Appendix A. Search Strategies

Resources Searched

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

Name	Date Limits	Platform/Provider
Cochrane Central Register of Controlled Trials (CENTRAL)	2012 through September 17, 2018	Wiley
Cochrane Database of Systematic Reviews (Cochrane Reviews)	2012 through September 17, 2018	Wiley
Cumulative Index of Nursing and Allied Health Literature (CINAHL)	2012 through September 13, 2018	EBSCOhost
Database of Abstracts of Reviews of Effects (DARE) (part of the Cochrane Library)	2012 through September 17, 2018	Wiley
EMBASE (Excerpta Medica)	2012 through September 26, 2018	Embase.com
Health Technology Assessment Database (HTA) (part of the Cochrane Library)	2012 through September 17, 2018	Wiley
MEDLINE	Inception [1966] through November 1, 2016 (KQ1) Inception through June 22, 2016 (KQ2)	Embase.com
PubMed (In Process citations)	Inception [1966] through November 3, 2016 (KQ1) Inception through September 13, 2018	NLM
U.K. National Health Service Economic Evaluation Database (NHS EED) (part of the Cochrane Library)	2012 through September 17, 2018	Wiley

Other Gray Literature Resources

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

Hand Searches of Journal and Gray Literature

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

Topic-specific Search Terms

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

Topic-specific Search Terms

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

Concept	Controlled Vocabulary	Keywords
		Dermis Dressing* Epidermal Epidermis Scaffold* Skin Tissue* Wound*
Tradenames		Affinity Amniotic Alloderm Allomax Allopatch Alloskin Allowrap Amnioband Amnioexcel Amniofix Amniomatrix Aongen matrix Architect matrix Apligraf Artacent Arthrex amnion Atlas wound matrix Arthroflex Avagen wound dressing Biobrane Bionnekt Biodfence Biodexcel bioDFactor biodmatrix Biomembrane Bioskin Biovance amniotic Celaderm Clarix Collagen sponge Collaguard CollaSorb Collawound Collexa Conexa reconstructive matrix CorMatrix Cytal wound matrix Cygnus Cymetra Dermacell Dermagraft Dermapure Dermaspan Dermavest Dresskin Endoform Epicel

Concept	Controlled Vocabulary	Keywords
		Epicord Epidex Ez-derm Flex HD Floweramnioflo Floweramniopathc Flowerderm Flowerflo Fortaderm Gammagraft Gelapin Grafix GrafixPL Graftjacket Graftskin Helicoll Hyalograft Hyalomatrix Hmatrix Hyalomatrix tissue reconstruction matrix Integra Keramatrix Kerecis Kollagen Laserskin Lyofoam Lyomousse Matriderm Matristem Matrix hd Mediskin Memoderm Miroderm neoPatch NEOX wound allografts Nushield placental Oasis Omnigraft Orcel PalinGen amniotic Permacol Permaderm Plurivest Primatrix Promatrix Promogran Puraply Puros dermis Renoskin Repliform Repriza Revita Revitalon Stratagraft Strattice

Concept	Controlled Vocabulary	Keywords
		Suprathel Syspur-derm Syspurderm Talymed Tensix Theraskin Tielle non-adhesive Tissuemend Transcyte Tranzgraft Truskin Vitro-skin Woundex UBM hydrated wound dressing UBM lyophilized wound dressing Xcm biologic tissue matrix

Search Strategies

EMBASE/MEDLINE (searched via Embase.com)

Set Number	Concept	Search Statement
1	Skin substitutes	'acellular dermal matrix'/exp OR 'artificial skin'/exp OR 'biological dressing'/exp OR 'engineered cartilage graft'/exp OR 'engineered skin autograft'/exp OR 'tissue engineering'/exp OR 'tissue scaffold'/exp OR 'engineered skin graft'/exp
2		((acellular OR artificial* OR bioengineer* OR biosynthetic* OR engineer* OR equivalen* OR regenerat* OR replac* OR synthetic* OR substitut* OR templat*) NEAR/2 (epidermal OR epidermis OR dermis OR dermal OR skin OR tissue*)):ab,ti OR ((matrices OR matrix) NEAR/2 (acellular OR extracellular OR decellular* OR dermal OR skin OR tissue* OR wound*)):ab,ti OR (scaffold* NEAR/2 (dermal OR engineer* OR repair* OR tissue* OR skin)):ab,ti
3		(acellular NEAR/2 allograft*):ab,ti OR ((amniot* OR cadaver*) NEAR/2 (skin* OR tissue*)):ab,ti OR (biologic* NEXT/1 dressing*):ab,ti OR (collagen NEAR/2 (bovine OR porcine)):ab,ti OR (regenerat* NEAR/2 (template* OR matrix)):ab,ti OR 'bilayer* living cell*' OR hadm

Set Number	Concept	Search Statement
4		(affinity NEAR/2 amniotic) OR alloderm OR allomax OR allopatch OR alloskin OR allowrap OR (AMNIO next/1 wound) OR amnioband OR amnioexcel OR amniofix OR amniomatrix OR (aongen NEAR/2 matrix) OR (architect NEAR/2 matrix) OR apligraf OR artacent OR (arthrex NEXT/1 amnion) OR 'atlas wound matrix' OR arthroflex OR 'avagen wound dressing' OR biobrane OR 'bio-connekt' OR 'biodfence' OR 'biodexcel' OR 'bioDFactor' OR 'biodmatrix' OR 'biomembrane' OR 'bioskin' OR 'biovance amniotic' OR celaderm OR clarix OR 'collagen sponge' OR 'collaguard' OR 'collaSorb' OR 'collawound' OR 'collexa' OR 'conexa reconstructive matrix' OR 'CorMatrix' OR 'Cytal wound matrix' OR 'cygnus' OR cymetra OR dermacell OR dermagraft OR 'dermapure' OR 'dermaspan' OR 'dermavest' OR dresskin OR 'Endoform' OR epicel OR epicord OR epidex OR 'ez-derm' OR 'flex hd' OR floweramnioflo OR floweramniopatch OR flowerderm OR flowerflo OR fortaderm OR gammagraft OR gelapin OR grafix OR grafixPL OR graftjacket OR graftskin OR helicoll OR hyalograft OR hyalomatrix OR hmatrix OR 'hyalomatrix tissue reconstruction matrix' OR integra OR keramatrix OR kerecis OR kollagen OR laserskin OR lyofoam OR lyomousse OR matriderm OR matristem OR 'matrix hd' OR mediskin OR memoderm OR miroderm OR neoPatch OR 'NEOX wound allografts' OR 'nushield placental' OR oasis OR omnigraft OR orcel OR 'PalinGen amniotic' OR permacol OR permaderm OR plurivest OR primatrix OR promatrix OR promogran OR puraply OR 'puros dermis' OR renoskin OR repliform OR repriza OR revita OR revitalon OR stratagraft OR strattice OR suprathel OR 'syspur-derm' OR syspurderm OR talymed OR tensix OR theraskin OR 'tielle non-adhesive' OR tissuemend OR transcyte OR tranzgraft OR truskin OR 'vitro- skin' OR woundex OR 'UBM hydrated wound dressing' OR 'UBM lyophilized wound dressing' OR 'xcm biologic tissue matrix'
5	Chronic wounds	bedsore* OR 'chronic wound'/exp OR decubitus/exp OR 'diabetic foot'/exp OR ((injur* OR wound* OR ulcer*) NEAR/2 (chronic* OR intractab* OR 'non-healing' OR nonhealing OR persisten*)):ab,ti OR ((bed OR foot OR feet OR diabet* OR leg OR legs OR pressure OR venous) NEAR/2 (sore* OR ulcer*)):ab,ti OR (diabet* NEAR/2 (feet or foot)):ab,ti
6	Combine sets	(#1 OR #2 OR #3 OR #4) AND #5
7	Apply language and date restrictions. Remove unwanted study designs	#6 AND ([english]/lim AND [humans]/lim AND [2012-2018]/py) NOT (abstract:nc OR annual:nc OR book/de OR 'case report'/de OR conference:nc OR 'conference abstract':it OR 'conference paper'/de OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR editorial/de OR editorial:it OR erratum/de OR letter:it OR note/de OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/de OR symposium:nc)
8	RCTs	#7 AND ('randomized controlled trial'/de OR random*:ti)
9	Meta-Analyses	#7 AND ('meta analysis'/de OR ((meta* NEXT/1 anal*):ti))
10	Systematic Reviews	#7 AND ('systematic review'/de OR systematic*:ti)
11	Combine sets	#9 OR #10 OR #11
12	Wounds except diabetic foot	#7 AND (Bedsore* OR 'decubitus'/exp OR ((bed OR foot OR feet OR leg OR legs OR pressure OR venous OR arterial) NEAR/2 (sore* OR ulcer*)):ti,ab)
13	Controlled trials	'controlled clinical trial'/exp OR ((controlled OR control*) NEAR/2 group) OR controls:ab
14	Combine sets	#12 AND #13
15	Combine sets	#11 OR #14

