. Nie X, Cai JK, Yang HM, et al. Successful application of tissue-engineered skin to refractory ulcers. Clin Exp Dermatol 2007 Nov;32(6):699-701. PMID: 17725663

210. Mermet I, Pottier N, Sainthillier JM, et al. Use of amniotic membrane transplantation in the treatment of venous leg ulcers. Wound Repair Regen 2007 Jul-Aug;15(4):459-64. PMID: 17650088

211. Yonezawa M, Tanizaki H, Inoguchi N, et al. Clinical study with allogeneic cultured dermal substitutes for chronic leg ulcers. Int J Dermatol 2007 Jan;46(1):36-42. PMID: 17214717

212. Gibbs S, van den Hoogenband HM, Kirtschig G, et al. Autologous full-thickness skin substitute for healing chronic wounds. Br J Dermatol 2006 Aug;155(2):267-74. PMID: 16882162

213. Martin BR, Sangalang M, Wu S, et al. Outcomes of allogenic acellular matrix therapy in treatment of diabetic foot wounds: an initial experience. Int Wound J 2005 Jun;2(2):161-5. PMID: 16722865

214. Moustafa M, Simpson C, Glover M, et al. A new autologous keratinocyte dressing treatment for non-healing diabetic neuropathic foot ulcers. Diabet Med 2004 Jul;21(7):786-9. PMID: 15209775

215. Redekop WK, McDonnell J, Verboom P, et al. The cost effectiveness of Apligraf treatment of diabetic foot ulcers. Pharmacoeconomics 2003;21(16):1171-83. PMID: 14594438

216. Phillips TJ, Manzoor J, Rojas A, et al. The longevity of a bilayered skin substitute after application to venous ulcers. Arch Dermatol 2002 Aug;138(8):1079-81. PMID: 12164746

217. Browne AC, Vearncombe M, Sibbald RG. High bacterial load in asymptomatic diabetic patients with neurotrophic ulcers retards wound healing after application of Dermagraft. Ostomy Wound Manage 2001 Oct;47(10):44-9. PMID: 11890078

218. Sibbald RG, Torrance GW, Walker V, et al. Cost-effectiveness of Apligraf in the treatment of venous leg ulcers. Ostomy Wound Manage 2001 Aug;47(8):36-46. PMID: 11890002

219. Yamaguchi Y, Kubo T, Tarutani M, et al. Epithelial-mesenchymal interactions in wounds: treatment of palmoplantar wounds by nonpalmoplantar pure epidermal sheet grafts. Arch Dermatol 2001 May;137(5):621-8. PMID: 11346340

220. Falabella AF, Valencia IC, Eaglstein WH, et al. Tissue-engineered skin (Apligraf) in the healing of patients with epidermolysis bullosa wounds. Arch Dermatol 2000 Oct;136(10):1225-30. PMID: 11030768

221. Brem H, Balledux J, Bloom T, et al. Healing of diabetic foot ulcers and pressure ulcers with human skin equivalent: a new paradigm in wound healing. Arch Surg 2000 Jun;135(6):627-34. PMID: 10843357

222. Monami M, Vivarelli M, Desideri CM, et al. Autologous skin fibroblast and keratinocyte grafts in the treatment of chronic foot ulcers in aging type 2 diabetic patients. J Am Podiatr Med Assoc 2011 Jan-Feb;101(1):55-8. PMID: 21242471

223. Kerstein MD, Brem H, Giovino KB, et al. Development of a severity scale for evaluating the need for Graftskin in nonhealing venous ulcers. Adv Skin Wound Care 2002 Mar-Apr;15(2):66-71. PMID: 11984049

224. Sopata M, Luczak J, Ciupinska M. Effect of bacteriological status on pressure ulcer healing in patients with advanced cancer. J Wound Care 2002 Mar;11(3):107-10. PMID: 11933727

225. Chockalingam N, Ashford RL, Dunning D. The influence of four wound dressings on the kinetics of human walking. J Wound Care 2001 Oct;10(9):371-4. PMID: 12964282

226. Micallef L, Lebreton C, Bordeau N, et al. Evaluation of human bone marrow-derived mesenchymal stem cell capacities to support epidermis development in a skin substitute. Comparative study with human dermal fibroblasts. Wound Repair Regen 2010 Nov-Dec;18(6):A88.

227. Tauzin H, Rolin G, Viennet C, et al. Development of a skin substitute for therapeutic use, based on human amnion. J Invest Dermatol 2009 Sep;129:S20.

228. Upton Z, Shooter G, Van Lonkhuyzen D, et al. Positive clinical results with vitronectin: IGF complexes for the treatment of chronic wounds. Growth Horm IGF Res 2010;20:S68-9.

229. Tang J, Guo WC, Yu L, et al. Clinical efficacy of artificial skin combined with vacuum sealing drainage in treating large-area skin defects. Chin J Traumatol 2010 Oct;13(5):289-92.

230. Faulhaber J, Felcht M, Teerling G, et al. Long-term results after reconstruction of full thickness scalp defects with a dermal regeneration template. J Eur Acad Dermatol Venereol 2010 May;24(5):572-7.

231. Hiles M, Nihsen E, Hodde J. Biologics in fistula surgery: parallels with chronic wounds. Semin Colon Rectal Surg 2009 Mar;20(1):32-7.

232. Huldt-Nystrom T, Meuleneire F, Acton C. Xelma, an advanced wound treatment for venous ulcers: a European perspective. Wounds UK 2008 Mar;4(1):84-8.

233. Russo G, Crippa M, Lorenzi G, et al. Bioengineered skin grafts after revascularization in the treatment of ischemic ulcers. Chirurgia 2006 Aug;19(4):253-6.

234. Boyce ST. Fabrication, quality assurance, and assessment of cultured skin substitutes for treatment of skin wounds. Biochem Eng J 2004 Aug 15;20(2-3):107-12.

235. Eming SA, Smola H, Krieg T. Treatment of chronic wounds: state of the art and future concepts. Cells Tissues Organs 2002;172(2):105-17.

236. Cavorsi JP. Venous ulcers of the lower extremities: current and newer management techniques. Top Geriatr Rehabil 2000;16(2):24-34.

237. Moneta GL, Falanga V, Altman MI, et al. Nonoperative management of venous leg ulcers: evolving role of skin substitutes. Vasc Surg 1999 Mar;33(2):197-210.

238. Shaikh FM, Giri SK, Durrani S, et al. Experience with porcine acellular dermal collagen implant in one-stage tension-free reconstruction of acute and chronic abdominal wall defects. World J Surg 2007 Oct;31(10):1966-72.

Appendix A: Methods of Identifying the Literature

Electronic Database Searches

Table 17. Databases searched for relevant information

Name	Date Limits	Platform/Provider
CINAHL	1996–May 29, 2012	EBSCO
Clinicaltrials.gov	May 29, 2012	www.clinicaltrials.gov
Cochrane Library	1996–May 17, 2012	Wiley
EMBASE (Excerpta Medica)	1996–May 17, 2012	OVID
Health Devices Alerts	1996–August 16, 2011	ECRI Institute
Health Technology Assessment Information Services (HTAIS)	1996–August 15, 2011	ECRI Institute
Healthcare Product Comparison System (HCPCS)	1996–August 16, 2011	ECRI Institute
Healthcare Standards Database	1996–August 15, 2011	ECRI Institute
MEDLINE	1996–May 17, 2012	OVID
National Institute for Health and Clinical Effectiveness	August 17, 2011	National Health Service (UK)
PubMed (In process and Publisher subsets)	1996–May 17, 2012	National Library of Medicine
U.S. Food and Drug Administration	August 12, 2011	www.fda.gov
U.S. National Guideline Clearinghouse™ (NGC)	August 15, 2011	www.ngc.gov

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications and conference proceedings 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.)

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE and MEDLINE. A parallel strategy was used to search CINAHL, PUBMED, and the databases comprising the Cochrane Library.

Regulatory

In order to address Key Question 1, an extensive search of the U.S. Food and Drug Administration (FDA) Web site was conducted to determine regulatory classification and status of skin substitute products. The following FDA resources were searched:

- Device Classification database
- Premarket Approval (PMA) database
- 510(k) Marketing Clearance database
- List of Humanitarian Device Exemptions

- Code of Federal Regulations
- Center for Biologics Evaluation and Research

Medical Subject Headings (MeSH), EMTREE and Keywords

Conventions:

OVID

$	=	truncation character (wildcard)
Exp	=	"explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.de. or /	=	limit controlled vocabulary heading
.fs.	=	floating subheading
.hw.	=	limit to heading word
.md.	=	type of methodology (PsycINFO)
.mp.	=	combined search fields (default if no fields are specified)
.pt.	=	publication type
.ti.	=	limit to title
.tw.	=	limit to title and abstract fields

PubMed

[mh]	=	MeSH heading
[majr]	=	MeSH heading designated as major topic
[pt]	=	publication type
[sb]	=	subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)
[sh]	=	MeSH subheading (qualifiers used in conjunction with MeSH headings)
[tiab]	=	keyword in title or abstract

Table 18. Topic-specific search terms

Concept	Controlled Vocabulary	Keywords
Skin substitutes	Skin, artificial/ Artificial skin/ Tissue scaffold/ Tissue scaffolds/	Acellular dermal matrix$ hADM artificial dermis artificial skin autologous epidermal cell culture$ bilayer$ living cell$ bioengineered skin composite substitute dermal construct$ dermal equivalent$ dermal regeneration template$ dermal repair scaffold$ dermal substitute$ dermal template$ engineered skin epidermal equivalent$ extracellular matrix skin equivalent$ skin replacement$ skin substitute$ smart matrix

Concept	Controlled Vocabulary	Keywords
Skin substitute products	NA	Alloderm Apligraf Dermagraft Integra Oasis Primatrix TheraSkin Matristem Hyalomatrix Graftjacket Gammagraft Cymetra FlexHD AllopatchHD AlloMax AlloSkin Arthroflex DermACELL MemoDerm Matrix HD Strattice Biobrane Celaderm DressSkin Epicel Epidex EZ-Derm Graftskin Laserskin Lyofoam Lyomousse Matriderm Orcel Permacol Permaderm Puros dermis Suprathel Syspurderm Syspur-derm Tissuemend transcyte

Concept	Controlled Vocabulary	Keywords
Wounds	Exp wounds/ Exp injuries/ Exp wound healing/ Exp injury/ Diabetic foot/ Exp skin ulcer/ Exp skin ulcers Chronic wound/	Wound$ Ulcer$ Sore$ Bedsore$ Decubitus Pressure sore$ Pressure ulcer$ Diabet$
Chronic	Chronic disease/ Chronic wound/	Chronic Intractable Persistent Nonhealing Non healing

EMBASE/Medline

Table 19. English language, human, randomized controlled trial/systematic review/meta-analysis/ remove overlap

Set Number	Concept	Search Statement	# Downloaded
	Sets 1–3 represent the interventions of interest		
1	Skin substitutes	skin, artificial/ or artificial skin/ or tissue scaffold/ or tissue scaffolds/	
2		(Accellular dermal matrix or hADM or artificial dermis or artificial skin or autologous epidermal cell culture$ or bilayer$ living cell$ or bioengineered skin or composite substitute or dermal construct$ or dermal equivalent$ or dermal regeneration template$ or dermal repair scaffold$ or dermal substitute$ or dermal template$ or engineered skin or epidermal equivalent$ or extracellular matrix or skin equivalent$ or skin replacement$ or skin substitute$ or smart matrix).mp.	
3		(alloderm or apligraf or dermagraft or integra or oasis or primatrix or TheraSkin or matristem or hyalomatrix or graftjacket or gammagraft or cymetra or Flex HD or AlloPatch HD or AlloMax or AlloSkin or Arthroflex or DermACELL or MemoDerm or Matrix HD or Strattice OR biobrane OR celaderm OR dresskin OR epicel OR epidex OR EZ-derm OR graftskin OR laserskin OR lyofoam OR lyomousse OR matriderm OR orcel OR permacol OR permaderm OR puros dermis OR suprathel OR syspurderm OR syspur-derm OR tissuemend OR transcyte)	
4		or/1-3	
	Sets 5 through 6 represent the condition of interest		

Set Number	Concept	Search Statement	# Downloaded
5	Chronic wounds	((exp wounds/ and injuries/) or exp wound healing/ or exp injury/) and (chronic disease/ or chronic.hw. or chronic.mp. or intractable.mp. or persistent.mp. or nonhealing.mp. or nonhealing.mp.)	
6		Diabetic foot/ or exp skin ulcer/ or exp skin ulcers/ or chronic wound/ or decubitus.mp. or bedsore$.mp. or ((bed or diabet$ or pressure) adj2 (sore$ or ulcer$)).mp.	
7		or/5-6	
8	Set 8 encompasses all three key questions	4 and 7	115
		Remove 18 references with a primary focus of burn patients and 2 duplicate references	95

Table 20. Documents that were retrieved and then excluded

Reference	Comparisons	Reason for Exclusion
Chern et al. 2010[1]	Acute surgical wounds and applicability to dermatologic surgery	Review
Steinberg et al. 2010[162]	Apligraf vs. standard therapy	Not original research, reanalysis of published studies
Teng et al. 2010[163]	Diabetic foot ulcers	Systematic Review
Gibbs et al. 2009[164]	Tissue-engineered, full thickness autologous skin, Tiscover, consisting of a differentiated and pigmented epidermis on fibroblast populated human dermis, is cultured from 3 mm skin biopsies vs. standard treatment	Abstract only
Langer and Rogowski 2009[165]	Chronic leg ulcers, diabetic foot ulcers	Systematic Review
Barber et al. 2008[166]	Chronic leg ulcers, diabetic foot ulcers	Systematic Review
Blozik and Scherer 2008[167]	Diabetic foot ulcers	Systematic Review
Cardinal et al. 2008[168]	Dermagraft, retrospective reanalysis	Reanalysis of published studies
Chow et al. 2008[169]	Diabetic foot ulcers	Health economic review
Jones and Nelson 2007[98]	Venous leg ulcers	Systematic Review
Vowden et al. 2007[170]	Amelogenin extracellular matrix protein plus compression vs. compression therapy alone	Not a skin substitute, not FDA approved
O'Donnell and Lau 2006[171]	Chronic venous ulcer	Systematic Review
Brigido et al. 2004[172]	Graftjacket vs. conventional treatment	No outcomes of interest were reported because study lasted only 4 weeks.
Ehrlich 2004[173]	Understanding experimental biology of skin equivalent: from laboratory to clinical use in patients with burns and chronic wounds	Review
Payne et al. 2004[174]	Dermagraft vs. conventional therapy	Outcomes were reported from less than 50% of the enrolled patients

Reference	Comparisons	Reason for Exclusion
Tausche et al. 2004[175]	EpiDex trade mark, a tissue-engineered, fully differentiated autologous epidermal equivalent derived from keratinocytes vs. split-thickness skin autografting	Not a commercially available product
Hanft and Surprenant 2002[176]	Dermagraft vs. saline-moistened gauze alone	Part of a larger study already included in the report
Falanga 2000[177]	Graftskin (Apligraf) vs. compression therapy alone	Review
Harding et al. 2000[178]	Chronic venous leg ulcers and pressure sores	Systematic Review
Falanga et al. 1999[161]	Apligraf vs. compression therapy alone	Subgroup analysis of prior published study