EMBASE.com Syntax:

* = truncation character (wildcard)

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

NEXT/*n*	=	search terms within a specified number (*n*) of words from each other in the order specified
/	=	search as a subject heading
exp	=	"explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
mj	=	denotes a term that has been searched as a major subject heading
:de	=	search in the descriptors field (controlled terms and keywords)
:lnk	=	floating subheading
/lim	=	limiter
:it,pt.	=	source item or publication type
:ti.	=	limit to title
:ti,ab.	=	limit to title and abstract fields

PubMed (PreMEDLINE)

PubMed In-Process Citations

Set Number	Concept	Search Statement
1	Skin substitutes	(acellular[tiab] OR artificial*[tiab] OR bioengineer*[tiab] OR biosynthetic*[tiab] OR engineer*[tiab] OR equivalen*[tiab] OR regenerat*[tiab] OR replac*[tiab] OR synthetic*[tiab] OR substitut*[tiab] OR templat*[tiab]) AND (epidermal[tiab] OR epidermis[tiab] OR dermis[tiab] OR dermal[tiab] OR skin[tiab] OR tissue*[tiab])
2		(matrices[tiab] OR matrix[tiab]) AND (acellular[tiab] OR extracellular[tiab] OR decellular*[tiab] OR dermal[tiab] OR skin[tiab] OR tissue*[tiab] OR wound*[tiab])
3		scaffold*[tiab] AND (dermal[tiab] OR engineer*[tiab] OR repair*[tiab] OR tissue*[tiab] OR skin[tiab])
4		(acellular[tiab] AND allograft*[tiab]) OR ((amniot*[tiab] OR cadaver*[tiab]) AND (skin*[tiab] OR tissue*[tiab])) OR biologic*dressing*[tiab] OR (collagen[tiab] AND (bovine[tiab] OR porcine [tiab])) OR (regenerat*[tiab] AND (template*[tiab] OR matrix[tiab])) OR bilayer* living cell* OR hadm
5		affinity amniotic OR alloderm OR allomax OR allopatch OR alloskin OR allowrap OR AMNIOwound OR amnioband OR amnioexcel OR amniofix OR amniomatrix OR aongen matrix OR architect matrix OR apligraf OR artacent OR arthrex amnion OR "atlas wound matrix" OR arthroflex OR "avagen wound dressing" OR biobrane OR bio-connekt OR biodfence OR biodexcel OR bioDFactor OR biodmatrix OR biomembrane OR bioskin OR "biovance amniotic"
6		celaderm OR clarix OR "collagen sponge" OR collaguard OR collaSorb OR collawound OR collexa OR "conexa reconstructive matrix" OR CorMatrix OR "Cytal wound matrix" OR cygnus OR cymetra OR dermacell OR dermagraft OR dermapure OR dermaspan OR dermavest OR dresskin OR Endoform OR epicel OR epicord OR epidex OR ez-derm OR "flex hd" OR floweramnioflo OR floweramniopatch OR flowerderm OR flowerflo OR fortaderm OR gammagraft OR gelapin OR grafix OR grafixPL OR graftjacket

Set Number	Concept	Search Statement
7		graftskin OR helicoll OR hyalograft OR hyalomatrix OR hmatrix OR "hyalomatrix tissue reconstruction matrix" OR integra OR keramatrix OR kerecis OR kollagen OR laserskin OR lyofoam OR lyomousse OR matriderm OR matristem OR "matrix hd" OR mediskin OR memoderm OR miroderm OR neoPatch OR "NEOX wound allografts" OR "nushield placental" OR oasis OR omnigraft OR orcel OR "PalinGen amniotic" OR permacol OR permaderm OR plurivest OR primatrix OR promatrix OR promogran OR puraply
8		"puros dermis" OR renoskin OR repliform OR repriza OR revita OR revitalon OR stratagraft OR strattice OR suprathel OR "syspur-derm" OR syspurderm OR talymed OR tensix OR theraskin OR "tielle non-adhesive" OR tissuemend OR transcyte OR tranzgraft OR truskin OR "vitro-skin" OR woundex OR "UBM hydrated wound dressing" OR "UBM lyophilized wound dressing" OR "xcm biologic tissue matrix"
9	Combine skin substitute sets	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
10	Chronic wounds	bedsore* OR “chronic wound” OR decubitus ulcer* OR diabetic foot
11		(injur*[tiab] OR wound*[tiab] OR ulcer*[tiab]) AND (chronic* [tiab] OR intractab*[tiab] OR non-healing[tiab] OR nonhealing[tiab] OR persisten*[tiab])
12		(bed[tiab] OR foot[tiab] OR feet[tiab] OR diabet*[tiab] OR leg [tiab] OR legs[tiab] OR pressure[tiab] OR venous[tiab]) AND (sore*[tiab] OR ulcer*[tiab])
13		diabet*[tiab] AND (feet[tiab] OR foot[tiab])
14	Combine chronic wound sets	#10 OR #11 OR #12 OR #13
15	Combine sets	#9 AND #14
16	Limit to in process publications	#15 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb])
17	Remove animal studies	#16 NOT (mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rabbit*[ti] OR sheep[ti])
18	Meta-analyses & Systematic Reviews	#16 AND (meta-analysis OR meta-analysis[pt] OR “metaanalytic"[tiab] OR metaanaly*[tiab] OR "research synthesis"[tiab] OR systematic review[tiab] OR systematic[ti])
19	RCTs	#16 AND (“randomized controlled” OR random*[ti])
20	Non-RCT controlled trials	#16 AND ((control*[tiab] AND trial*[tiab]) OR “control group” OR controls[ab] OR “comparative effectiveness” OR “prospective controlled”
21	Combine sets	#18 OR #19 OR #20
22	Limit to English	#21 AND eng[la]
23	Remove unwanted publication types	#22 NOT (year-old[tiab] OR "case report"[ti] OR comment[ti])
24	Limit by date	#23 AND 2012:2018[edat]