Table 21. Articles excluded at the abstract level

Reference	Reason for Exclusion
Warriner and Cardinal 2011[179]	Not an RCT
Landsman et al. 2011[180]	Not an RCT
Romanelli et al. 2008[181]	Not a skin substitute
Romanelli et al. 2008[182]	Review
Hu et al. 2006[183]	Acute wound
Vowden et al. 2006[184]	Not a skin substitute
Chester et al. 2004[185]	Review
Jeschke et al. 2004[186]	Acute wound
Omar et al. 2004[187]	Less than 10 patients per treatment arm
Saap et al. 2004[188]	Not an RCT
Sams et al. 2002[189]	Less than 10 patients per treatment arm
Bass and Phillips 2007[190]	Review
Grey et al. 1998[191]	Not an RCT
Fivenson and Scherschum 2003[192]	Not an RCT
Kirsner et al. 2002[193]	Not an RCT
Brem et al 2001[194]	Not an RCT
Dougherty 2008[195]	Not an RCT
Karr 2011[196]	Not an RCT
Ortega-Zilic et al. 2010[197]	Not an RCT
Mizune et al. 2010[198]	Not an RCT
Kirsner et al. 2010[199]	Not an RCT
Clerici et al. 2010[200]	Not an RCT
Chen et al. 2010[201]	Not an RCT
Brigido et al. 2009[202]	Not an RCT
Han et al. 2009[203]	Not an RCT
Renner et al. 2009[204]	Not an RCT
Ramelet et al. 2009[205]	Not an RCT
Canonico et al. 2009[206]	Not an RCT
Vriens et al. 2008[207]	Not an RCT

Reference	Reason for Exclusion
Winters et al. 2008[208]	Not an RCT
Nie et al. 2007[209]	Not an RCT
Mermet et al. 2007[210]	Not an RCT
Yonexawa et al. 2007[211]	Not an RCT
Gibes et al. 2006[212]	Not an RCT
Martin et al. 2005[213]	Not an RCT
Moustafa et al. 2004[214]	Not an RCT
Redekop et al. 2003[215]	Not an RCT
Phillips et al. 2002[216]	Not an RCT
Browne et al. 2001[217]	Not an RCT
Sibbald et al. 2001[218]	Not an RCT
Yamaguchi et al. 2001[219]	Not an RCT
Falabella et al. 2000[220]	Not an RCT
Brem et al. 2000[221]	Not an RCT
Monami et al. 2011[222]	Not an RCT
Kerstein et al. 2002[223]	Not an RCT
Sopata et al. 2002[224]	Not a skin substitute
Chockalingam et al. 2001[225]	Not a skin substitute
Micallef et al. 2010[226]	Not an RCT
Tauzin et al. 2009[227]	Not an RCT
Upton et al 2010[228]	Not an RCT
Tang et al. 2010[229]	Not an RCT
Faulhaber et al. 2010[230]	Not an RCT
Hiles et al. 2009[231]	Not a chronic wound
Huldt-Nystrom et al. 2008[232]	Not an RCT
Russo et al. 2006[233]	Not an RCT
Boyce 2004[234]	Review
Eming et al. 2002[235]	Review
Cavorsi 2000[236]	Review
Moneta et al. 1999[237]	Review
Shaikh et al. 2007[238]	Acute wound

RCT: Randomized controlled trial

Appendix B: Risk of Bias in the Evidence Base

Key Question 2

Risk-of-Bias Questions:

Selection Bias

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

Detection Bias

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

Performance Bias

7. Outside of the skin substitute and comparator, did patients receive identical treatment for their wounds?

Attrition Bias

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

Table 22. Risk-of-bias assessments for Apligraf and Graftskin studies (rated as low, moderate, or high risk)

Study	1	2	3	4	5	6	7	8	9	Risk of Bias
DiDomenico et al. 2011[64]	NR	NR	Y	NR	NR	N	Y	Y	Y	Moderate
Edmonds M. 2009[53]	Y	Y	Y	Y	Y	NR	Y	Y	Y	Low
Veves et al. 2001[67]	Y	Y	Y	Y	Y	NR	Y	Y	Y	Low
Falanga et al. 1998[63]	Y	N	Y	NR	Y	NR	Y	Y	Y	Low

Based on complete wound healing as the primary outcome of interest.
DiDomenico et al. compared Apligraf with TheraSkin
N: No; NR: Not reported; Y: Yes

Table 23. Risk-of-bias assessments for Dermagraft studies (rated as low, moderate, or high risk)

Study	1	2	3	4	5	6	7	8	9	Risk of Bias
Krishnamoorthy et al. 2003[55]	Y	Y	NR	NR	NR	N	Y	Y	N	Moderate
Marston et al. 2003[56]	N	N	Y	N	NR	NR	Y	N	NR	Moderate
Naughton et al. 1997[62]	NR	NR	NR	NR	NR	NR	NR	N	Y	Unclear
Gentzkow et al. 1996[65]	N	Y	N	N	NR	NR	Y	Y	Y	Moderate

Based on complete wound healing as the primary outcome of interest
N: No; NR: Not reported; Y: Yes

Table 24. Risk-of-bias assessments for Graftjacket studies (rated as low, moderate, or high risk)

Study	1	2	3	4	5	6	7	8	9	Risk of Bias
Reyzelman et al. 2009[66]	Y	Y	N	Y	Y	N	Y	Y	Y	Low
Brigido SA. 2006[59]	NR	NR	NR	NR	NR	N	Y	Y	Y	Moderate

Based on complete wound healing as the primary outcome of interest
N: No; NR: Not reported; Y: Yes

Table 25. Risk-of-bias assessments for HYAFF and Talymed studies (rated as low, moderate, or high risk)

Study	1	2	3	4	5	6	7	8	9	Risk of Bias
Kelechi et al. 2011[61]	Y	Y	Y	Y	N	N	Y	Y	Y	Low
Uccioli et al. 2011[68]	Y	Y	N	Y	Y	N	Y	Y	Y	Low
Caravaggi et al. 2003[58]	N	Y	Y	Y	Y	N	Y	N	Y	Low

Based on complete wound healing as the primary outcome of interest
Kelechi et al. 2011 compared Talymed (pGlcNAc) to nonadherent absorptive primary dressing
N: No; Y: Yes

Table 26. Risk-of-bias assessments for Oasis studies (rated as low, moderate, or high risk)

Study	1	2	3	4	5	6	7	8	9	Risk of bias
Romanelli et al. 2010[57]	NR	NR	Y	Y	NR	N	Y	Y	Y	Moderate
Landsman et al. 2008[54]	N	NR	Y	NR	NR	N	Y	Y	Y	Moderate
Romanelli et al. 2007[60]	N	NR	Y	Y	NR	N	Y	Y	Y	Moderate
Mostow et al. 2005[69]	Y	Y	Y	NR	NR	N	Y	Y	Y	Low
Niezgoda et al. 2005[70]	Y	Y	Y	NR	N	n	Y	N	Y	Moderate

Based on complete wound healing as the primary outcome of interest
N: No; NR: Not reported; Y: Yes

Appendix C: Evidence Tables

Key Question 2

Table 27. Basic study design and conduct information for studies of Apligraf and Graftskin

Study	Study Detail	Description
DiDomenico et al. 2011[64]	Specific wound treatment comparison	Apligraf vs. TheraSkin
	Wound type	DFU
	Country	U.S.
	Institutes involved	Ankle and Foot Centers, Boardman, Ohio
	Study objective	To compare rate of wound closure and number of grafts between TheraSkin and Apligraf
	Method of patient recruitment	NR
	Patients enrolled	28 patients (29 wounds)
	Date range of study	2008–2009
	Care setting	Large multi-office podiatric practice
	Method of measuring wound condition at enrollment	Documentation of clinical appearance, wound measurements (cross-sectional area, depth, and wound stage)
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	12 weeks
	Source of Funding	Soluble Systems, LLC
Edmonds M. 2009[53]	Specific wound treatment comparison	Apligraf vs. nonadherent dressing
	Wound type	DFU
	Country	European Union and Australia
	Institutes involved	NS
	Study objective	To compare the efficacy and safety of Apligraf plus nonadherent dressing vs. nonadherent dressing alone to treat neuropathic DFUs
	Method of patient recruitment	NR
	Patients enrolled	106 screened, 82 randomized, 72 treated
	Date range of study	2000 to 2002
	Care setting	NS
	Method of measuring wound condition at enrollment	Planimetry
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	6 months
	Source of funding	Organogenesis Inc.
Veves et al. 2001[67]	Specific wound treatment comparison	Graftskin vs. saline-moistened gauze
	Wound type	DFU
	Country	U.S.

Study	Study Detail	Description
Veves et al. 2001[67] (continued)	Institutes involved	24 centers including Joslin-Beth Israel Deaconess Foot Center and Harvard Medical School, Boston, MA; the Department of Dermatology and Skin Surgery, Roger Williams Medical Center, Providence, RI; the Boston University School of Medicine, Boston MA; and the Department of Surgery, Southern Arizona Veterans Affairs Medical Center, Tucson, AZ.
	Study objective	To evaluate the effectiveness of applying Graftskin weekly to treat plantar DFU
	Method of patient recruitment	NR
	Patients enrolled	208
	Date range of study	NR
	Care setting	Outpatient
	Method of measuring wound condition at enrollment	Computer planimetry of wound tracing
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	6 months
	Source of funding	Organogenesis Inc.
Falanga et al. 1998[63]	Specific wound treatment comparison	Apligraf with compression vs. compression therapy
	Wound type	Venous leg ulcers
	Country	U.S.
	Institutes involved	15 centers including Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, FL; Department of Dermatology, University of Pennsylvania Medical Center, Philadelphia, PA; University Wound Healing Clinic and the Division of Dermatology, Robert Wood Johnson Medical School, New Brunswick, NJ; Silver Lake Medical Inc., Providence, RI; and the Diabetic Foot and Wound Healing Center, Denver, CO
	Study objective	To test the safety, efficacy, and immunological impact of a cultured allogeneic human skin equivalent to treat venous ulcers
	Method of patient recruitment	NR
	Patients enrolled	293
	Date range of study	NR
	Care setting	Outpatient
	Method of measuring wound condition at enrollment	Computer planimetry of surface tracings, photographs
	Stratification of results (wound severity or comorbidities)	Ulcer severity and duration
	Length of study	12 months
	Source of funding	Organogenesis Inc.

DFU: Diabetic foot ulcer
NR: Not reported
NS: Not specified

Table 28. Basic study design and conduct information for studies of Dermagraft

Study	Study Detail	Description
Krishnamoorthy et al. 2003[55]	Specific wound treatment comparison	Dermagraft® plus multilayered compression bandage therapy (Profore™) vs. multilayered compression therapy
	Wound type	Venous leg ulcers
	Country	United Kingdom and Canada
	Institutes involved	6
	Study objective	To examine the safety and effectiveness of Dermagraft® in conjunction with conventional therapy to promote healing of chronic venous leg ulcers compared with conventional therapy
	Method of patient recruitment	Upon presentation at each center
	Patients enrolled	63 enrolled/53 randomized
	Date range of study	NR
	Care setting	Wound center
	Method of measuring wound condition at enrollment	Traced at the edge of the intact skin epithelium, re-traced onto an ulcer area grid; 3 photos and one biopsy taken
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	12 weeks
	Source of funding	Smith & Nephew/Advanced Tissue Sciences Inc. Joint Venture, La Jolla, CA
Marston et al. 2003[56]	Specific wound treatment comparison	Dermagraft vs. conventional therapy
	Wound type	Diabetic foot ulcers
	Country	U.S.
	Institutes involved	35
	Study objective	To evaluate the safety and efficacy of Dermagraft in the healing of diabetic foot ulcers
	Method of patient recruitment	NR
	Patients enrolled	245
	Date range of study	December 1998 to March 2000
	Care Setting	NR
	Method of measuring wound condition at enrollment	NR at day 0
	Stratification of results (wound severity or comorbidities)	Patients were stratified into 2 groups based on wound size (≥1 to ≤2, >2 to ≤20 cm^2) and then randomized. Results do not reflect these groupings.
	Length of study	12 weeks
	Source of funding	Advanced Tissue Sciences, Inc. (La Jolla, CA) and Smith & Nephew, Inc. (Largo, FL)
Naughton et al. 1997[62]	Specific wound treatment comparison	Dermagraft vs. SOC
	Wound type	Diabetic foot ulcers

Study	Study Detail	Description
Naughton et al. 1997[62] (continued)	Countries	U.S.
	Institutes involved	20; Sites NS
	Study objective	To compare percentage of patients receiving Dermagraft® reaching complete closure by Week 12 to patients receiving saline-moistened gauze
	Method of patient recruitment	NR
	Patients enrolled	281
	Date range of study	NR
	Care setting	NR
	Method of measuring wound condition at enrollment	NR
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	32 weeks
	Source of funding	Advanced Tissue Sciences, Inc. (La Jolla, CA)
Gentzkow et al. 1996[65]	Specific wound treatment comparison	Dermagraft® vs. saline-moistened gauze
	Wound type	DFU
	Country	U.S.
	Institutes involved	5; Sites NS
	Study objective	To assess the effect of Dermagraft® o healing of DFU
	Method of patient recruitment	NR
	Patients enrolled	50
	Date range of study	NR
	Care setting	NR
	Method of measuring wound condition at enrollment	Computer planimetry study of an ulcer tracing and by the alginate mold technique
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	12 weeks
	Source of funding	Advanced Tissue Sciences, Inc. (La Jolla, CA)

DFU: Diabetic foot ulcer
NR: Not reported

Table 29. Basic study design and conduct information for studies of Graftjacket

Study	Study Detail	Description
Reyzelman et al. 2009[66]	Specific wound treatment comparison	Graftjacket vs. moist wound therapy with alginates, foams, hydrocolloids, or hydrogels
	Wound type	DFU
	Country	U.S.
	Institutes involved	11 sites; NS
	Study objective	To compare healing rates at 12 weeks between patients receiving acellular matrix (AM) therapy vs. moist wound therapy with alginates, foams, hydrocolloids, or hydrogels
	Method of patient recruitment	NR
	Patients enrolled	93 (7 did not meet inclusion criteria and were reported as failures; 86 patients randomized)
	Date range of study	NR
	Care setting	NR
	Method of measuring wound condition at enrollment	Acetate tracings and photographs
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	12 weeks
	Source of Funding	Wright Medical Technology (Arlington, TN)
Brigido SA. 2006[59]	Specific wound treatment comparison	Graftjacket vs. weekly debridement, Curasol wound hydrogel and gauze dressing
	Wound type	DFU
	Country	U.S.
	Institutes involved	Foot and Ankle Center at Coordinated Health, East Stroudsburg, PA
	Study objective	To assess the safety and effectiveness of Graftjacket AM tissue for treating full-thickness (Wagner grade-2) lower extremity wounds compared with sharp débridement only
	Method of patient recruitment	NR
	Patients enrolled	28
	Date range of study	NR
	Care setting	Foot and Ankle Center
	Method of measuring wound condition at enrollment	Tracing on wound film; wound depth by disposable sterile ruler
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	16 weeks
	Source of funding	Wright Medical Technology (Arlington, TN)