PubMed Syntax

*	=	truncation character (wildcard)
[mh]/[MesH]	=	controlled vocabulary term
[sb]	=	subset
[ti]	=	limit to title field
[tiab]	=	limit to title and abstract fields
[tw]	=	text word

CINAHL

Set Number	Concept	Search Statement
1	Skin substitutes	(MH "Biological Dressings") OR (MH "Skin, Artificial") OR (MH "Tissue Engineering") OR (MH "Tissue Scaffolds")
2		(acellular OR artificial* OR bioengineer* OR biosynthetic* OR engineer* OR equivalen* OR regenerat* OR replac* OR synthetic* OR substitut* OR templat*) N2 (epidermal OR epidermis OR dermis OR dermal OR skin OR tissue*)
3		(matrices OR matrix) N2 (acellular OR extracellular OR decellular* OR dermal OR skin OR tissue* OR wound*)
4		scaffold* N2 (dermal OR engineer* OR repair* OR tissue* OR skin)
5		(acellular N2 allograft*) OR ((amniot* OR cadaver*) N2 (skin* OR tissue*)
6		biologic* dressing* OR (collagen N2 (bovine OR porcine)) OR (regenerat* N2 (template* OR matrix)) OR bilayer* living cell* OR hadm
7		(affinity N2 amniotic) OR alloderm OR allomax OR allopatch OR alloskin OR allowrap OR AMNIOwound OR amnioband OR amnioexcel OR amniofix OR amniomatrix OR (aongen N2 matrix) OR (architect N2 matrix) OR apligraf OR artacent OR arthrex amnion OR atlas wound matrix OR arthroflex OR avagen wound dressing OR biobrane OR bio-connekt OR biodfence
8		biodexcel OR bioDFactor OR biodmatrix OR biomembrane OR bioskin OR biovance amniotic OR celaderm OR clarix OR collagen sponge OR collaguard OR collaSorb OR collawound OR collexa OR "conexa reconstructive matrix" OR CorMatrix OR "Cytal wound matrix" OR cygnus OR cymetra OR dermacell OR dermagraft OR dermapure OR dermaspan OR dermavest OR dresskin OR Endoform
9		epicel OR epicord OR epidex OR ez-derm OR "flex hd" OR floweramnioflo OR floweramniopatch OR flowerderm OR flowerflo OR fortaderm OR gammagraft OR gelapin OR grafix OR grafixPL OR graftjacket OR graftskin OR helicoll OR hyalograft OR hyalomatrix OR hmatrix OR "hyalomatrix tissue reconstruction matrix" OR integra OR keramatrix OR kerecis OR kollagen OR laserskin OR lyofoam OR lyomousse
10		matriderm OR matristem OR "matrix hd" OR mediskin OR memoderm OR miroderm OR neoPatch OR "NEOX wound allografts" OR "nushield placental" OR oasis OR omnigraft OR orcel OR "PalinGen amniotic" OR permacol OR permaderm OR plurivest OR primatrix OR promatrix OR promogran OR puraply
11		puros dermis" OR renoskin OR repliform OR repriza OR revita OR revitalon OR stratagraft OR strattice OR suprathel OR "syspur-derm" OR syspurderm OR talymed OR tensix OR theraskin OR "tielle non-adhesive" OR tissuemend OR transcyte OR tranzgraft OR truskin OR vitro-skin OR woundex OR "UBM hydrated wound dressing" OR "UBM lyophilized wound dressing" OR "xcm biologic tissue matrix"
12	Combine skin substitutes sets	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
13	Chronic wounds	(MH "Pressure Ulcer+") OR (MH "Leg Ulcer+") OR (MH "Foot Ulcer+") OR (MH "Diabetic Foot") OR (MH "Venous Ulcer") OR (MH "Wounds, Chronic")
14		bedsore* OR decubitus ulcer*
15		(injur* OR wound* OR ulcer*) N2 (chronic* OR intractab* OR 'non-healing' OR nonhealing OR persisten*)
16		(bed OR foot OR feet OR diabet* OR leg OR legs OR pressure OR venous) N2 (sore* OR ulcer*)

Set Number	Concept	Search Statement
17		(diabet* N2 (feet or foot)
18	Combine wound sets	S13 OR S14 OR S15 OR S16 OR S17
19	Combine sets	S12 AND S18
20	Meta-analyses	(MH "Meta Analysis")
21		TI meta* anal*
22	Systematic Reviews	(MH "Systematic Review")
23		TI systematic*
24	RCTs	(MH "Randomized Controlled Trials")
25		TI random*
26	Combine study types	S20 OR S21 OR S22 OR S23 OR S24 OR S25
27	Combine sets and apply limits	(S19 AND S26) AND Limiters – Exclude MEDLINE records;Published Date: 20120101-20181231; English Language

CINAHL Syntax

+ = explode

* = truncation character (wildcard)

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

TI = limit to title field

AB = limit to title and abstract fields

MH = MeSH heading

MJ = MeSH heading designated as major topic

PT = publication type

FDA Classification Database

Highly relevant codes

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

Possibly relevant codes

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

Other related codes

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

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

Duplicate Study or Duplicate Reporting of Patients

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

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

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

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

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

Included in Skin Substitutes for Treating Chronic Wounds

Kelechi TJ, Mueller M, Hankin CS, Bronstone A, Samies J, Bonham PA. A randomized, investigator-blinded, controlled pilot study to evaluate the safety and efficacy of a poly-N-acetyl glucosamine-derived membrane material in patients with venous leg ulcers. Journal Of The American Academy Of Dermatology. June 2012. 66:e209-e215

No Outcomes of Interest

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

Not a Comparator of Interest (Inadequate Standard of Care)

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

Not a Comparator of Interest (Dissimilar Standard of Care)

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

Not a Study of Interest

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

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

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

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

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

Not a Study Design of Interest

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

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

Not an Intervention of Interest

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

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

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

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

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

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

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

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

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

Primary Studies Published Before 2012

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

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

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

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

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

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

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

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

Appendix C. Clinical Evidence

Table C-1. Characteristics of systematic reviews

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

Citation	Objective	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Interventions	Relevant Findings	Authors' Conclusions
Guo et al. 2017[42]	To compare the efficacy and safety of acellular dermal matrix (ADM) to SOC in DFU	PubMed, MEDLINE, EMBASE, and Cochrane library were searched up to August 2016 for comparative studies involving ADM in the management of DFU. 266 articles were eligible for inclusion.	RCTs (>10 patients per arm) comparing ADM to SOC in DFU reporting an outcome of interest (healing rate, time to heal, wound area reduction and adverse events).	Studies: 6 RCTs (n=632) published from 2004 to 2015. ADM is human-derived in five studies and animal-derived in one study. Enrollment (range): 28 to 307 Followup: 4 weeks (1 study), 12 weeks (2 studies), 16 weeks (3 studies) Heterogeneity among studies: estimated using I^2 statistic. Substantial heterogeneity was represented by an I^2 value > 50%.	1 study each examined SOC with AlloPatch Pliable, and Integra Dermal Regeneration Template. 3 studies examined GraftJacket vs. SOC; 1 study examined Graftjacket vs. DermACELL vs. SOC SOC was described as including several "routine methods" including sharp debridement, glucose control, infection control, offloading, and daily dressing change. Dressings were described as alginate, advanced moist therapy, 0.9% sodium chloride/ge/foam/gauze, alginate/hydrocolloids/hydrogel/foam, and wound gel with gauze dressings (2 studies).	Complete wound healing at 12 weeks (6 studies, n=632): RR 2.31, 95% CI: 1.42 to 3.76; I^2=74% Complete wound healing at 16 weeks (3 studies, n=467): RR 1.57, 95% CI: 1.28 to 1.93; I^2=37% Time to heal (weeks)(4 studies, n=193): MD -2.98, 95% CI: -5.15 to -0.82; I^2=77% Adverse events (6 studies, n=632): RR 0.98, 95% CI: 0.58 to 1.67 Heterogeneity for the outcomes complete wound healing at 12 weeks (6 studies) and time to heal (4 studies) was signfiicant. For complete wound healing, the authors noted that moderate heterogeneity remained after removing one study measuring the healing rate in the first four weeks. For time to heal, one study was noted as having overly influenced the heterogeneity.	"Compared with standard of care, acellular dermal matrix may accelerate the healing velocity of uninfected, non-ischemic, full-thickness diabetic foot ulcer. Acellular dermal matrix showed superiority compared with standard of care alone, while generating no more complications."

Citation	Objective	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Interventions	Relevant Findings	Authors' Conclusions
Haugh et al. 2017[43]	To describe and meta-analyze studies comparing commercially available amniotic tissue products with standard wound care in RCTs	PubMed, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched. Publication dates were not reported.	RCTs comparing amniotic tissue products with SOC for use in nonhealing DFUs published in peer-reviewed English language journals were included. Studies solely comparing amniotic tissue products with bioengineered skin substitutes were excluded. 596 articles were identified as relevant.	Studies: 5 RCTs (n=311) published from 2013 to 2016. 52 patients treated with a bioengineered skin substitute (Apligraf) were excluded resulting in 259 being analyzed. 4 studies analyzed dehydrated amniotic products (EpiFix and AmnioExcel). 1 study analyzed a cryopreserved amniotic product (Grafix). Enrollment (range): 25 to 100 Followup: 6 weeks (2 studies), 12 weeks (3 studies) Heterogeneity among studies: Heterogeneity was assessed using Q and I^2 statistics. I^2 values of 25%, 50%, and 75% were considered indicative of a low, moderate, and high amount of heterogeneity, respectively.	Three studies compared EpiFix with SOC. One study each compared SOC to AmnioExcel or Grafix. Standard of care was described in 3 studies. All 3 studies included debridement. 1 study also reported using appropriate moist wound therapy and compression dressings. 1 study reported hemostasis, moist wound dressings, offloading, and infection surveillance. 1 study also reported offloading and nonadherent dressings.	Complete wound healing (5 RCTs, n=311): RR 2.75 (2.06 to 3.66; I^2 = 50.5%	"The current meta-analysis indicates that the treatment of diabetic foot ulcers with amniotic membrane improves healing rates in diabetic foot ulcers. Further studies are needed to determine whether these products also decrease the incidence of subsequent complications, such as amputation or death, in diabetic patients."

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

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

Citation	Title	Risk of Bias Tool	Risk-of-bias Assessment
Paggiaro et al. 2018[41]	*Biological effects of amniotic membrane on diabetic foot wounds: a systematic review*	Cochrane Handbook for systematic reviews of interventions Version 5.1.0	Authors noted selection bias (due to unclear/lack of allocation concealment in 50% of studies), detection bias (unclear/lack of blinding assessors in 50% of studies), and attrition bias (incomplete outcome data in 50% of studies) as study limitations.
Guo et al. 2017[42]	*Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: A systematic review and meta-analysis*	Cochrane Handbook for systematic reviews of interventions Version 5.1.0	Authors noted selection bias (due to unclear allocation concealment), performance bias (unclear/lack of blinding patients and personnel), detection bias (lack of blinding assessors in 50% of studies), and other bias (not described) as study limitations.
Haugh et al. 2017[43]	*Amnion Membrane in Diabetic Foot Wounds: A Meta-analysis*	Based on guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology Collaboration	Findings not reported.

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

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Bianchi et al. 2018[35]	1 cm^2 to 25 cm^2	≥30 days	ABI >0.75. No VLU penetrating into muscle, tendon or bone; No signs of ulcer infection or cancer. No VLU located on the dorsum of the foot or more than 50% of the ulcer below the malleolus. Wounds did not reduce in size by at least 25% with moist dressings and multilayer compression during the 2 week run-in.	No NPWT or HBOT in the last 7 days or treatment with other advanced wound care products within the past 30 days.	Hypertension, diabetes, smokers, alcohol use, obese