DFU: Diabetic foot ulcer
NR: Not reported
NS: Not specified

Table 30. Basic study design and conduct information for studies of HYAFF and Talymed

Study	Study Detail	Description
Kelechi et al. 2011[61]	Specific wound treatment comparison	Talymed poly-N-acetyl glucosamine (pGlcNAc) with compression vs. nonadherent absorptive primary dressing with compression
	Wound type	Venous leg ulcers
	Country	U.S.
	Institutes involved	St. Francis Hospital, Charleston, SC; Regional Medical Center of Orangeburg, Orangeburg, SC; and ESU Inc., Pooler, GA
	Study objective	To evaluate the efficacy, safety and tolerability of pGlcNAc to treat patients with venous leg ulcers
	Method of patient recruitment	NR
	Patients enrolled	82 recruited, 71 completed
	Date range of study	October 2008 to December 2009
	Care setting	Wound centers
	Method of measuring wound condition at enrollment	Length and width measured by study nurses
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	20 weeks
	Source of funding	Marine Polymer Technologies Inc.
Uccioli et al. 2011[68]	Specific wound treatment comparison	Hyalograft 3D autograft/Laserskin vs. nonadherent paraffin gauze
	Wound type	DFU
	Country	Italy
	Institutes involved	Policlinico of Tor Vergata, Rome, Italy; S Orsola-Malpighi Hospital, Bologna, Italy; Cisanello Hospital, Pisa, Italy; S Donato Hospital, Arezzo, Italy; Monteluce Hospital, Perugia, Italy; S Michele Hospital, Cagliari, Italy; Policlinico Gemelli, Rome, Italy
	Study objective	To evaluate efficacy and safety of a 2-step HYAFF autograft compared with standard care for treating DFUs
	Method of patient recruitment	NR
	Patients enrolled	180
	Date range of study	September 1999 to January 2006
	Care setting	Diabetic foot centers
	Method of measuring wound condition at enrollment	Photograph/tracing measured later by computerized morphometry
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	20 weeks
	Source of funding	Anika Therapeutics srl

Study	Study Detail	Description
Caravaggi et al. 2003[58]	Specific wound treatment comparison	Hyalograft 3D autograft/Laserskin vs. nonadherent paraffin gauze
	Wound type	DFU
	Country	Italy
	Institutes involved	Centre for the Study and Treatment of Diabetic Foot Pathology, Ospedale di Abbiategrasso, Milan, Italy; the Policlinico Multimedica, Sesto San Giovanni, Milan, Italy; the Centro per la Prevenzione e la Cura Del Piede Diabetico-Fondazione Maugeri, Pavia, Italy; the Casa di Cura Villa Berica, Vicenza, Italy; the Divisione Medicina, Ospedale San Carolo, Milan, Italy; the Ospedale San Bortolo, Vicenza, Italy; and the Institute of Medical Statistics and Biometry, University of Milan, Milan, Italy
	Study objective	To evaluate the efficacy and safety of Hyalograft 3D autograft/Laserskin for treating DFUs
	Method of patient recruitment	NR
	Patients enrolled	79
	Date range of study	NR
	Care setting	Outpatient
	Method of measuring wound condition at enrollment	Tracing with a transparent plastic grid, Op-Site (Smith & Nephew) and recorded by photograph
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	NR
	Source of funding	Fidia Advanced Biopolymers (Abano Terme, Italy)

HYAFF: Benzyl esters of hyaluronic acid
DFU: Diabetic foot ulcer
NR: Not reported

Table 31. Basic study design and conduct information for studies of Oasis

Study	Study Detail	Description
Romanelli et al. 2010[57]	Specific wound treatment comparison	Oasis Wound Matrix vs. a petrolatum-impregnated gauze
	Wound type	Mixed arterial/venous or venous ulcers
	Country	Italy
	Institutes involved	Wound Healing Research Unit, Department of Dermatology, University of Pisa
	Study objective	To compare the efficacy and tolerability of a standard moist dressing with Oasis, a biologically active ECM
	Method of patient recruitment	Patients visiting the outpatient leg ulcer clinic were recruited
	Patients enrolled	50 adults
	Date range of study	NR
	Care setting	Wound clinic
	Method of measuring wound condition at enrollment	NS; measured by “clinical and instrumental assessment”
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	8 weeks
	Source of funding	NR
Landsman et al. 2008[54]	Specific wound treatment comparison	Oasis Wound Matrix vs. Dermagraft
	Wound type	DFU
	Country	U.S.
	Institutes involved	Weil Foot and Ankle Institute, Des Plaines, IL; Coastal Podiatry, Inc., Virginia Beach, VA; Ocean County Foot and Ankle Surgical Associates, Toms River, NJ; The Foot and Ankle Institute of South Florida, South Miami, FL
	Study objective	To compare patient outcomes following DFU treatment by Oasis and Dermagraft
	Method of patient recruitment	Once a qualified individual was identified by the institute, an independent site (MED Institute, West Lafayette, IN) randomly assigned the patient to treatment arms
	Patients enrolled	40 screened, 31 enrolled
	Date range of study	NR
	Care setting	Wound institutes
	Method of measuring wound condition at enrollment	Photographed before and after débridement; ulcer location, duration, and a description of the wound base recorded
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	12 weeks
	Source of funding	NR

Study	Study Detail	Description
Romanelli et al. 2007[60]	Specific wound treatment comparison	Oasis vs. Hyaloskin (contains hyaluronan)
	Wound type	Mixed arterial/venous
	Country	Italy
	Institutes involved	Wound Healing Research Unit, Department of Dermatology, University of Pisa
	Study objective	To compare the effectiveness of two ECM-based products to achieve complete wound healing
	Method of patient recruitment	Patients visiting the outpatient leg ulcer clinic were recruited
	Patients Enrolled	54
	Date range of study	NR
	Care setting	Wound clinic
	Method of measuring wound condition at enrollment	NS; measured by “clinical and instrumental assessment”
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	16 weeks
	Source of funding	Healthpoint, Ltd.
Mostow et al. 2005[69]	Specific wound treatment comparison	Oasis with compression vs. compression
	Wound type	Venous leg ulcers
	Countries	U.S., U.K. and Canada
	Institutes involved	12 outpatient sites; institutes not specified
	Study objective	To test the hypothesis that chronic full-thickness leg ulcers treated with the SIS wound matrix in addition to standard care would lead to a greater proportion of healed ulcers at 12 weeks than standard care alone
	Method of patient recruitment	Patients attending 12 outpatient sites
	Patients enrolled	120
	Date range of study	NR
	Care setting	Outpatient clinic (89%) and home setting (10%)
	Method of measuring wound condition at enrollment	NR
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	12 weeks
	Source of funding	NR

Study	Study Detail	Description
Niezgoda et al. 2005[70]	Specific wound treatment comparison	Oasis vs. Regranex Gel
	Wound type	Full-thickness diabetic foot ulcers
	Country	U.S. and Canada
	Institutes involved	9 institutions in U.S. and Canada
	Study objective	To evaluate whether treatment of full-thickness diabetic foot ulcers with Oasis would result in similar 12-week healing rates as Regranex Gel
	Method of patient recruitment	Limited to 40 patients per site; methods not reported
	Patients enrolled	98
	Date range of study	NR
	Care setting	Outpatient
	Method of measuring wound condition at enrollment	Photo planimetry or by measuring the length and width of the ulcer
	Stratification of results (wound severity or comorbidities)	NR
	Length of study	12 weeks
	Source of funding	Cook Biotech Incorporated provided all study supplies

ECM: Extra cellular matrix
NR: Not reported
NS: Not specified

Table 32. Assessment of wound closure in included trials

Study	Comparison	Wound Type	Use of Run-in Period	Minimum Clinically Important Difference	Primary Outcome	Method of measuring wound condition at enrollment	Reported assessment and reassessment of wound closure
DiDomenico et al. 2011[64]	Apligraf vs. TheraSkin	DFU	NR	NR	Wounds closed at 12 and 20 weeks	Documentation of clinical appearance, wound measurements (cross-sectional area, depth, and wound stage)	Weekly first 12 weeks; then bi-weekly through the 20th week.
Kelechi et al. 2011[61]	Talymed poly-N-acetyl glucosamine (pGlcNAc) with compression vs. nonadherent absorptive primary dressing with compression	Leg	NR	NR	Wounds closed at 20 weeks	Length and width measured by study nurses	Weekly until wound closure. No reassessment was described.
Uccioli et al. 2011[68]	Hyalograft 3D autograft/LaserSkin vs. nonadherent paraffin gauze	DFU	After a 2 week run-in period with nonadherent paraffin gauze only, patients with an ulcer area ≥1 cm^2 received the treatment they were randomly assigned to at the baseline visit	NR	Wounds closed at 12 and 20 weeks	Photograph/tracing measured later by computerized morphometry	The authors do not describe reassessment of healed wounds.
Romanelli et al. 2010[57]	OASIS Wound Matrix vs. a petrolatum-impregnated gauze	Leg	NR	NR	Wounds closed at 8 weeks	NR; measured by "clinical and instrumental assessment"	After 8-week study period, patients followed monthly for 6 months to assess wound closure.

Table 32. Assessment of wound closure in included trials, continued

Study	Comparison	Wound Type	Use of Run-in Period	Minimum Clinically Important Difference	Primary Outcome	Method of measuring wound condition at enrollment	Reported assessment and reassessment of wound closure
Edmonds 2009[53]	Apligraf vs. non-adherent dressing	DFU	Subjects completed a 14-day screening period before treatment. Patients with ulcers that showed >40% reduction in area) were excluded from the study.	The sample size was calculated assuming an incidence of complete wound healing of 50% in the Apligraf group and 32% in the control group. These assumptions were based on the results from an earlier study of Apligraf in diabetic foot ulcers	Wounds closed at 12 weeks	Planimetry	For patients whose ulcer healed in the treatment phase, there was a confirmatory visit one week after the ulcer was reported healed to confirm sustained healing and then visits at week 14 for a safety assessment, and weeks 16, 20 and 24 to observe any signs of ulcer recurrences and safety assessments.
Reyzelman et al. 2009[66]	Graftjacket acellular matrix vs. moist wound therapy with alginates, foams, hydrocolloids, or hydrogels	DFU	NR	NR	Wounds closed at 12 weeks	Acetate tracings and photographs	Weekly evaluations took place until week 12. The authors do not describe reassessment of healed wounds.

DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 32. Assessment of wound closure in included trials, continued

Study	Comparison	Wound Type	Use of Run-in Period	Minimum Clinically Important Difference	Primary Outcome	Method of measuring wound condition at enrollment	Reported assessment and reassessment of wound closure
Landsman et al. 2008[54]		DFU	1 week phase in period before being randomly assigned to treatment	NR	Wounds closed at 12 weeks	Photographed before and after debridement; ulcer location, duration, and a description of the wound base recorded	Patients were examined at least once weekly for the first 8 weeks, and subsequently, every other week until closure was achieved, for up to 12 weeks. An extended observation period of 8 additional weeks followed. In cases where wound closure was confirmed, the wounds were re-evaluated 1 week later to reconfirm closure.
Romanelli et al. 2007[60]	OASIS wound matrix vs. Hyaloskin (contains hyaluronan)	Leg	NR	NR	Wounds closed at 16 weeks	NR; measured by "clinical and instrumental assessment"	During the 16-week study, we evaluated the percentage of patients achieving complete wound closure. The authors do not describe reassessment of healed wounds.
Brigido 2006[59]	Graftjacket tissue matrix vs. weekly debridement, Curasol wound hydrogel and gauze dressing	DFU	NR	NR	Wounds closed at 16 weeks	Tracing on wound film; wound depth by disposable sterile ruler	Weekly evaluations took place until week 16. The authors do not describe reassessment of healed wounds.

DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 32. Assessment of wound closure in included trials, continued

Study	Comparison	Wound Type	Use of Run-in Period	Minimum Clinically Important Difference	Primary Outcome	Method of measuring wound condition at enrollment	Reported assessment and reassessment of wound closure
Mostow et al. 2005[69]	OASIS Wound Matrix with compression vs. compression alone	Leg	2-week screening period before enrollment, the target ulcer was treated with standard care and compression therapy. Ulcers that exhibited a greater than 50% reduction in surface area during the screening period were excluded.	Detect a 20% difference in 12-week healing of OASIS wound matrix–treated patients vs. standard of care.	Wounds closed at 12 weeks	NR	Patients were observed for up to 12 weeks…..No standardized regimen was recommended after the study treatment period; however, efforts were made to see all patients at a final 6-month follow-p visit to determine the durability of ulcer closure.
Niezgoda et al. 2005[70]	OASIS Wound Matrix vs. Regranex Gel (contains platelet-derived growth factor)	DFU	NR	NR	Wounds closed at 12 weeks	Photo planimetry or by measuring the length and width of the ulcer	Patients were followed for up to 12 weeks, and were given the option of cross-over treatment if healing did not occur. Recurrence at 6 months was also evaluated.
Krishnamoorthy et al. 2003[55]	Dermagraft plus multi-layer compression bandage therapy (Profore™) vs. multi-layer compression therapy	Leg	14 day screening period. Patients were excluded if their wound healed by more than 50%	NR	Wounds closed at 12 weeks	Traced at the edge of the intact skin epithelium, re-traced onto an ulcer area grid; 3 photos and one biopsy taken	Complete wound healing was regarded as a closed wound at two consecutive weekly visits.
Marston et al. 2003[56]	Dermagraft vs. saline-moistened gauze	DFU	NR	NR	Wounds closed at 12 weeks	“At each visit, tracings of the wound margins were made for computer planimetry to document changes in wound size, and photographs were taken for a visual record.”	An ulcer was considered healed only after closure was confirmed at the next weekly visit.

DFU: Diabetic foot ulcer

HYAFF: Benzyl esters of hyaluronic acid

NR: Not reported

Table 32. Assessment of wound closure in included trials, continued

Study	Comparison	Wound Type	Use of Run-in Period	Minimum Clinically Important Difference	Primary Outcome	Method of measuring wound condition at enrollment	Reported assessment and reassessment of wound closure
Caravaggi et al. 2003[58]	Hyalograft 3D autograft/LaserSkin vs. non-adherent paraffin gauze	DFU	After 15 days of run in all patients with an ulcer area <1 cm^2 were excluded from the study.	Estimated mean healing time of 30 days with 70% healing in the treatment group and 30% in the control group.	Wounds closed at 11 weeks	Tracing with a transparent plastic grid, Op-Site (Smith & Nephew) and recorded by photograph	The authors do not describe reassessment of healed wounds.
Veves et al. 2001[67]	Graftskin vs. saline-moistened gauze alone	DFU	All patients were required to complete a 7-day screening period during which the response to treatment by debridement and saline-moistened gauze was assessed. Patients whose ulcers responded during the screening period, as defined by a 30% decrease in the size of the ulcer, were not entered into the study.	NR	Wounds closed at 12 weeks	Computer planimetry of wound tracing	Evaluated for efficacy at 12 weeks; followed once a month for another 3 months for safety evaluations.
Falanga et al 1998[63]	Apligraf with compression vs. compression therapy with a Unna boot	Leg	NR	NR	Wounds closed at 8 weeks	Computer planimetry of surface tracings, photographs	After 8 weeks, they were evaluated at 12 weeks and every 3 months thereafter for up to 12 months.

DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 32. Assessment of wound closure in included trials, continued

Study	Comparison	Wound Type	Use of Run-in Period	Minimum Clinically Important Difference	Primary Outcome	Method of measuring wound condition at enrollment	Reported assessment and reassessment of wound closure
Naughton et al. 1997[62]	Dermagraft vs. saline-moistened gauze	DFU	NR	NR	Wounds closed at 12 weeks	Wound tracing techniques with computer planimetry at Day 0 and at each subsequent visit up to week 32.	Weekly until week 12, then every 4 weeks until week 32 to determine if wounds were completely healed.
Gentzkow et al. 1996[65]	Dermagraft vs. saline-moistened gauze	DFU	NR	NR	Wounds closed at 12 weeks	Computer planimetric study of an ulcer tracing and by the alginate mold technique	Weekly for 12 weeks…..healed ulcers were followed as long as possible to determine if they recurred.

DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 33. Methods used for wound measurement at time of enrollment in trials

Study	Comparison	Describes use of computer	Describes use of photos	Describes use of tracings	Describes training/validation	Notes
DiDomenico et al. 2011[64]	Apligraf vs. TheraSkin	NR	NR	NR	NR	Documentation of clinical appearance, wound measurements (cross-sectional area, depth, and wound stage)
Kelechi et al. 2011[61]	Talymed poly-N-acetyl glucosamine (pGlcNAc) with compression vs. nonadherent absorptive primary dressing with compression	NR	NR	NR	NR	Linear measurements
Uccioli et al. 2011[68]	Hyalograft 3D autograft/LaserSkin vs. nonadherent paraffin gauze	X (morphometry)	X	X	NR	
Romanelli et al. 2010[57]	OASIS Wound Matrix vs. a petrolatum-impregnated gauze	NR	NR	NR	NR	Measured by “clinical and instrumental assessment”
Edmonds 2009[53]	Apligraf vs. non-adherent dressing	X	NR	NR	NR	
Reyzelman et al. 2009[66]	Graftjacket acellular matrix vs. moist wound therapy with alginates, foams, hydrocolloids, or hydrogels	NR	X	X	NR	
Landsman et al. 2008[54]	Oasis wound matrix vs. Dermagraft	NR	X	NR	NR	
Romanelli et al. 2007[60]	OASIS wound matrix vs. Hyaloskin (contains hyaluronan)	NR	NR	NR	NR	Measured by “clinical and instrumental assessment”

Table 33. Methods used for wound measurement at time of enrollment in trials, continued

Study	Comparison	Describes use of computer	Describes use of photos	Describes use of tracings	Describes training/validation	Notes
Brigido 2006[59]	Graftjacket tissue matrix vs. weekly debridement, Curasol wound hydrogel and gauze dressing	NR	NR	X	NR	Wound depth measured by disposable sterile ruler.
Mostow et al. 2005[69]	OASIS Wound Matrix with compression vs. compression alone	NR	NR	NR	NR	
Niezgoda et al. 2005[70]	OASIS Wound Matrix vs. Regranex Gel (contains platelet-derived growth factor)	X	X	NR	NR	Also used linear measurements
Krishnamoorthy et al. 2003[55]	Dermagraft plus multi-layer compression bandage therapy (Profore™) vs. multi-layer compression therapy	NR	X (3 photos)	X	NR	Biopsy also taken.
Marston et al. 2003[56]	Dermagraft vs. saline-moistened gauze	X	X	X	NR	
Caravaggi et al. 2003[58]	Hyalograft 3D autograft/LaserSkin vs. non-adherent paraffin gauze	NR	X	X	NR	Tracing with a transparent plastic grid, Op-Site (Smith & Nephew)
Veves et al. 2001[67]	Graftskin vs. saline-moistened gauze alone	X	NR	X	NR	
Falanga et al 1998[63]	Apligraf with compression vs. compression therapy with a Unna boot	X	X	X	NR	

X: Study reported this method
DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 33. Methods used for wound measurement at time of enrollment in trials, continued

Study	Comparison	Describes use of computer	Describes use of photos	Describes use of tracings	Describes training/validation	Notes
Naughton et al. 1997[62]	Dermagraft vs. saline-moistened gauze	X	NR	X	NR	Wound tracing techniques with computer planimetry at Day 0 and at each subsequent visit up to Week 32.
Gentzkow et al. 1996[65]	Dermagraft vs. saline-moistened gauze	X	NR	X	NR	Used the alginate mold technique

X: Study reported this method
DFU: Diabetic foot ulcer
HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 34. Patient enrollment criteria for studies of Apligraf and Graftskin

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
DiDomenico et al. 2011[64]	0.5 cm^2 (max 4 cm^2)	4 weeks	Wagner 1 or University of Texas 1a ulcer with Type 1 or 2 diabetes ABI >0.75 Palpable pulses on study foot (at least dorsalis pedis or posterior tibial artery) No exposed bone, tendon, or joint capsule Absence of infection No evidence of gangrenous tissue or abscesses No adjuvant therapy such as hyperbaric oxygen or topical formulations containing growth factors	Only patients with HgA1c <12; patients must be able to comply with off-loading regimen	Type 1 and Type 2 diabetes
Edmonds M. 2009[53]	1–16 cm^{2*}	≥2 weeks	Ulcer has no sign of infection Plantar region of the forefoot Through the dermis but without sinus tract, tendon, capsule or bone exposure Adequate vascular supply to the target extremity During 14-day screening period ulcer was not considered healed (i.e., >40% reduction)	Inclusion criteria included need for patients having glycemic control (measured by HA1C). Excluded were patients with active Charcot foot and patients with inactive Charcot foot if the ulcer cannot be properly off-loaded; nonneuropathic ulcers; evidence of skin cancer within or adjacent to target site; osteomyelitis at any location; ulcers infected with cellulitis, gangrene or deep tissue infection; clinical significant medical conditions such as renal impairment, hepatic impairment or immunocompromised; within 4 weeks have received systemic corticosteroids, immunosuppressive agents, or radiation therapy or chemotherapy; history of drug or alcohol abuse.	Type I diabetes: Apligraf: 16 (48.5%) Nonadherent dressing: 13 (33.3%) Type II diabetes: Apligraf: 17 (51.5%) Nonadherent dressing: 26 (66.7%)

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Veves et al. 2001[67]	≥1 cm^2	≥2 weeks	Dorsalis pedis and posterior tibial pulses audible by Doppler Full-thickness neuropathic ulcer (excluding the dorsum of the foot and the calcaneus) No sign of infection ABPI ≥0.65 During a 7-day screening period, ulcer did not respond (i.e., 30% decrease in size) to saline-moistened gauze	Patients with active Charcot's disease determined by clinical and radiographic examination; an ulcer of nondiabetic pathophysiology; or significant medical conditions that might impair wound healing were excluded.	Type I diabetes: Apligraf: 36.6% Saline-moistened gauze: 27.1% Type II diabetes: Apligraf: 61.6% Saline-moistened gauze: 72.9%
Falanga et al. 1998[63]	Greater than ½ x ½ inch and less than 4 x 8 inches	At least one month duration	Presence of clinical signs and symptoms of venous ulceration Absence of significant arterial insufficiency (ABPI >0.65) Evidence of venous insufficiency by air plethysmography or photoplethysmography, with venous refilling time being less than 20 seconds Free of cellulitis and exudation indicative of heavy bacterial contamination Does not contain eschar or obvious necrotic material	No clinical signs of cellulitis, vasculitis, or collagen vascular diseases, uncontrolled diabetes mellitus, and other clinically significant medical conditions that would impair wound healing, inclusive of renal, hepatic, hematologic, neurologic, or immunological disease. Also excluded were patients who had received corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy within 1 month prior to entry into the study.	NR

*Post-débridement

ABPI: Ankle brachial pressure index
DFU: Diabetic foot ulcer
NR: Not reported
NS: Not specified

Table 35. Patient enrollment criteria for studies of Dermagraft

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Krishnamoorthy et al. 2003[55]	3–25 cm^2	2 months	APBI ≥7 During 14-day screening period, ulcer did not heal by more than 50% following use of a multilayered compression bandage	Ulcerations due to rheumatoid vasculitis or diabetic foot ulcer; severe leg edema uncontrolled by compression; soft-tissue infections that would interfere with wound healing; impaired mobility or underlying medical condition such as significant peripheral vascular disease; and patient's whose ulcers healed by >50% during 2 week screening period were excluded.	Deep vein thrombosis was present in 31%, 38%, 29%, and 38% of Group 1, 2, 3, and 4 respectively.
Marston et al. 2003[56]	1–20 cm^2	2 weeks*	Ulcer could extend through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone, or joint capsule AAI by Doppler ≥0.7 on study limb Ulcer on plantar surface of the forefront or heel Free of necrotic debris and appears to have healthy vascularized tissue During screening period, ulcers did not decrease or increase in size by 50% or more	Patients aged ≥18 years with type I or II diabetes and adequate circulation of the foot measured by palpable pulse were included. Excluded were patients with gangrene present on any part of the affected foot; ulcer over a Charcot deformity; ulcer total surface area >20 cm^2; change in ulcer size by 50% or more during screening period; severe malnutrition present as evidenced by albumin <2.0; random blood sugar reading >450 mg/dl; urine ketones "small, moderate, or large"; a nonstudy ulcer on study foot located within 7.0 cm of the study ulcer on day 0; receiving oral or parenteral corticosteroids, immunosuppressive, or cytotoxic agents, Coumadin, or heparin; history of bleeding disorder; AIDS or HIV-positive; cellulitis, osteomyelitis, or other evidence of infection.	Type I Diabetes: Dermagraft: 32 Saline-moistened gauze: 27 Type II Diabetes: Dermagraft: 98 Saline-moistened gauze: 88
Naughton et al. 1997[62]	≥1.0 cm^2	NR	Neuropathic full-thickness plantar surface foot ulcers of the forefoot or heel During screening period, did not show rapid healing in response to saline-moistened gauze	NR	Diabetes (type NS)

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Gentzkow et al. 1996[65]	>1 cm^2	NR	Diabetic ulcers of plantar surface or heel without signs of healing for one month Free of necrotic tissue and infection; suitable for skin graft (i.e., no exposed tendon, bone or joint; no tunnels or sinus tracts that are unable to be débrided). AAI >0.7	Patients must have their diabetes (Type I/II) under control; could not have more than one hospitalization during previous 6 months due to hyperglycemia or ketoacidosis. Use of corticosteroids, immunosuppressive, or cytotoxic agents were also excluded.	Diabetes (Type I/II)

* At the interim analysis, a relationship between treatment and ulcer duration of >6 weeks was observed. Additional patients (with ulcer duration >6 weeks) were then enrolled until the required Bayesian sequential procedure stopping end point was achieved (98.4 percent probability of benefit).

AAI: Ankle arm index
ABPI: Ankle brachial pressure index
NR: Not reported
NS: Not specified

Table 36. Patient enrollment criteria for studies of Graftjacket

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Reyzelman et al. 2009[66]	1 cm^2 (max 25 cm^2)	NR	Absence of infection UT Grade 1 or 2 DFU Adequate circulation to the affected extremity (based on 1 of 3 criteria including ABPI 0.7 to 1.2)	Only patients with good metabolic control (HgA1c <12% within the previous 90 days) or serum creatinine levels <3.0 mg. were included. Excluded were patients with sensitivity to gentamicin, cefoxilin, lincomycin, polymyxin B or vancomycin; non revascularable surgical sites; ulcers probing to bone (UT grade 3A to D); and wounds treated with biomedical or topical growth factors within the past 30 days.	Type I diabetes: Graftjacket: 5 (10.9%) Moist wound therapy: 2 (5.1%) Type II diabetes: Graftjacket: 41 (89.1%) Moist wound therapy: 37 (94.9%)
Brigido SA. 2006[59]	NR Note: mean wound size and mean wound duration were also not reported	6 weeks	Ulcer without epidermal coverage Absence of infection Palpable/audible pulse to the affected lower extremity Wagner Grade-2 ulcer	NR	Diabetes (Type NS)

ABI: Ankle brachial index
ABPI: Ankle brachial pressure index
DFU: Diabetic foot ulcer
NR: Not reported
NS: Not specified
UT: University of Texas

Table 37. Patient enrollment criteria for studies of HYAFF and Talymed

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Kelechi et al. 2011[61]	2 cm^2	NR Maximum 6 months	• Extending through epidermis and into the dermis • No recent skin grafts or use of growth factors • Granulation tissue ≥ 90% free of necrotic debris • Wound size between 2 and 20 cm^2 • No sign of infection • ABI >0.8 or <1.3	Patients with a history of collagen vascular disease, severe arterial disease, organ transplant, Charcot disease, or sickle cell disease were excluded. Radiation therapy to wound site, current hemodialysis, or treatment with another investigational drug or device within 30 days of study initiation were also exclusionary criteria.	Hypertension, n (%) Group A: 14 (70) Group B: 16 (72.7) Group C: 15 (75) Group D: 16 (80)* Diabetes, n (%) Group A: 12 (60%) Group B: 12 (54.5) Group C: 14 (70) Group D: 12 (60)* Class III obesity, n (%) Group A: 8 (40) Group B: 12 (54.5) Group C: 10 (50) Group D: 7 (35) Arthritis, n (%) Group A: 6 (30) Group B: 12 (54.6) Group C: 10 (50) Group D: 10 (50) Blood clotting disorders, n (%) Group A: 4 (20) Group B: 9 (40.9) Group C: 2 (10) Group D: 4 (20)
Uccioli et al. 2011[68]	≥2 cm^2	1 month	• Plantar or plantar-marginal surface (excluding calcaneum) or dorsum of the foot without signs of healing • Wagner score 1-2 • $TcPO_2$ ≥20 mmHg • ABPI ≥0.5 • No sign of infection, osteomyelitis, inability to tolerate off-loading or peripheral revascularization <30 days prior to enrollment • After 2 week run-in period, only patients with ulcer area >1 cm^2 were randomized to treatment	NR	Type I diabetes Treatment: 11 (14%) Control: 6 (8%) Type II diabetes Treatment: 68 (85%) Control: 74 (92%)

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Caravaggi et al. 2003[58]	≥2 cm^2	1 month	• On plantar surface or dorsum of the foot • Wagner score 1-2 • $TcPO_2$ ≥30 mmHg • ABPI ≥0.5 • No sign of infection, exposed bone, osteomyelitis diagnosed by radiography, or inability to tolerate an off-loading cast • After 15 day run-in period, only patients with ulcer area >1 cm^2 were randomized to treatment	Patients with poor-prognosis disease were excluded.	Type I diabetes Treatment: 9 Control: 3 Type II diabetes Treatment: 34 Control: 33