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Zelen et al. 2018[44]	< 25 cm^2	≥4 weeks	Noninfected wound, diabetic in origin, larger than 1 cm^2, and located on the foot (beginning below the malleoli of the ankle) Wound with documented failure of prior treatment to heal the wound No additional wounds present within 3 cm of the index wound HbA1c <12% (before randomization) No wound probing to bone (UT Grade IIIA-D) No active infection at index wound site Adequate circulation to the affected extremity, as demonstrated by 1 of the following in the past 60 days: dorsum TCOM ≥30 mm Hg, ABI ≥0.7 and ≤1.2, triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg	Type 1 or type 2 DM (based on ADA diagnostic criteria) Serum creatinine <3.0 mg/dL No wound treated with a biomedical or topical growth factor in the previous 30 days No HbA1c >12% in previous 90 days No patients with known or suspected local skin malignancy to the index wound No patients with ongoing radiation therapy or chemotherapy No patients with uncontrolled autoimmune connective tissues diseases No nonrevascularizable surgical sites No pathology that would limit the blood supply and compromise healing No pregnancy or breastfeeding No patients taking immune system modulators that could affect graft incorporation No Cox-2 inhibitor No wounds heal >20% during the screening period	Diabetes, obese, smokers, drinks alcohol
Alvarez et al. 2017[40]	NR	>2 months	DFU located on the plantar surface of the foot with a grade I-A DFU (University of Texas Classification System) Adequate arterial circulation to the foot (e.g., ABI >0.75, toe-brachial index >0.65, toe systolic pressure >50 mmHg. No clinical signs of infection No evidence of osteomyelitis No nondiabetic etiology	Type 1 or type 2 DM No previous cancer (other than cutaneous epithelioma) or in remission Not pregnant or lactating Not receiving oral or parenteral corticosteroids No other advance wound therapy (e.g., autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, ECM) Not receiving topical collagenase Aged 18 to 85 years	Type 1 or type 2 DM, Charcot foot, partial amputation
Alvarez et al. 2017[49]	NR	NR	NR	NR	Obese

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
DiDomenico et al. 2016[45]	>1 cm^2	4 weeks	Anatomically on the foot as defined by beginning below the malleoli of the ankle Additional wounds may not be within 3 cm of the study wound Adequate circulation to the affected extremity, as demonstrated by 1 of the following in the past 60 days: dorsum transcutaneous oxygen test ≥30 mm Hg; ABI with results of ≥0.7 and ≤1.2; or Doppler arterial waveforms, which are triphasic or biphasic at the ankle of affected leg No wound probing to bone (UT grade IIIA–D) No index wound >25 cm^2 No active infection at index wound site No patients with wounds healing >20% during the screening period	Type 1 or type 2 DM (ADA diagnostic criteria) Serum creatinine <3.0 mg/dL HbA1c <12% at randomization or no HbA1c >12% in previous 90 days No serum creatinine level ≥3.0 mg/dL No patients currently receiving radiation therapy or chemotherapy No patients with known or suspected local skin malignancy to the index wound No patients with uncontrolled autoimmune connective tissues diseases No nonrevascularizable surgical sites No pathology that would limit the blood supply and compromise healing No patients who have received a biomedical or topical growth factor for their wound within the previous 30 days No patients who are pregnant or breast feeding No patients who are taking medications considered immune system modulators that could affect graft incorporation No patients taking a Cox-2 inhibitor.	Obese, smoker, alcohol use

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Snyder et al. 2016[46]	1 cm^2 to 25 cm^2	≥1 month	At least 1 wound that is Wagner grade 1 or superficial 2 No signs of infection or osteomyelitis Closed <30% in area during screening period Located on the foot, distal to malleolus Adequate circulation to the affected extremity (ABI 0.7 to 1.2, or triphasic or biphasic Doppler arterial waveform at the ankle of the affected leg, or dorsum transcutaneous oxygen test ≥30 mm Hg No active Charcot deformity of the study foot No known or suspected malignancy of the current ulcer No exposed bone, tendon, or joint capsule in the study ulcer.	Diagnosis of type 1 or 2 DM, HbA1c <12%, serum creatinine of <3.0 mg/dL or CrCl >30 mL/min, No receiving radiation or chemotherapy, No active malignant disease, Not receiving hemodialysis or peritoneal dialysis, No sickle cell anemia or Raynaud's syndrome, No diagnosis of autoimmune connective tissue disease, Not receiving a biologic agent, growth factor, xenograft, or skin equivalent to the ulcer 30 days before consent, Not taking medications considered to be immune system modulators.	Type 1 or 2 DM, obesity

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Driver et al. 2015[47]	≥1 cm^2 and ≤12 cm^2	≥30 days	Adequate vascular perfusion of the affected limb. Ulcer was diagnosed as a full-thickness DFU located distal to the malleolus. Minimum 2 cm margin between the qualifying study ulcer and any other ulcers on the specified foot (postdebridement) Wagner grade 1 or 2 Depth ≤5 mm with no exposed capsule, tendon, or bone and no tunneling, undermining, or sinus tracts. No suspected or confirmed signs/symptoms of gangrene or wound infection on any part of the affected limb. No osteomyelitis with necrotic soft bone No study ulcer size following debridement decreased by more than 30% during the run-in period.	Type 1 or 2 diabetes, HbA1c ≤12%, Not pregnant, Able to maintain the required offloading and dressing changes, No sensitivity of bovine collagen and/or chondroitin, No excessive lymphedema that could interfere with wound healing, No unstable Charcot foot or Charcot with boney prominence, No ulcers secondary to a disease other than diabetes, No Chopart amputation, No history of bone cancer or metastatic disease of the affected limb, No chemotherapy within the 12 months before randomization, No treatment with wound dressings that include growth factors (or engineered tissues or skin substitutes) within 30 days of randomization or scheduled to receive such treatment during the study, No treatment with HBOT within 5 days of screening or schedule to receive this treatment during the study, No non-study ulcer requiring treatment that could not be treated during the study with moist wound therapy, No history of intercurrent illnesses or conditions (other than diabetes) that would compromise the safety of the subject or the normal wound healing process.	Type 1 or 2 DM

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Lavery et al. 2014[39]	1 and 15 cm^2	4 to 52 weeks	Wound located below the malleoli on plantar or dorsal surface of the foot and ulcer No evidence of active infection including osteomyelitis or cellulitis Adequate circulation to the affected foot (ABI 0.70 to 1.30, or toe brachial index ≤0.5 or Doppler study with inadequate arterial pulsation, No exposed muscle, tendon, bone, or joint capsule No reduction of wound area by ≥30% during the screening period	Type I or type II diabetes, No hemoglobin A1c above 12% Age between 18 and 80 years	Type 1 and 2 DM, obesity
Serena et al. 2014[37]	2 cm^2 to 20 cm^2	≥1 month	ABI >0.75 VLU extending through the full thickness of the skin but not down to muscle, tendon, or bone Treated with compression therapy for at least 14 days Ulcer has a clean, granulating base with minimal adherent slough No ulcer caused by a medical condition other than venous insufficiency No clinical signs and symptoms of infection No history of radiation at ulcer site Not undergone 12 months of continuous high-strength compression therapy over ulcer duration Not previously treated with tissue- engineered materials (e.g., Apligraf or Dermagraft) or other scaffold materials (e.g., Oasis, Matristem) win the last 30 days No ulcers on the dorsum of the foot or with more than 50% of the ulcer below the malleolus	No uncontrolled diabetes (HbA1c >10%); No suspicion of cancer; No history of more than 2 weeks treatment with immunosuppressant's, cytotoxic chemotherapy, or application of topical steroids within 1 month; No investigational drug(s) or therapeutic device(s) within 30 days; No known history of AIDS or HIV; Not needing NPWT therapy or HBOT; No NYHA Class III and IV CHF; Not pregnant or breast feeding; No allergy to gentamicin and streptomycin	Obesity