* Control group

ABPI:	Ankle brachial pressure index
DFU:	Diabetic foot ulcer
Class III obesity:	BMI ≥40 kg/m^2
HYAFF:	Benzyl esters of hyaluronic acid
mmHg:	Millimeters of mercury
NR:	Not reported
NS:	Not specified
$TcPO_2$:	Transcutaneous partial pressure of oxygen

Table 38. Patient enrollment criteria for studies of Oasis

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Romanelli et al. 2010[57]	2.5 cm^2	>6 months	50% of granulation tissue on wound bed ABI range 0.6 to 0.8	Patients with sign of infection or known allergy to treatment products were excluded.	NR
Landsman et al. 2008[54]	≥1 cm^2	4 weeks	Ulcers extend through the epidermis and dermis with no exposed tendon or bone Viable wound bed with granulation tissue as determined by bleeding post-débridement ABI ≥0.65 After a 1 week phase-in period, patients who met inclusion criteria were randomized to treatment	Exclusion criteria included malnourished (defined by albumin <2.5 g/dL); known allergy to porcine-derived products, dextran, EDTA, or gelatin; known hypersensitivity to the components of the Dermagraft product; history of radiation therapy to the ulcer site; use corticosteroids >10 mg prednisone daily; use of any immune suppressive, or severely immunocompromised patients; ulcer of nondiabetic pathophysiology; vasculitis, severe rheumatoid arthritis, or other collagen vascular disease; erythema or purulence associated with a severe infection of the wound site; signs and symptoms of cellulitis, osteomyelitis, necrotic or avascular ulcer beds; undergoing hemodialysis; uncontrolled diabetes (HgbA1c >12%); deficient blood supply to ulcers (e.g., capillary fill time >3 seconds at tips of toes); active Charcot's neuroarthropathy determined by clinical and/or radiographic examination; and sickle cell disease	Non-insulin dependent or insulin-dependent diabetes mellitus
Romanelli et al. 2007[60]	2.5 cm^2	>6 weeks	50% of granulation tissue on wound bed ABI range 0.6 to 0.8	Patients with sign of infection, diabetics, and smokers, necrotic tissue on the wound bed or known allergy to treatment products were excluded.	NR

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health Requirements	Comorbidities
Mostow et al. 2005[69]	1–64 cm^2	>1 month	Viable wound bed with granulation tissue ABI >0.80 Ulcers could not exhibit >50% reduction in surface area during the screening period (treatment by usual care and compression therapy)	Patients with severe rheumatoid arthritis; history of radiotherapy to the ulcer site; uncontrolled congestive heart failure; receiving corticosteroids or immune suppressive; history of collagen vascular disease; malnourished, known allergy to porcine-derived products; sign of wound infection, uncontrolled diabetes, previous organ transplantation; undergoing hemodialysis; signs of cellulitis, osteomyelitis, or necrotic or avascular ulcer beds; active sickle cell disease; were excluded.	Status of several comorbidities taken but specific data not reported
Niezgoda et al. 2005[70]	1–49 cm^2	>1 month and nonhealing	Grade 1, Stage A (University of Texas classification) Viable wound bed with granulation tissue	Patients with exposed bone, tendon or fascia; clinically defined and documented severe arterial disease; history of radiation therapy to the ulcer site; ulcer of nondiabetic pathophysiology; receiving corticosteroids or immune suppressive; history of collagen vascular disease; malnutrition (albumin <2.5 g/dL); known allergy to porcine-derived products; known hypersensitivity to any component of Regranex Gel; uncontrolled diabetes (A1C >12%); previous organ transplant; ulcer clinically infected; signs of cellulitis, osteomyelitis, necrotic or avascular ulcer bed; undergoing hemodialysis; insufficient blood supply to the ulcer ($TcPO_2$ <30 mm Hg or toe-brachial index <0.70); active Charcot or sickle cell disease.	Type 1 or type 2 diabetes

ABI: Ankle brachial index
NR: Not reported

Table 39. Description of treatments in studies of Apligraf and Graftskin

Study	Prior Wound Therapy	Ancillary Wound Treatment	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
DiDomenico et al. 2011[64]	NR	Debridement Off-loading with fixed ankle walker	During the first week no dressing changes were performed to allow for the graft material to become incorporated into the wound. Dressing changes were then performed every other day on a daily basis dependent upon wound exudate. Apligraf was covered with a porous, nonadherent dressing before gauze dressing was applied. Patients were allowed up to five applications of Apligraf per the manufacturer's recommendations.	During the first week no dressing changes were performed to allow for the graft material to become incorporated into the wound. Dressing changes were then performed every other day on a daily basis dependent upon wound exudate. TheraSkin was covered with a porous, nonadherent dressing before gauze dressing was applied. Patients were allowed up to five applications of TheraSkin per the manufacturer's recommendations.	NR
Edmonds M. 2009[53]	NR	Extensive sharp debridement Saline-moistened dressings Nonweight-bearing regimen Removal of necrotic tissue	Apligraf was placed directly on the ulcer bed. A nonadherent dressing (Mepitel) was then applied. Secondary dressings including small normal saline-moistened gauze, dry gauze, and a bandage were taped onto the ulcer. Primary and secondary dressings were changed weekly. Additional Apligrafs could be applied at weeks 4 and 8 (3 total) if needed. By study end, 13 received one application, 15 received two applications, and 5 subjects received three applications. On average, 1.8 applications of Apligraf were provided.	Mepitel (Mölnlycke Health Care AB), a porous wound contact layer consisting of a flexible polyamide, was applied as a primary nonadherent dressing. Secondary dressings included saline moistened gauze, dry gauze, and a bandage held in place with tape.	Routine laboratory testing and spontaneous adverse event reporting

Study	Prior Wound Therapy	Ancillary Wound Treatment	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Veves et al. 2001[67]	NR	Aggressive débridement and saline-moistened gauze (screening period) Wounds not healed by week 5 received a layer of saline-moistened gauze, a layer of petrolatum gauze, and wrapped with a layer of Kling. Patients were instructed to change this dressing twice/day and attend weekly evaluations during weeks 6-12. Off-loading	Graftskin was trimmed and placed directly over the wound. The site was then covered with saline-moistened Tegapore, secured by hypoallergenic tape. The wound was then covered with a layer of dry gauze, a layer of petroleum gauze, and wrapped with Kling. Graftskin could be re-applied at weeks 1–4 (maximum 5). Complete dressing changes were performed mid-week during weeks 1, 2, 3, and 4. After visits, patients changed secondary dressings (dry gauze, petrolatum gauze and Kling) once daily until next mid-week visit.	Saline moistened Tegapore (3M Health Care), covered with a layer of saline moistened gauze (Kendall Health Care Products), dry gauze, and petrolatum gauze wrapped in Kling (Johnson & Johnson Medical)	Intervention to improve glucose control when clinically indicated, routine laboratory testing and spontaneous adverse event reporting
Falanga et al. 1998[63]	NR	Graded elastic stockings	Apligraf was placed directly on the ulcer bed. A nonadherent dressing (Tegapore) was then applied. Additional dressings included a cotton gauze dressing folder as a bolster, and self-adherent elastic compression wrap (Coban, 3M Health Care) to immobilize the Apligraf. Ulcer sites with percent take estimated at greater than 50% were not permitted an additional application of Apligraf. Overall, no patients received more than 5 applications. After 8 weeks of treatment, subsequent dressing changes were the same for both groups.	Non adherent primary dressing (Tegapore, 3M Health Care), gauze bolster, zinc oxide impregnated paste bandage (Unna boot) and self-adherent elastic compression wrap (Coban, 3M Health Care). Compression therapy was reapplied weekly for the first 8 weeks. After 8 weeks of treatment, subsequent dressing changes were the same for both groups.	Routine laboratory testing and spontaneous adverse event reporting

NR: Not reported

Table 40. Description of treatments in studies of Dermagraft

Study	Prior Wound Therapy	Ancillary Wound Treatment	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Krishnamoorthy et al. 2003[55]	NR	Cleansing Débridement	Dermagraft was applied directly to the wound and covered by a nonadherent dressing (Dermanet™). Lastly, a multilayered bandaging system (Profore) was used to apply compression to the leg. 12, 4 and 1 application of Dermagraft to Group 1, 2 and 3 respectively. Subsequent pieces of Dermagraft were "implanted on the surface of previously applied pieces."	A nonadherent dressing (Dermanet™) and a multilayered bandaging system (Profore) was used to apply compression to the patient's leg.	NR
Marston et al. 2003[56]	NR	Sharp débridement Saline-moistened gauze Pressure-relieving orthotics Infection control	A nonadherent interface, saline-moistened gauze to fill the ulcer, dry gauze, and adhesive fixation sheets (Hypafix). Patients received their first application of Dermagraft on day 0 and subsequent applications at weekly intervals over the 12 week study period.	A nonadherent interface, saline-moistened gauze to fill the ulcer, dry gauze, and adhesive fixation sheets (Hypafix).	NR
Naughton et al. 1997[62]	NR	Débridement Infection control Standard off weighting	Saline-moistened gauze plus 8 applications of Dermagraft (Day 0 and weekly for 7 weeks)	Saline-moistened gauze dressings	NR
Gentzkow et al. 1996[65]	NR	Sharp débridement Pressure-relieving orthotics	Dermagraft was first applied. Ulcer was then covered with a nonadherent interface, saline-moistened gauze to fill the remaining volume of ulcer, secured by an adhesive covering. 8 Dermagraft® pieces over 8 applications, 8 pieces over 4 applications, and 4 pieces over 4 applications were distributed to Group A, B and C, respectively.	A nonadherent interface, saline-moistened gauze to fill the ulcer, secured by an adhesive covering.	NR

NR: Not reported

Table 41. Description of treatments in studies of Graftjacket

Study	Prior Wound Therapy	Ancillary Wound Treatment	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Reyzelman et al. 2009[66]	NR	Débridement Cleansing with a sterile normal saline solution before dressing placement Rinsing/swabbing/ irrigating Off loading	A single application of Graftjacket® Regenerative Tissue Matrix (Wright Medical Technology, Arlington TN) was sutured/stapled into place; a silver-based nonadherent dressing (Silverlon; Argentum Medical LLC, Chicago, IL) was then applied. Secondary dressings including hydrogel bolsters or moist gauze were applied at the discretion of the investigator until complete epithelialization or 12 weeks.	Moist-wound therapy with alginates, foams, hydrocolloids, or hydrogels. For heavily exudative wounds, foam and alginates were used. For minimal exudative wounds, hydrocolloids or hydrogels were used. Dressings were changed daily but at the discretion of the physician. Moist wound therapy was applied until complete epithelialization or 12 weeks.	NR (antibiotic if infection occurred)
Brigido SA. 2006[59]	NR	Sharp debridement initially in both groups Removal of necrotic tissue until a bleeding wound base Off loading	A single application of Graftjacket® was cut to fit the wound. Once identified as "ready for application," the shiny or reticular side of the scaffold was applied to the wound bed; the dull or basement membrane surface of the scaffold was exposed to the compression dressing. After Graftjacket® was sutured/stapled into place, a mineral oil-soaked fluff compressive dressing was applied. The compressive dressing was changed and reapplied at days 5, 10 and 15. Based on the amount of granular incorporation in the scaffold, the area was either covered with a dry sterile dressing and nonadherent dressing (if matrix was fully incorporated) or the compressive dressing was reapplied.	Curasol (Healthpoint Ltd, Fort Worth, TX) wound hydrogel was applied followed by gauze dressing. Sharp wound debridement was performed initially and weekly for the duration of the study.	NR

NR: Not reported

Table 42. Description of treatments in studies of HYAFF and Talymed

Study	Prior Wound Therapy	Ancillary Wound Treatment	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Kelechi et al. 2011[61]	NR	Nonadherent absorptive primary dressing (Mepilex, Mölnlycke Health Care, Norcross, GA) Compression	Poly-N-acetyl glucosamine (pGlcNAc) wound product (a tissue paper thin material) was applied directly to the wound prior to administration of nonadherent absorptive primary dressing and compression Group A: received pGlcNAc once during week 1 Group B: received pGlcNAc once every second week Group C: received pGlcNAc once every third week	Nonadherent absorptive primary dressing (Mepilex, Molnlycke Health Care, Norcross, GA) and compression	4 patients received treatment for systemic infections reported as unrelated to their wounds; treatment not specified
Uccioli et al. 2011[68]	NR	• Débridement • Patients with plantar ulcers received standard care for pressure relief; patients with dorsal ulcers received therapeutic shoes with a rigid insole	Dermal tissue-engineered autografts (Hyalograft 3D autograft) was covered with nonadherent paraffin gauze and a secondary bandage (sterile cotton pads and gauze). The nonadherent gauze remained intact for 7 days; the secondary bandaging could be changed after 5 days. The epidermal tissue-engineered autograft (Laserskin autograft) was applied approximately two weeks later with coverings similar to Hyalograft. Second applications of either autograft were allowed.	Nonadherent paraffin gauze (Jelonet; Smith and Nephew, Hull, UK) covered with a secondary bandage (sterile cotton pads and gauze). Daily or frequent change was allowed dependent on wound bed.	NR
Caravaggi et al. 2003[58]	NR	• Aggressive and extensive débridement • Off-loading cast (plantar ulcers) • Therapeutic shoes (dorsal ulcers)	Autologous fibroblasts on Hyalograft 3D were grafted onto the wound bed and covered with nonadherent paraffin gauze. A secondary dressing consisting of sterile cotton pads and gauze was then applied. 7-10 days after grafting, the ulcer received autologous keratinocytes grown on Laserskin. One additional placement of Hyalograft and Laserskin was permitted. Seven days after graft application, patients changed the paraffin gauze every 2 days at home after cleaning the ulcer with physiologic solution. Ulcers were analyzed on weekly visits for 11 weeks or until wound healing.	Nonadherent paraffin gauze (Jelonet; Smith & Nephew) plus covered with a secondary dressing of sterile cotton pads and gauze. Dressing changes and visits were similar to treatment group.	Antibiotic was provided to treat infections

HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 43. Description of treatments in studies of Oasis

Study	Prior Wound Therapy	Ancillary Wound Treatment	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Romanelli et al. 2010[57]	NR	Patients changed secondary dressing at home Evaluated twice/week in the clinic	Cut to a size slightly larger than the wound, positioned directly on wound, and moistened with saline. A secondary nonadherent dressing was then applied.	A petrolatum-impregnated gauze applied together with a secondary nonadherent dressing	NR
Landsman et al. 2008[54]	NR	Débridement Off-loading	Oasis was applied to the wound and backed by saline moistened gauze which was left in place for 1 week. If more than one-half of the graft didn't adhere to the wound, the product was reapplied. Gentle irrigation with sterile solution was applied upon appearance of a caramel colored gel on the wound. Before reapplying product, any nonadherent portions of Oasis were trimmed. A total of 8 dressings were permitted.	Dermagraft was applied to the wound and backed by saline moistened gauze which was left in place for 1 week. Dermagraft could be reapplied at weeks 2 and 4 if closure was not achieved. A maximum of 3 grafts were permitted.	NR
Romanelli et al. 2007[60]	NR	Evaluated twice/week Dressings changed only when necessary No compression	Cut to a size slightly larger than the wound, moistened with saline and covered with a secondary nonadherent dressing.	Hyaloskin (contains hyaluronan) cut to a size slightly larger than the wound, moistened with saline and covered with a secondary nonadherent dressing.	NR
Mostow et al. 2005[69]	NR	Wound cleansing Débridement Dressing changes Compression therapy	Cut to a size slightly larger than the wound, moistened with sterile saline, applied directly to the wound bed, and covered with a nonadherent dressing (Allevyn; Smith & Nephew) and a four-layer compression bandaging system (Profore; Smith & Nephew).	Nonadherent dressing (Allevyn; Smith & Nephew) and a four-layer compression bandaging system (Profore; Smith & Nephew).	NR
Niezgoda et al. 2005[70]	NR	• Patients evaluated weekly • Wounds cleansed and débrided when necessary • Pressure-relief shoes were provided to all sites but not mandatory	Cut to a size slightly larger than the wound, applied directly to the wound bed, and moistened with sterile saline. A secondary dressing was then applied. "The amount of Oasis applied was based on the amount of matrix observed on the surface of the wound and the extent of epithelialization at each change of the secondary dressing."	Regranex Gel (contains platelet-derived growth factors) was applied daily by the patient to the full area of the wound bed. A saline-moistened gauze dressing was then applied and left in place for 12 hours. Patients then removed the dressing after 12 hours, rinsed the ulcer with saline to remove the residual gel, and then recover the wound with a new piece of gauze.	

NR: Not reported

Table 44. Patient characteristics in studies of Apligraf and Graftskin

Study	Characteristic	Skin Substitute	Control
DiDomenico et al. 2011[64]	Number of patients	Apligraf (n=16)	TheraSkin (n=12)
	Mean age ±SD (years)	NR	NR
	% male	NR	NR
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	1.89	1.82
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	Wagner 1 or University of Texas 1a ulcer	Wagner 1 or University of Texas 1a ulcer
	Comorbidities	Diabetes	Diabetes
	Completion rate	100%	100%
Edmonds M. 2009[53]	Number of patients (ITT)	33	39
	Mean age ±SD (years)	56.4 ±11.6 (35–81)	60.6 ±9.8 (40–84)
	% male	87.9%	84.6%
	Wound type	DFU	DFU
	Mean wound size (cm^2)	3.0 cm^2	3.0 cm^2
	Mean wound duration	2.0 years	1.7 years
	Wound severity	NR	NR
	Comorbidities	Type I diabetes: 16 Type II diabetes: 17	Type I diabetes: 13 Type II diabetes: 26
	Completion rate (6 months)	90.9%	84.6%
Veves et al. 2001[67]	Number of patients (ITT)	112	96
	Mean age ±SD (years)	58 ±10	56 ±10
	% male	79%	77%
	Wound type	DFU	DFU
	Mean wound size (cm^2) (range)	2.97 ±3.10	2.83 ±2.45
	Mean wound duration (months)	11.5 ±13.3	11.1 ±12.5
	Wound severity	NR	NR
	Comorbidities	Type I diabetes: 41 Type II diabetes: 71	Type I diabetes: 26 Type II diabetes: 70
	Completion rate (6 months)	80%	77%

Study	Characteristic	Skin Substitute	Control
Falanga et al. 1998[63]	Number of patients	146	129
	Mean age ±SD (years) (min, max)	60.2 ±14.7	60.4 ±15.1
	% male	53.4%	50.4%
	Wound type	Venous leg	Venous leg
	Mean wound size (cm^2) (range)	1.33 ±2.69	1.05 ±1.61
	Mean wound duration <6 months 6 months to 1 year 1–2 years >2 years	NR 29.5% 17.1% 17.8% 35.6%	NR 31.8% 25.6% 9.3% 33.3%
	Wound severity	NR	NR
	Comorbidities (from PMA labeling information)	Diabetes: 25 of 130	Diabetes: 11 of 110
	Completion rate (12 months)	80.1%	74.4%

DFU: Diabetic foot ulcer
ITT: Intent to treat
NR: Not reported
SD: Standard deviation

Table 45. Patient characteristics in studies of Dermagraft

Study	Characteristic	Skin Substitute	Control
Krishnamoorthy et al. 2003[55]	Number of patients	Group 1: 13 Group 2: 13 Group 3: 13	13
	Mean age ±SD (years)	Group 1: 72.8 ±13.6 Group 2: 62.5 ±14.5 Group 3: 72.0 ±11.7	68.7 ±14.7
	% male	Group 1: 38% Group 2: 31% Group 3: 50%	46%
	Wound type	Venous leg ulcers	Venous leg ulcers
	Median wound size (cm^2) (min, max)	Group 1: 8.6 (3.2, 22.1) Group 2: 5.6 (3.6, 20.2) Group 3: 6.8 (3.3, 25.2)	9.2 (3.7, 25.0)
	Median wound duration (days) (min, max)	Group 1: 34.7 (13.0, 260.0) Group 2: 52.0 (9.0, 260.0) Group 3: 43.3 (11.7, 238.3)	73.7 (8.7, 260.0)
	Wound severity	NR	NR
	Comorbidities	NR	NR
	Completion Rate	Group 1: 100% Group 2: 92% Group 3: 77%	92%
Marston et al. 2003[56]	Number of patients (a subgroup population with ulcer duration >6 weeks)	130	115
	Mean age ±SD (years)	55.8 (27–83)	55.5 (31–79)
	% male	69%	79%
	Wound type	DFU	DFU
	Mean wound size (cm^2) (range)	2.31 (0.75–16.7)	2.53 (0.5–18.0)
	Mean wound duration (weeks)	41	67
	Wound severity	NR	NR
	Comorbidities	Diabetes Type 1: 32 Type 2: 98	Diabetes Type 1: 27 Type 2: 88
	Completion rate	19% discontinued; not specified by treatment group	
Naughton et al. 1997[62]	Number of patients	139	142
	Mean age ±SD (years)	NR	NR
	% male	NR	NR
	Wound type	DFU	DFU
	Mean wound Size (cm^2)	NR	NR
	Mean wound duration	NR	NR
	Wound severity	NR	NR
	Comorbidities	Diabetes	Diabetes
	Completion rate	78% (109/139)	89% (126/142)

Study	Characteristic	Skin Substitute	Control
Gentzkow et al. 1996[65]	Number of patients	Group A: 12 Group B: 14 Group C: 11	Group D: 13
	Mean age (SE)	Group A: 62.7 Group B: 66.2 Group C: 62.7	Group D: 53.8
	% male	Group A: 67% Group B: 78% Group C: 64%	Group D: 69%
	Wound type	DFU	DFU
	Mean (±SE) wound size (cm^2)	Group A: 2.2 Group B: 2.3 Group C: 3.3	Group D: 1.9
	Wound duration (weeks)	Group A: 50.4 Group B: 40.7 Group C: 43.2	Group D: 87.0 (p=0.249)
	Wound severity	NR	NR
	Comorbidities	Diabetes	Diabetes
	Completion rate	100%	100%

DFU: Diabetic foot ulcer
NR: Not reported
SD: Standard deviation

Table 46. Patient characteristics in studies of Graftjacket

Study	Characteristic	Skin Substitute	Control
Reyzelman et al. 2009[66]	Number of patients randomized (93 enrolled; 7 did not meet inclusion criteria and were listed as failures)	47	39
	Mean age ±SD (years)	55.4 ±9.6 (n=46)	58.9 ±11.6
	% male	NR	NR
	Wound type	DFU	DFU
	Mean wound size (cm^2) (range)	3.6 ±4.3 (0.6–23.3)	5.1 ±4.8 (0.4–18.9)
	Mean wound duration (weeks) (range)	23.3 ±22.4 (0.00–96.00)	22.9 ±29.8 (3.00–139.00)
	Wound severity	NR	NR
	Comorbidities	Diabetes	Diabetes
	Completion rate	87.2%	94.8%
Brigido SA. 2006[59]	Number of Patients	14	14
	Mean age ±SD (years) (min, max)	61.43 ±7.18 (42, 71)	66.21 ±4.37 (59, 73)
	% male	NR	NR
	Wound type	DFU	DFU
	Mean wound size (cm^2) (range)	NR	NR
	Mean wound duration (weeks)	NR	NR
	Wound severity	Wagner Grade-2	Wagner Grade-2
	Comorbidities	Diabetes	Diabetes
	Completion rate	100%	100%

DFU: Diabetic foot ulcer
NR: Not reported
SD: Standard deviation

Table 47. Patient characteristics in studies of HYAFF and Talymed

Study	Characteristic	Skin Substitute	Control
Kelechi et al. 2011[61]	Number of patients	Group A: 20 Group B: 22 Group C: 20	Group D: 20
	Mean age ±SD (years)	Group A: 59 (13.5) Group B: 63.2 (14.8) Group C: 60.8 (12.2)	Group D: 63.0 (15.3)
	% male	Group A: 25% Group B: 59.1% Group C: 65%	Group D: 50%
	Wound type	Venous leg	Venous leg
	Mean wound size (cm^2)	Group A: 12.1 (11.3) Group B: 9.8 (7.3) Group C: 10.5 (10.3)	Group D: 12.8 (12.0)
	Mean wound duration (month)	Group A: 3.4 (1.5) Group B: 3.6 (1.8) Group C: 2.7 (2.1)	Group D: 2.7 (1.6)
	Wound severity	NR	NR
	Comorbidities	Hypertension, diabetes, obesity, arthritis, blood clotting disorders	Hypertension, diabetes, obesity, arthritis, blood clotting disorders
	Completion rate	82.2%	100%
Uccioli et al. 2011[68]	Number of patients (ITT)	80	80
	Mean age ±SD (years)	61 ±10	62 ±11
	% male	NR	NR
	Wound type	25 dorsal, 52 plantar	30 dorsal, 50 plantar
	Mean wound size (cm^2) Dorsal Plantar	8.8 ±9.4 7.35 ±5.71 9.04 ±10.07	6.7 ±7.7 5.53 ±5.37 7.60 ±9.26
	Mean wound duration (months) Dorsal Plantar	7.4 ±6.6 6.82 ±5.09 7.44 ±6.88	7.3 ±7.8 5.43 ±4.83 8.41 ±8.91
	Wound severity	NR	NR
	Comorbidities	Diabetes	Diabetes
	Completion rate	88.8%	88.8%
Caravaggi et al. 2003[58]	Number of patients (ITT)	43	36
	Mean age ±SD (years)	NR	NR
	% male	NR	NR
	Wound type	21 dorsal, 22 plantar	16 dorsal, 20 plantar
	Mean wound size (cm^2) Total Dorsal ulcers Plantar ulcers	 5.3 ±6.76 4.6 ±5.74 5.9 ±7.69	 6.2 ±7.58 8.3 ±9.67 4.5 ±4.86

Study	Characteristic	Skin Substitute	Control
Caravaggi et al. 2003[58] (continued)	Median wound duration (months)(interquartile range) Total Dorsal ulcers Plantar ulcers	 4.0 4.0 3.5	 4.0 4.0 4.0
	Wound severity	NR	NR
	Comorbidities	Diabetes (Type I and II)	Diabetes (Type I and II)
	Completion rate	81.3%	72.2%

HYAFF: Benzyl esters of hyaluronic acid
ITT: Intent to treat
NR: Not reported

Table 48. Patient characteristics in studies of Oasis

Study	Characteristic	Skin Substitute	Control
Romanelli et al. 2010[57]	Number of patients	25	25
	Mean age ±SD	NR	NR
	% male	52%	44%
	Wound type	Overall mix reported as 46% mixed A/V; 54% venous	Overall mix reported as 46% mixed A/V; 54% venous
	Mean wound size (cm^2)	23.5	25.2
	Mean wound duration (weeks)	7.2	6.9
	Wound severity	NR	NR
	Comorbidities	NR	NR
	Completion rate	100%	92%
Landsman et al. 2008[54]	Number of patients	13	13
	Mean age ±SD	63.4±9.84	62.17±12.17
	% male	61.5%	76.9%
	Wound type	DFU	DFU
	Average wound size (cm^2)	1.88 ±1.39	1.85±1.83
	Mean wound duration (weeks)	NR	NR
	Wound severity	NR	NR
	Comorbidities	Diabetes	Diabetes
	Completion rate	83.8% overall (26/31)	83.8% overall (26/31)
Romanelli et al. 2007[60]	Number of patients	27	27
	Mean age ±SD	64 ±13	62 ±8
	% male	52%	44%
	Wound type	Mixed A/V	Mixed A/V
	Mean wound size (cm^2)	6.3	5.6
	Mean wound duration (weeks)	8.3	7.2
	Wound severity	NR	NR
	Comorbidities	NR	NR
	Completion rate	96%	89%

Study	Characteristic	Skin Substitute	Control
Mostow et al. 2005[69]	Number of patients	62	58
	Mean age (SD)	63 ±2	65 ±2
	% male	47%	36%
	Wound type	Venous leg ulcers	Venous leg ulcers
	Mean wound size (cm^2)	10.2 ±1.51	12.1 ±1.98
	Wound duration 1–3 months 4–6 months 7–12 months >1 year Not specified	 23 (37%) 12 (19%) 5 (8%) 21 (34%) 1 (2%)	 18 (31%) 7 (12%) 7 (12%) 23 (40%) 3 (5%)
	Wound severity	NR	NR
	Comorbidities	NR	NR
	Completion rate	81%	79%
Niezgoda et al. 2005[70]	Number of patients	50	48
	Mean age (SE)	58 ±2.3	57 ±1.9
	% male	62%	58%
	Wound type Plantar surface location Other	DFU 72% 28%	DFU 58% 42%
	Mean (±SE) wound size (cm^2)	5.0 ±1.4	3.2 ±0.5
	Wound duration 1–3 months 4–6 months 7–12 months >12 months	 17 (46%) 8 (22%) 5 (13%) 7 (19%)	 19 (53%) 4 (11%) 6 (17%) 7 (19%)
	Wound severity	NR	NR
	Comorbidities Type 1 diabetes Type 2 diabetes	 18 (49%) 19 (51%)	 8 (22%)* 28 (78%)
	Completion rate	74%	75%

*Significant at 0.01 level

AV: Arterial venous
DFU: Diabetic foot ulcer
NR: Not reported
SD: Standard deviation
SE: Standard error

Table 49. Clinical results related to wound healing in studies of Apligraf and Graftskin