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities Among Enrolled Patients
Zelen et al. 2013[36]	>1 and <25 cm2	≥4 weeks	No clinical signs of infection Serum creatinine <3.0 mg/dl HbA1c <12% Adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test ($TcPO_2$) ≥30 mmHg, ABI between 0.7 and 1.2 or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg No Charcot foot No index ulcer probing to bone	History of type 1 or 2 diabetes; Agrees to adhere with study procedures and followup evaluations; Not currently receiving radiation or chemotherapy; No known or suspected malignancy of current ulcer; No diagnosis of autoimmune connective tissue disease; Not receiving a biomedical or topical growth factor for their wound within the previous 30 days; Not pregnant or breast feeding; Not taking medications considered to be immune system modulators; No allergy to gentamicin or streptomycin	Type 1 and Type 2 diabetes, obese

*Age of enrollment ≥18 years unless noted

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

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

Study	Characteristic	Skin Substitute	Control
Bianchi et al. 2018[35]	Number of patients	EpiFix plus MLCT (n=52)	SOC (dressings and MLCT) (n=57)
	Mean age ±SD (years)	61.5±14.9	60.0±10.6
	% male	63%	68%
	Wound type	VLU	VLU
	Median wound size (cm^2) (range)	5.2 (range, 1.1 to 24.3)	6.2 (range, 1.2 to 24.2)
	Mean wound duration (weeks) (range)	41.9±60.0	58.9±72.6
	Wound severity	NR	NR
	Comorbidities	31% smokers, 33% alcohol use, obese (BMI 36.0±11.2), 27% diabetes, 15% hypertension	49% smokers, 42% alcohol use, obese (BMI 37.2±11.0), 35% diabetes, 12% hypertension
	Completion rate	81.2%	89%
Zelen et al. 2018[44]	Number of patients	AlloPatch Pliable (n=40)	SOC (n=40)
	Mean age ±SD (years)	59±12	62±13
	% male	70%	60%
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	3.2±4.0	2.7±2.4
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	NR (excluded UT Grade IIIA-D)	NR (excluded UT Grade IIIA-D)
	Comorbidities	Obese (mean±SD BMI 35±7.9), 28% smokers, 18% drinks alcohol	Obese (mean±SD BMI 34±8.8), 18% smokers, 23% drinks alcohol
	Completion rate	87.5%	42.5%
Alvarez et al. 2017[40]	Number of patients	MatriStem Wound Matrix* (urinary bladder matrix (UBM) (n=11)	SOC (n=6)
	Mean age ±SD (years)	57.5	55.2
	% male	82%	84%
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	14±12.3	17±13.4
	Mean wound duration (months) (range)	6.5	4.8
	Wound severity	Grade I-A (University of Texas Wound Classification System)	Grade I-A (University of Texas Wound Classification System)
	Comorbidities	1% Charcot foot, 54.5% partial amputation	1% Charcot foot, 33.3% partial amputation
	Completion rate	100%	100%
Alvarez et al. 2017[49]	Number of patients	Hyalomatrix Wound Matrix plus compression (n=9)	SOC (nonadherent primary dressing plus a multilayer compression bandage) (n=7)
	Mean age ±SD (years)	60	58
	% male	44.6%	36.8%
	Wound type	VLU	VLU
	Average wound size (mm^2)(range)	489 (range NR)	535 (range NR)
	Mean wound duration (months)	10	7
	Wound severity	NR	NR
	Comorbidities	Obese (mean BMI 30)	Obese (mean BMI 29)
	Completion rate	100%	100%

Study	Characteristic	Skin Substitute	Control
DiDomenico et al. 2016[45]	Number of patients	Amnioband (n=20)	SOC (n=20)
	Mean age ±SD (years)	59±13	58±9
	% male	55%	80%
	Wound type	DFU	DFU
	Average wound size (cm^2) (SD)	2.0±0.90	3.3±4.35
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	NR	NR
	Comorbidities	Obese (mean BMI 37), 20% smokers, 15% drank alcohol	Obese (mean BMI 37), 10% smokers, 25% drank alcohol
	Completion rate	95%	60%
Snyder et al. 2016[46]	Number of patients	AmnioExcel dehydrated amniotic membrane allograft (n=15)	SOC (n=14)
	Mean age ±SD (years)	57.9±12.49	58.6±6.97
	% male	80%	92.9%
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	4.7 (range, 1.2 to 16.5)	6.9 (range, 1.1 to 21.1)
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	Percent Wagner grade 1 or superficial 2 not reported	Percent Wagner grade 1 or superficial 2 not reported
	Comorbidities	Type 1 or 2 DM (% NR), obese (mean BMI 34.9; range, 24.9 to 55.7)	Type 1 or 2 DM (% NR), obese (mean BMI, 35.1; range, 28.2 to 50.2)
	Completion rate	73.3%	71.4%
Driver et al. 2015[47]	Number of patients	Integra Dermal Regeneration Template (n=154)	SOC (n=153)
	Mean age ±SD (years)	55.8±10.6	57.3±9.7
	% male	76.6%	74.5%
	Wound type	DFU	DFU
	Average wound size (cm^2) at end of 2-week run in	3.53±2.5	3.65±2.7
	Mean wound duration (days ±SD)	308±491	303±418
	Wound severity	70.8% Wagner grade 2	75.8% Wagner grade 2
	Comorbidities	18.2% tobacco use, mean±SD BMI 34.0±7.2	12.4% tobacco use, mean±SD BMI 34.1±8.4
	Completion rate	83.1% completed treatment phase, 68.8% completed follow-up phase	76.4% completed treatment phase, 53.5% completed follow-up phase
Lavery et al. 2014[39]	Number of patients	Grafix (n=50)	SOC (n=47)
	Mean age ±SD (years)	55.5±11.5	55.1±12.0
	% male	66.0%	74.5%
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	3.41±3.23	3.93±3.22
	Mean wound duration (days±SD)	115.0±72.6	122.9±83.9
	Wound severity	NR	NR
	Comorbidities	72% obese	53.2% obese
	Completion rate	84%	76.5%

Study	Characteristic	Skin Substitute	Control
Serena et al. 2014[37]	Number of patients	EpiFix plus MLCT (n=53)	MLCT (n=31)
	Mean age ±SD (years)	59.0±17.75	62.6±13.53
	% male	58.5%	48.4%
	Wound type	VLU	VLU
	Average wound size (cm^2) (range)	6.0±4.33	6.3±5.27
	Mean wound duration (weeks) (range)	13.8±20.83	13.0±16.40
	Wound severity	NR	NR
	Comorbidities	69.8% obese	74.2% obese
	Completion rate	96.2%	94.1%
Zelen et al. 2013[36]	Number of patients	EpiFix (n=13)	SOC (n=12)
	Mean age ±SD (years)	56.4±14.7	61.7±10.3
	% male	NR	NR
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	2.6±1.9	3.4±2.9
	Mean wound duration (weeks) (range)	14.1±13.0	16.4±15.5
	Wound severity	NR	NR
	Comorbidities	Obese (mean BMI 30.4), percent Type 1 and Type DM not reported	Obese (mean BMI 35.4), percent Type 1 and Type DM not reported
	Completion rate	92.3%	16.6%