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
DiDomenico et al. 2011[64]	Wounds closed at 12 weeks	Full epithelialization	41.3% (Apligraf)	66.7% (TheraSkin)
	Wounds healed after 12 weeks (20 weeks)		47.1%	66.7%
	Average time to wound closure (weeks[SD])		6.86 (4.12)	5.00 (3.43)
	Number of patients with infected wounds and increase in wound size		5	3
	Other wound healing outcomes Average number of grafts (weeks[SD])		1.53(1.65)	1.38(0.29)
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		0	1 (due to infection)
	Return to function or activities of daily living		NR	NR
	Pain		NR	NR
	Exudate		NR	NR
	Odor		NR	NR
Edmonds M. 2009[53]	Wounds closed at 12 weeks	Full epithelialization with no drainage	51.5% (17/33)	26.3% (10/38) (p=0.049, Fisher's exact test)
	Wounds healed after 12 weeks			
	Median time to wound closure (SD)		84 days "As shown in Figure 2, Kaplan-Meier curves of time to complete wound healing showed a trend to shorter time to complete healing in the Apligraf group compared with the control group during the 12 week period (p=0.059, log-rank test)."	"Because fewer than 50% of subjects in the control group did not attain complete wound closure, the median time to healing could not be estimated by Kaplan-Meier methods."
	Wounds infected during 12 weeks		Osteomyelitis during treatment phase and cellulitis in the followup phase: 1; Localized foot infection: 1	Osteitis (resulting in amputation): 1

Table 49. Clinical results related to wound healing in studies of Apligraf and Graftskin, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Edmonds M. 2009[53] (continued)	Amputation		0	1 (due to osteitis)
	Reoccurrence (3 month followup)		7.0% (1/15)	10% (1/10) (p=1.000)
	Hospitalization (at 6 months)		30.3%	23.1
	Return to function or activities of daily living		NR	NR
	Pain relief		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR
Veves et al. 2001[67]	Wounds closed at 12 weeks The estimated hazard ratio (Cox's proportional hazards regression analysis) indicated that an average Graftskin patient had a 1.59-fold better chance for closure per unit time that a patient receiving saline-moistened gauze (95% CI: 1.26 to 2.00)	Full epithelialization with absence of drainage	56% (63/112)	38%; p<0.01 (36/96) (OR 2.14; 95% CI: 1.23 to 3.74)
	Wounds healed after 12 weeks		NR	NR
	Kaplan-Meier estimate of time to wound closure (median) (days) (min, max)		65 (7, 88)	90 (15, 92); p=0.0026 (log-rank test)
	Wounds infected		10.7% (12/112)	13.5% (13.96)
	Amputation		6.3% (7/112)	15.6% (15/96); p=0.028 (Fisher's exact test)
	Reoccurrence (6 months)		5.9% (3/51)	12.9% (4/31) Not significant
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain/discomfort		NR	NR
	Exudate reduction (week 12)		Both groups showed a statistically significant improvement. A statistically significant difference was reported between the 2 groups for exudates (p<0.05), maceration (p<0.05), and eschar (p<0.05).	
	Odor reduction		NR	NR

NR: Not reported
NS: Not specified
SD: Standard deviation
VAS: Visual analogue scale

Table 49. Clinical results related to wound healing in studies of Apligraf and Graftskin, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Falanga et al. 1998[63]	Wounds closed at 12 weeks		NR	NR
	Wounds healed after 12 weeks (6 months)	Full epithelialization with no drainage	63% (92/146)	48.8% (63/129)
	Median time to wound closure (SD)(days)(range) Median days to 50% wound closure (range) Median days to 75% wound closure (range)		61 (9–233) 23 (3–185) 30 (3–189)	181(10–232); p=0.003 29 (3–232); p=0.02 50 (4–232); p=0.02
	Subgroups (median days to complete healing) Patients with ulcers >6 months duration Patients with ulcers <6 months duration Patients with Stage III ulcers Patients with Stage II ulcers Patients with large ulcers (>1000 mm^2) Patients with small ulcers (<1000 mm^2)		 92 46 83 57 181 56	 190; p=0.001, log-rank 89; p>0.05 183; p=0.003, log-rank 98; p>0.05, log-rank 231; p=0.02 98; p=0.04
	Wounds infected (12 months)	"No statistically significant difference in the number of wound infections attributed to the 2 treatment groups."	Number NS	Number NS
	Amputation		NR	NR
	Reoccurrence (12 month followup)		12% (11/92 healed)	15.9% (10/63 healed); p=0.48, 2-tailed Fisher exact test
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain/discomfort (from PMA application)	"One of the three most commonly reported adverse effects." Recorded as none, mild, moderate, extreme at Study Visits Day 3-5, Weeks 1, 2, 3 and 4 and Month 6	Showed significant improvement, not different from control	Showed significant improvement, not different from skin substitute

NR: Not reported
NS: Not specified
SD: Standard deviation
VAS: Visual analogue scale

Table 49. Clinical results related to wound healing in studies of Apligraf and Graftskin, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Falanga et al. 1998[63] (continued)	Exudate reduction (from PMA application)	Recorded as none, mild, moderate, severe at Study Visits Day 3-5, Weeks 1, 2, 3 and 4 and Month 6	Statistically significant increase in exudate over baseline at Day 3–5 and a decrease at Month 6	Statistically significant decrease in exudate over baseline at Month 6 only. At Week 2 there was statistically significantly more exudate in the skin substitute group compared with control; no other statistically significant results were seen between groups at any other time point
	Odor reduction		NR	NR

NR: Not reported
NS: Not specified
SD: Standard deviation
VAS: Visual analogue scale

Table 50. Clinical results related to wound healing in studies of Dermagraft

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Krishnamoorthy et al. 2003[55]	Wounds closed at 12 weeks	A "closed wound" was defined as full epithelialization of the wound without drainage, i.e., without exudate or a scab. A wound closed for 2 consecutive weekly visits was considered "completely healed." Serial wound tracings and photographs were taken until complete wound healing occurred.	Group 1: 38% (5/13) Group 2: 38% (5/13) Group 3: 7% (1/14)	15% (2/13)
	Wounds healed after 12 weeks		NR	NR
	Median time to wound closure		Group 1: 35 weeks Group 2: 52 weeks Group 3: 43 weeks	74 weeks
	Wounds infected during 12 weeks		Group 2: 1	0
	Other wound healing outcomes Reduction in ulcer area (median)		Group 1: 81.4% Group 2: 88.6% Group 3: 59.4%	78.1%
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain relief		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR

Table 50 Clinical results related to wound healing in studies of Dermagraft, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Marston et al. 2003[56]	Wounds closed at 12 weeks	Wound closure was defined as "full epithelialization of the wound with the absence of drainage." Wound was considered "healed" when closure was confirmed at a subsequent visit. Tracings of wound margins were made for computer planimetry to document change in wound size. Photographs were also taken.	Interim analysis: 27% (19/71) Final analysis: 30% (39/130)	Interim analysis: 13% (9/70) Final analysis: 18% (21/115) P=0.02 for difference at final analysis
	Forefoot/toe ulcers		29.5% (33/112)	19.6% (20/102) (p=0.065)
	Heel ulcers		33% (6/18)	8% (1/13) (p=0.10)
	Wounds healed after 12 weeks		NR	NR
	Mean time to wound closure (SD)		A significantly faster time to complete wound closure was reported for Dermagraft-treated compared with controls (p=0.04). Time points not specified.	
	Wounds infected during 12 weeks (n=314)		10.4% (17/163)	17.9% (27/151)
	Other wound healing outcomes		NR	NR
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		8% (13/163)	15% (22/151)
	Return to function or activities of daily living		NR	NR
	Comfort (mean VAS score)		NR	NR
	Pain		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR

NR: Not reported
NS: Not specified
SD: Standard deviation
VAS: Visual analogue scale

Table 50 Clinical results related to wound healing in studies of Dermagraft, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Naughton et al. 1997[62]	Wounds closed at 12 weeks Evaluable Dermagraft group (n=109) Control group (n=126)	Complete healing was defined as "full epithelialization of the wound with absence of drainage." Wound tracing techniques with computer planimetry were used to measure change in wound size.	38.5%	31.7% (NS)
	Patients receiving therapeutically active product at first implant and later implants (n=76)		48.7% (p=0.008)	NR
	Patients receiving therapeutically active product at their first 2 implants and a majority of all implants (n=61)		50.8% (p=0.006)	NR
	Patients continuously receiving therapeutically active product (n=37)		54.1% (p=0.007)	NR
	Wounds healed after 12 weeks (32 weeks)	A statistically significant number of healed ulcers was reported in Dermagraft patients compared with control. Data not specified.		
	Median time to wound closure (SD) (32 weeks)		13 weeks	28 weeks
	Wounds infected during 12 weeks		No significant differences in reports of occurrence. Data not specified.	
	Other wound healing outcomes		NR	NR
	Amputation		NR	NR
	Reoccurrence (median time to)		12 weeks	7 weeks
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain relief		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR
	Wounds closed at 12 weeks		Group A: 50.0 Group B: 21.4 Group C: 18.2	Group D: 7.7% (Group A vs. Group D; p=0.03)

NR: Not reported
NS: Not specified
SD: Standard deviation
VAS: Visual analogue scale

Table 50 Clinical results related to wound healing in studies of Dermagraft, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Gentzkow et al. 1996[65]	Percentage of patients achieving complete wound closer by week 12		Group A (8 pieces, 8 applications) Group B (8 pieces, 4 applications) Group C (4 pieces, 4 applications)	
	Percent achieving 50% wound closure by 12 weeks		Group A: 75% Group B: 50.0% Group C: 18.2%	Group D: 23.1% (Group A vs. Group D; p=0.017)
	Wounds healed after 12 weeks		NR	NR
	Median time to wound closure (SD)		Group A: 12 weeks Group B: >12 weeks Group C: >12 weeks	Group D: >12 weeks
	Median time to 50% wound closure		Group A: 2.5 weeks Group B: NR Group C: NR	Group D: >12 weeks (Group A vs. Group D; p=0.0047)
	Wounds infected during 12 weeks		Group A: 17% Group B: 29% Group C: 27%	Group D: 23%
	Other wound healing outcomes		See above	See above
	Amputation		NR	NR
	Reoccurrence (mean 14 month f/u)		0/11 healed (average 17 months f/u for 8 living patients; 2, 6, and 11 month f/u for 3 patients who died)	0/1 healed (2 months f/u)
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR

NR: Not reported
NS: Not specified
SD: Standard deviation
VAS: Visual analogue scale

Table 50 Clinical results related to wound healing in studies of Dermagraft, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Gentzkow et al. 1996[65] (continued)	Pain/discomfort		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR

NR: Not reported
NS: Not specified
SD: Standard deviation
VAS: Visual analogue scale

Table 51. Clinical results related to wound healing in studies of Graftjacket

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Reyzelman et al. 2009[66]	Wounds closed at 12 weeks (1 Graftjacket-treated deviated from wound management at week 2 and was not included in analysis - The Graftjacket treatment completely dislodged from the plantar wound)	100% re-epithelialization without drainage	69.6% (32/46)	46.2% (18/39) (p=0.0289, OR=2.7)
	Wounds healed after 12 weeks		NR	NR
	Mean time to wound closure (SD)(range)		5.7 ±3.5 (1.0–12.0)	6.8 ±3.3 (2.0–12.0)
	Wounds infected during 12 weeks		1 (amputation followed)	0
	Other wound healing outcomes At least 90% healed at 12 weeks		21.4% (3/14)	28.6% (6/21)
	Decrease in ulcer size		85% (12/14 non-closers)	71.4% (15/21 non-closers)
	No change in ulcer size		14.3% (2/14)	0%
	Increase in ulcer size		0%	23.8% (5/21)
	Nonhealing rate (at 12 weeks)		30.4%	53.8% (p=0.0075)
	Final wound size (cm^2) (nonhealers) (mean ±SD) (range)		1.9 ±2.3 (0.01–9.0) (n=14)	3.5 ±5.2 (0.02–19.5) (n=20)
	Percent healed (presentation versus final wound size) (%) (mean ±SD) (range)		49.1 ±35.9 (0.00–99.9) (n=14)	47.2 ±52.0 (-64.1 to 99.4) (n=20)

Table 51. Clinical results related to wound healing in studies of Graftjackent, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Reyzelman et al. 2009[66] (continued)	Amputation		1	1 (unrelated to study treatment)
	Reoccurrence		NR	NR
	Hospitalization		1 (required vascular surgery to treat a blocked artery)	1
	Return to function or activities of daily living		NR	NR
	Pain		NR	NR
	Exudate		NR	NR
	Odor		NR	NR
Brigido SA. 2006[59]	Wounds closed at 12 weeks		NR	NR
	Wounds healed after 12 weeks (16 weeks)	Full epithelialization with the absence of drainage	85.71% (12/14)	28.57% (4/14) p=0.006
	Depth healed		100% (14/14)	78.57% (11/14) p=0.222
	Mean time to wound closure (SD)(weeks)		11.92 ±2.87	13.50 ±3.42 (NS)
	Wounds infected during 12 weeks		0 (systemic) See Table 8	0 (systemic) See Table 8
	Other wound healing outcomes Final ulcer area (mean ±SD) (min, max)		 1.00 ±2.57 (0, 8)	 31.14 ±43.74 (0, 132) p=0.005
	Final ulcer depth (mean ±SD) (min, max)		0.00 ±0.00 (0, 0)	0.21 ±0.43 (0, 1) p=0.090
	Final ulcer volume (mean ±SD) (min, max)		0.00 ±0.00 (0, 0)	13.50 ±36.43 (0, 132) p=0.091
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Comfort (mean VAS score)		NR	NR
	Pain		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR

NR: Not reported
NS: Not specified
VAS: Visual analogue scale

Table 52. Clinical results related to wound healing in studies of HYAFF and Talymed

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Kelechi et al. 2011[61]	Wounds closed at 12 weeks		NR	NR
	Wounds healed after 12 weeks (20 weeks)	Complete wound epithelialization and closure	Group A: 9 (45%) Group B: 19 (86.4%) Group C: 13 (65%)	Group D: 9 (45%)
	Mean time to wound closure (weeks[SD])		NR	NR
	Wounds infected during 20 weeks		1 patient developed methicillin-resistant *Staphylococcus aureus* after a prior surgical procedure. 3 patients previously diagnosed and treated for *Clostridium difficile* developed a recurrence.	1 patient developed methicillin-resistant *Staphylococcus aureus* after a prior surgical procedure. 3 patients previously diagnosed and treated for *Clostridium difficile* developed a recurrence.
	Other wound healing outcomes		NR	NR
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain		0	0
	Exudate		NR	NR
	Odor		NR	NR
Uccioli et al. 2011[68]	Wounds closed at 12 weeks	Complete re-epithelialization without exudates and eschar	19 (24%)	17 (21%)
	Wounds healed after 12 weeks (20 weeks)		50%	43%
	Mean time to wound closure (days)		50	58
	Wounds infected during 12 weeks Severe infection		13 (15.4%) 1	10 (11.4%) 0
	Other wound healing outcomes Mean time to 50% reduction in ulcer area (days)		40	50
	Weekly percentage reduction		29%	14%
	Mean number of grafts			

Table 52. Clinical results related to wound healing in studies of HYAFF and Talymed, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Uccioli et al. 2011[68] (continued)	Hyalograft -3D		1.3 ±0.47	
	Laserskin		1.5 ±0.59	
	Amputation		2	0
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain		NR	NR
	Exudate		NR	NR
	Odor		NR	NR
Caravaggi et al. 2003[58]	Wounds closed at 12 weeks (11 weeks)* Total		65.3%	49.6%; p=0.191, log-rank test
	Plantar		55% (12/22)	50% (10/20); p=1.00
	Dorsal		66.7% (14/21)	31.25% (5/16); p=0.049 (OR 4.44; 95% CI: 1.09 to 17.7, p=0.037)
	Wounds healed after 12 weeks		NR	NR
	Kaplan-Meier median time to wound closure (days) Total		57	77
	Plantar		57	58.5
	Dorsal (mean time)		63	Not apparent by final visit (77 days)
	Wounds infected during 12 weeks		Improvement	Improvement
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain relief		Improvement	Improvement

Table 52. Clinical results related to wound healing in studies of HYAFF and Talymed, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Caravaggi et al. 2003[58] (continued)	Exudate reduction Total		Absent in 86%	Absent in 69.4%
	Dorsal (visit 7)		Absent in 71.4%	Absent in 31.3%; p=0.036
	Dorsal (visit 12)		Absent in 90.5%	Absent in 50%; p=0.013
	Odor reduction		Improvement	Improvement

*7 patients required a 2nd graft of autologous fibroblasts on Hyalograft 3D, 2 patients required a 2nd graft of autologous keratinocytes on Laserskin

HYAFF: Benzyl esters of hyaluronic acid
NR: Not reported

Table 53. Clinical results related to wound healing in studies of Oasis

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Romanelli et al. 2010[57]	Wounds closed at 12 weeks (8 weeks)		80% (20/25)	65% (15/23); p<0.05
	Wounds healed after 12 weeks		NR	NR
	Mean time to wound closure (SD)	Digital planimetry	5.4 weeks	8.3 weeks
	Wounds infected during 12 weeks (8 weeks)		0	0
	Other wound healing outcomes Amount of granulation tissue (%) Time to dressing change, mean	Color defragmentation software	Baseline: 50%; 8 weeks: 65% (+30%) 5.2 days	Baseline: 50%; 8 weeks: 38% (-24%) p<0.05 2.1 days; p<0.05
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain relief		0	0
	Exudate reduction		NR	NR
	Odor reduction		NR	NR
	Other		"On highly exudating wounds, an absorbent secondary dressing was required to maintain adherence of biologic ECM to the wound bed."	

Table 53. Clinical results related to wound healing in studies of Oasis, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Landsman et al. 2008[54]	Wounds closed at 12 weeks	Full epithelialization without any evidence of drainage or bleeding	76.9% (10/13)	84.6% (11/13)
	Wounds healed after 12 weeks		NR	NR
	Average time to wound closure (SD)		35.67±41.47 days	40.90±32.32 days
	Wounds infected during 12 weeks (16 weeks)		NR	NR
	Other wound healing outcomes		NR	NR
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Comfort (mean VAS score)		NR	NR
	Pain		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR
	Other: Average number of dressings		6.46±1.39	2.54±0.78
Romanelli et al. 2007[60]	Wounds closed at 12 weeks		NR	NR
	Wounds healed after 12 weeks (16 weeks)	A fully re-epithelialized area	82.6% (21/27)	46.2% (11/27); p<0.001
	Mean time to wound closure (SD)		NR	NR
	Wounds infected during 12 weeks (16 weeks)		NR	NR
	Other wound healing outcomes Time to dressing change (mean days ±SD)		6.4 ±1.4	2.4 ±1.6; p<0.05
	Amputation		NR	NR
	Reoccurrence		NR	NR
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR

Table 53. Clinical results related to wound healing in studies of Oasis, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Romanelli et al. 2007[60] (continued)	Comfort (mean VAS score)	Comfort defined by any technical aspect related to the dressing (e.g., dressing adherence to wound bed) Measured by 10 point VAS (0 = excellent)	2.5	6.7; p<0.01
	Pain	Pain scored on a VAS; (0 = none, 10 = severe)	3.7	6.2 p<0.05
	Exudate reduction		NR	NR
	Odor reduction		NR	NR
Mostow et al. 2005[69]	Wounds closed at 12 weeks	Full epithelialization of the wound with the absence of draining	55% (34/62)	34% (20/58) p=0.1096
	Wounds healed after 12 weeks (≥6 months; n=54)		67% 20/30	46% 11/24 (3 of 4 newly healed received Oasis during crossover period)
	Mean time to wound closure (SD) Estimated through Cox analysis	Treatment period during the weekly visit at which the surface area of the wound was noted as zero and completely healed	63%*	40%* p=0.0226
	Wounds infected during 12 weeks		1	6
	Other wound healing outcomes Wound worsening		 1	 3
	Intolerance to secondary dressing		5	3
	Average dressing changes		1.8	3.4
	Amputation		NR	NR
	Reoccurrence (6 months)		NR	3
	Hospitalization		2	0
	Return to function or activities of daily living		NR	NR
	Pain relief		NR	NR
	Exudate reduction		NR	NR
	Odor reduction		NR	NR

Table 53. Clinical results related to wound healing in studies of Oasis, continued

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Niezgoda et al. 2005[70]	Wounds closed at 12 weeks All patients		49% (18/37)	28% (10/36); p=0.055)
	Plantar ulcers		52% (14/27)	14% (3/21) (p=0.014)
	Type 1 diabetes		33% (6/18)	25% (2/8) (p=1.000)
	Type 2 diabetes		63% (12/19)	29% (8/28) (p=0.034)
	Wounds healed after 12 weeks (n=37)			
	Patients seen at 6 months followup		19	18
	Patients healed at 12 weeks		8	6
	Patients remaining healed at 6 months		6	4
	Mean time to wound closure (SD)	Computed as the day during the weekly visit at which the surface area of the wound was noted as zero and completely healed	67 days	73 days (p=0.245)
	Wounds infected during 12 weeks		9	3
	Other wound healing outcomes		NR	NR
	Amputation		NR	NR
	Reoccurrence (6 months)		25% (2/8)	33% (2/6)
	Hospitalization		NR	NR
	Return to function or activities of daily living		NR	NR
	Pain/discomfort		2	1
	Exudate reduction		NR	NR
	Odor reduction		NR	NR

*Estimated probability of successful healing based on Cox proportional hazards regression analysis

NR: Not reported
SD: Standard deviation
VAS: Visual analogue scale

Table 54. Studies reporting wound recurrence after 12 weeks

Study	Time When Initial Wound Healing Was Measured	Study Followup to Measure Reoccurrence	Skin Substitute Reoccurrence	Control Reoccurrence	Wound Type
Edmonds 2009[53]	12 weeks	12 weeks after each wound healed	Apligraf: 7.0% (1 reccurrence / 15 previously healed wounds)	Nonadherent dressing: 10% (1 recurrence/10 previously healed wounds) p=1.000	DFU
Niezgoda et al. 2005[70]	12 weeks	6 months	Oasis Wound Matrix: 25% (2/8)	Regranex Gel (contains platelet-derived growth factor): 33% (2/6)	DFU
Veves et al. 2001[67]	12 weeks	6 months	Graftskin: 5.9% (3/51)	Saline-moistened gauze alone: 12.9% (4/31), NS	DFU
Naughton et al. 1997[62]	32 weeks	Reported during the 32 weeks of the study	Dermagraft Median time to reoccurrence: 12 weeks Author reported that "ulcers recurred in a comparable minority of both groups."	Saline-moistened gauze Median time to reoccurrence: 7 weeks Author reported that "ulcers recurred in a comparable minority of both groups."	DFU
Gentzkow et al. 1996[65]	12 weeks	14 months (mean) Range: 2–22 months	Dermagraft: 0/11	Saline-moistened gauze: 0/1 (2 months followup)	DFU
Mostow et al. 2005[69]	12 weeks	6 months	Oasis Wound Matrix with compression: 0	Compression alone: 3	Leg
Falanga et al 1998[63]	6 months	12 months	Apligraf with compression bandage: 12% (11/92)	Compression therapy with a Unna boot: 15.9% (10/63) p=0.48; 2-tailed Fisher test	Leg

DFU: Diabetic foot ulcer
NR: Not reported
NS: Not significant

Key Question 3

Table 55. Reports of adverse events in studies of Apligraf and Graftskin

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
DiDomenico et al. 2011[64]	Apligraf (n=16)	0	0	0	0	0	Number of patients experiencing infection and increase in wound size: Apligraf: 5 TheraSkin: 3
	TheraSkin (n=12)	0	0	0	0	0	
Edmonds M. 2009[53]	Apligraf (n=33)	0	1*	0	0	0	Serious adverse events during treatment phase: Apligraf: 4 Control: 5 Serious adverse events during followup phase: Apligraf: 4 Control: 3 Squamous cell carcinoma at target ulcer site occurred in one patient from the control group.
	Nonadherent dressing (n=39)	0	0	0	0	0	
Veves et al. 2001[67]	Graftskin (n=112)	10 (8.9%)	0	0	3 (2.7%) p=0.04*	0	
	Saline-moistened gauze (n=96)	8 (8.3%)	0	0	10 (10.4%)	0	
Falanga et al. 1998[63a]	Apligraf (n=161)	Study site: 13 (8.1%) Non-study site: 12 (7.5%)	6 (3.7%)**	Study site: 4 (2.5%) Non-study site: 10 (6.2%)	Study site: 11 (8.1%) Non-study site: 13 (5.1%)	8 (5.0%)	Infection (non-wound): 4 (2.5%) Pain (non-study site): 5 (3.1%) Positive wound culture (study site): 4 (2.5%) Pruritus (non-study site) 5 (3.1%) Rash (study site): 3 (1.8%) Rash (non-study site): 2 (1.3%) Rhinitis: 4 (2.5%) Skin ulcer (non-study site: 6 (3.7%) Skin ulcer (study site): 5 (3.1%) Urinary tract infection: 2 (1.3%) The following adverse events occurred in less than 2% of patients who received Apligraf: Pain (overall body), congestive heart failure, accidental injury (musculoskeletal), dyspnea, pharyngitis, accidental injury (overall body), asthenia, arrhythmia, abscess (non-study site), arthralgia, cough increased, erythema (study site), and kidney failure.

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Falanga et al. 1998[63 a] (continued)	Compression therapy (n=136)	18	5 (3.7%)**	Study site: 2 (1.5%) Non-study site: 10 (7.4%)	0	7 (5.1%)	Infection (non-wound): 1 (0.7%) Pain (non-study site):4 (2.9%) Positive wound culture (study site): 3 (2.2%) Pruritus (non-study site) 2 (1.5%) Rash (study site): 2 (1.5%) Rash (non-study site): 5 (3.7%) Rhinitis: 1 (0.7%) Skin ulcer (non-study site: 5 (3.7%) Skin ulcer (study site): 3 (2.2%) Urinary tract infection: 5 (3.7%) The following adverse events occurred in less than 2% of patients who received compression therapy: Pain (overall body), congestive heart failure, accidental injury (musculoskeletal), dyspnea, pharyngitis, accidental injury (overall body), asthenia, arrhythmia, abscess (non-study site), arthralgia, cough increased, erythema (study site), and kidney failure.

* Due to myocardial infarction and not attributed to study treatment
** Reason not specified

Table 56. Reports of adverse events in studies of Dermagraft

Study	Group	Cellulitis	Osteomyelitis	General Comments
Krishnamoorthy et al. 2003[55]	Group 1-3 (Dermagraft) Group 4 (control)			Group 1 (n=13): 18 adverse events; 1 serious Group 2 (n=13): 15 adverse events; 1 serious Group 3 (n=14): 15 adverse events; 4 serious Group 4 (n=13): 17 adverse events; 0 serious Nontreatment-related serious or unexpected events included syncope; skin excoriation; bleeding subsequent to biopsy; latex allergy; development of bullous pemphigoid and cerebrovascular accident.
Marston et al. 2003[56]	Dermagraft®	7.4% (12/163)	8.6% (14/163)	See infection and hospitalization rates noted in outcome table
	Saline-moistened gauze	9.3% (14/151)	8.6% (13/151)	Dermagraft AEs (i.e., infection, osteo and cellulitis) were significantly lower in the than control (19% vs. 32%; p=0.007)
Naughton et al. 1997[62]				None identified.
Gentzkow et al. 1996[65]				See infection noted in outcome table

Table 57. Reports of adverse events in studies of Graftjacket

Study	Group	Abscess Secondary to Study Wound	Peri-wound Erythema/Local Cellulitis	Seroma (Mild)	General Comments
Reyzelman et al. 2009[66]	Graftjacket (n=46)	0 (0%)	0	0	See infection, amputation and hospitalization rates in Table 51
	Moist wound therapy (n=39)	1 (2.5%)	0	0	
Brigido SA. 2006[59]	Graftjacket (n=14)	0	3 (21.4%)	1	
	Weekly debridement, Curasol wound hydrogel and gauze dressing (n=14)	0	5 (35.7%)	0	

SOC: Standard of care

Table 58. Reports of adverse events in studies of HYAFF and Talymed

Study	Group	General Comments
Kelechi et al. 2011[61]	Talymed with compression vs. Nonadherent absorptive primary dressing with compression	The authors reported that no pain, edema or significant treatment-related adverse events occurred.
Uccioli et al. 2011[68]	Hyalograft/Laserskin (n=84)	Adverse events: 18 (21%) Serious adverse events: 7 (6 severe; 1 moderate) Amputation: 2 Hematemesis: 1 Myocardial failure: 1 (moderate) Joint effusion: 1 Infection: 1 Osteomyelitis: 1 At an 18 month followup of 51 patients from the treatment group, 1 adverse event was reported.
	Nonadherent paraffin gauze (n=87)	Adverse events: 14 (16%) Serious adverse events: 2 (moderate) Thrombophlebitis: 1 Pleural effusion: 1 At an 18 month followup of 52 patients in the control group, 8 adverse events were reported. One patient died however this was reported as unrelated to treatment.
Caravaggi et al. 2003[58]	HYAFF 11 (n=43) Nonadherent paraffin gauze (n=36)	Serious adverse events (n=82 randomized) HYAFF 11: 7 SOC: 10 Most frequent adverse events were infection, inflammation and worsening of ischemia. Overall, percent of patients experiencing “severe,” “moderate” and “low” events was 36.4%, 36.4%, and 36.4%, respectively.

HYAFF: Benzyl esters of hyaluronic acid
SOC: Standard of care

Table 59. Reports of adverse events in studies of Oasis

Study	Group	Allergic Reaction or Intolerance to Secondary Dressing	Death	Depression/ Mood Disorder	Gastro-intestinal Disorder	Infection in Non-study Ulcer	Limb Injury	New Ulcer Due to Compression	Non-target Wound Infection	Respiratory Tract Infection	Septic Arthritis	Seroma	Skin Injury
Romanelli et al. 2010[57]	No adverse events observed with either treatment												
Landsman et al. 2008[54]	Not reported												
Romanelli et al. 2007[60]	No adverse events observed with either treatment												
Mostow et al. 2005[69] (based on 23 patients)	Oasis (n=8)	3	1*					0	1			0	1
	Compression (n=15)	3	0					1	1			1	1
Niezgoda et al. 2005[70]	Oasis (n=17)			1	1	3	0			0	0		0
	Regranex (n=10)			0	0	1	2			1	1		1

*Due to cardiovascular disease