*Now branded as Cytal Wound Matrix (ACell, Inc., Columbia, MD)
BMI = body mass index; DFU = diabetic foot ulcer; DM = diabetes mellitus; MLCT = multi-layer compression therapy; NR = not reported; SD = standard deviation; SOC = standard of care; UBM = urinary bladder matrix; UT = University of Texas

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

Study	Study Detail	Description
Bianchi et al. 2018[35]	Specific wound treatment comparison	EpiFix® plus multilayer compression therapy (MLCT) vs. dressings and MLCT
	Wound type	VLU
	Country	USA
	Institutes involved	15 centers distributed throughout the USA; 9 private practice and 6 hospital-based centers
	Method of patient recruitment	Patients presenting for VLU care
	Patients enrolled	189 enrolled, 128 randomized
	Date range of study	March 19, 2015, to March 3, 2017
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photos and measurements using the Silhouette® camera
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	No
	Handling of dropouts	19 SOC patients who did not achieve 40% wound reduction by week 8 exited the study to receive advanced wound care. These patients were classified as completers and their non-healed status at 8 weeks with SOC was pulled forward for final analysis.

Study	Study Detail	Description
	Statistical power calculations	A 2-side log rank test indicated that an overall sample size of 120 subjects (60 in each group) would achieve approximately 87% power at a 5% significance level to detect a difference of 30% between the proportions of subjects whose ulcers are unhealed by 12 weeks in each arm.
	Length of study	16 weeks
	Source of funding	MiMedx Group, Inc., Marietta, GA, USA
Zelen et al. 2018[44]	Specific wound treatment comparison	AlloPatch Pliable (n=40) vs. SOC (n=40)
	Wound type	DFU
	Country	USA
	Institutes involved	5 centers
	Method of patient recruitment	NR
	Patients enrolled	92 screened, 80 randomized
	Date range of study	December 16, 2014, to March 29, 2017
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photo, tracings
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	"The sample size of 40 in each group was enough to detect a difference of 0.3 between the group proportions with 80% power. The proportion in the HR-ADM group was assumed to be 0.3 under the null hypothesis and 0.6 under the alternative hypothesis. The proportion in the SOC group was 0.3. The test statistic used was the 2-sided Z test with pooled variance, with significance level targeted at .05. The significance level actually achieved by this design was .048."
	Length of study	12 weeks
	Source of funding	Musculoskeletal Transplant Foundation, Edison, NJ
Alvarez et al. 2017[40]	Specific wound treatment comparison	MatriStem Wound Matrix* (urinary bladder matrix [UBM]) (n=11) vs. SOC (n=6)
	Wound type	DFU
	Country	USA
	Institutes involved	1 center
	Method of patient recruitment	NR
	Patients enrolled	17
	Date range of study	NR
	Care setting	Outpatient wound care center
	Use of run-in (length)	No
	Method of measuring wound condition at enrollment	Photodigital planimetry
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	NR
	Statistical power calculations	No
	Length of study	1 year
	Source of funding	ACell, Inc. (Columbia, MD)

Study	Study Detail	Description
Alvarez et al. 2017[49]	Specific wound treatment comparison	Hyalomatrix Wound Matrix plus compression vs. SOC (nonadherent primary dressing plus a multilayer compression bandage)
	Wound type	VLU
	Country	USA
	Institutes involved	University Wound Care Center, Center for Vascular Health (Bronx, NY)
	Method of patient recruitment	NR
	Patients enrolled	16 enrolled, 16 randomized
	Date range of study	NR
	Care setting	Outpatient wound care center
	Use of run-in (length)	No
	Method of measuring wound condition at enrollment	Photodigital planimetry
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	No
	Handling of drop outs	No
	Statistical power calculations	No
	Length of study	16 weeks
	Source of funding	Medline Industries, Inc. (Mundelein, IL)
DiDomenico et al. 2016[45]	Specific wound treatment comparison	Amnioband (dehydrated human amnion and chorion allograft) (n=20) vs. SOC (n=20)
	Wound type	DFU
	Country	USA
	Institutes involved	5 centers
	Method of patient recruitment	NR
	Patients enrolled	47 screened, 40 randomized
	Date range of study	March 23, 2015, to March 23, 2016
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Tracings, photos at a distance of 30 cm with a graded centimeter ruler present, with a legible label directly adjacent to the ulcer
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	“Sample sizes of 20 in each group were selected to achieve at least 80% power (84% actual) to detect a difference between the group proportions of 0.45. The proportion in group 1 (treatment group) was assumed to be 0.35 under the null hypothesis and 0.8 under the alternative hypothesis. The proportion in group 2 (control group) was 0.35. The test statistic used was the 2-sided Z test with pooled variance. The significance level actually achieved by this design was 0.052.”
	Length of study	12 weeks
	Source of funding	Musculoskeletal Transplant Foundation

Study	Study Detail	Description
Snyder et al. 2016[46]	Specific wound treatment comparison	AmnioExcel (n=15) vs. SOC (n=14)
	Wound type	DFU
	Country	USA
	Institutes involved	8 clinical study sites
	Method of patient recruitment	NR
	Patients enrolled	49 screened, 29 randomized
	Date range of study	NR
	Care setting	NR
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photo
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	NR
	Statistical power calculations	NR
	Length of study	6 weeks
	Source of funding	Derma Sciences, Princeton, NJ
Driver et al. 2015[47]	Specific wound treatment comparison	Integra Dermal Regeneration Template (IDRT) (n=154) vs. SOC (n=153)
	Wound type	DFU
	Country	USA
	Institutes involved	32 sites
	Method of patient recruitment	NR
	Patients enrolled	545 assessed, 307 randomized
	Date range of study	April 2010 to November 2013
	Care setting	Academic and private practice sites
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photo, tracings
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	A sample size of 296 subjects in the randomization/treatment phase was needed to have 80%% power to detect a clinically meaningful difference of 18% (46% in the active group vs. 28% in the control group) for the primary outcome using a two-sided 0.05 level test and assuming a 20% dropout rate.
	Length of study	28 weeks (16-week treatment, 12-week followup)
	Source of funding	Integra LifeSciences Corp.
Lavery et al. 2014[39]	Specific wound treatment comparison	Grafix vs. SOC
	Wound type	DFU
	Country	USA
	Institutes involved	NR
	Method of patient recruitment	NR
	Patients enrolled	139 screened, 97 randomized
	Date range of study	May 2012 through April 2013
	Care setting	Research centers throughout the USA
	Use of run-in (length)	1 week
	Method of measuring wound condition at enrollment	Tracing, photos
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes

Study	Study Detail	Description
	Handling of drop outs	NR
	Statistical power calculations	Based on closure rates of 30% and 50% in the control arm and Grafix arm, respectively, with a 30% dropout rate, 94 patients, who completed the treatment, in each treatment arm were required to meet the 2-sided type 1 error rate of 0.05 with 80% power.
	Length of study	24 weeks
	Source of funding	Osiris Therapeutics, Inc.
Serena et al. 2014[37]	Specific wound treatment comparison	EpiFix plus MLCT (n=53) vs. MLCT (n=31)
	Wound type	VLU
	Country	USA
	Institutes involved	8 centers in PA, MA, FL, OK, IN, and TX
	Method of patient recruitment	Patients presenting for care of a VLU
	Patients enrolled	88 screened, 84 randomly assigned
	Date range of study	March 2012 to March 2014
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Digital photo. Area calculated by multiplying length with width.
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of drop outs	LOCF
	Statistical power calculations	Sample sizes of 30 in each group were calculated to achieve a power of 81% when the difference between proportions healed at 4 weeks was 0.30 and the proportion healed in the MLCT group was 0.2. The test statistic used was the 2-sided likelihood ratio test with a significance level of 0.047.
	Length of study	4 weeks
	Source of funding	MiMedx Group, Inc., Marietta, GA.
Zelen et al. 2013[36]	Specific wound treatment comparison	EpiFix (n=13) vs. SOC (n=12)
	Wound type	DFU
	Country	USA
	Institutes involved	1 research institute in southwest Virginia
	Method of patient recruitment	NR
	Patients enrolled	25
	Date range of study	March and August 2012
	Care setting	Research institute
	Use of run-in	No
	Method of measuring wound condition at enrollment	Ulcer measurement with a graded centimeter ruler (length, width and depth)
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	No
	Handling of drop outs	NR
	Statistical power calculations	NR
	Length of study	12 weeks
	Source of funding	MiMedx (Kennesaw, GA)

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

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

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health and Age Requirements*	Comorbidities
Harding et al. 2013[31]	3–25 cm^2	≥2 months, <5 years	Patients were required to have a VLU located between the knee and ankle (at the level of, and including, the lateral and medial malleolus). No exposure of muscle, tendon, or bone and clean, granulating base with minimal adherent slough, suitable to receive a skin graft. Sufficient circulation to the study leg to make wound healing possible. ABI between 0.8 and 1.2 and venous disease had to be confirmed by duplex ultrasonography to demonstrate reflux of >0.5 seconds in saphenous, calf perforator, or popliteal veins. Ulcers that reduced in size (cm^2) by less than 50% while under compression therapy during the study's 2-week screening period were eligible for randomization into the study. No ulcers caused by a medical condition other than venous insufficiency. No evidence of sinus tracts in their ulcer or evidence of a wound infection (purulence and/or odor), cellulitis, and/or confirmed osteomyelitis. No skin diseases near study ulcer.	No morbid obesity, malignant disease within 5 years, severe PVD or renal disease, CHF, cell anemia, thalassemia, or uncontrolled diabetes. No use of immune suppressants, systemic corticosteroids, cytotoxic chemotherapy, or topical steroids for more than 2 weeks and within 1 month of initial screening or who had a history of radiation at the ulcer site. No known allergy to bovine products or components of the compression bandage or who could not tolerate compression bandage therapy, had received an investigational drug within 30 days of randomization, or had been previously treated with HFDS and/or other tissue-engineered materials.	NR

*Age of enrollment ≥18 years unless noted

ABI = ankle brachial index; CHF = congestive heart failure; HFDS = human fibroblast-derived dermal substitute; NR = not reported; PVD = peripheral vascular disease; VLU = venous leg ulcer

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

Study	Characteristic	Skin Substitute	Control
Harding et al. 2013[31]	Number of patients	Dermagraft plus 4-layer compression therapy (n=186)	4-layer compression therapy (n=180)
	Mean age ±SD (years)	67.9±13.8	69.1±12.4
	% male	46.2%	46.1%
	Wound type	VLU	VLU
	Median wound size (cm^2) (range)	7.4 (2.4 to 28.2)	7.2 (2.3 to 26.6)
	Median wound duration (weeks) (range)	49.7 (range, 8.9 to 262.1)	45.3 (range, 9.9 to 470.4)
	Wound severity	NR	NR
	Comorbidities	NR	NR
	Completion rate	100%	99.4%

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

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

Study	Study Detail	Description
Harding et al. 2013[31]	Specific wound treatment comparison	Dermagraft plus 4-layer compression therapy vs. 4-layer compression therapy
	Wound type	VLU
	Country	UK
	Institutes involved	25 centers (19 UK, 1 Canada, 5 USA)
	Method of patient recruitment	Referred to participating hospital or community-based VLU clinics in the UK, USA, or Canada
	Patients enrolled	573 screened, 366 randomly assigned
	Date range of study	NR
	Care setting	Hospital and community-based VLU clinics
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Tracing, planimetry analysis
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	Yes
	Handling of dropouts	NR
	Statistical power calculations	A sample size analysis indicated that 166 patients in each treatment group were required to detect a 15% difference in the proportion of patients who achieve complete healing at week 12. This calculation was based on a healing rate of 32% for controls and 47% for HFDS with a 0.05 two-sided significance level and at least 80% power.
	Length of study	24 weeks
	Source of funding	Financial support for editorial assistance was provided by Smith & Nephew Wound Management, Hull, UK, and Shire Regenerative Medicine, San Diego, CA, USA

HFDS = human fibroblast-derived dermal substitute; NR = not reported; VLU = venous leg ulcer

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

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health and Age Requirements*	Comorbidities
Cazzell et al. 2017[48]	≥1 cm^2 and <25 cm^2	30 days	Single-target DFU with a Wagner Ulcer Classification of 1 or 2 and absence of infection. Adequate circulation to the affected area, defined as having at least 1 of the following criteria within the past 60 days: transcutaneous oxygen measurement at the dorsum of the foot ≥30 mmHg, ABI ranging from 0.8–1.2, or at least biphasic Doppler arterial waveforms at the dorsalis pedis, and posterior tibial arteries. No wound treatments involving biomedical or topical growth factors 30-days before screening.	No circulating hemoglobin A1c exceeding 12% within 90 days of the screening visit, serum creatinine concentrations of 3.0 mg/dL or greater within 30 days before screening. No presence of peripheral vascular disease, active infection or untreated malignancy, Charcot's disease, or necrosis, purulence, or sinus tracts that could not be removed by debridement. No revascularization procedure aimed at increasing blood flow in the target limb or received a living skin equivalent within 4 weeks before screening. No sensitivity to lincomycin, gentamicin, polymyxin B, vancomycin, polysorbate 20, N-lauroyl sarcosinate, benzonase, or glycerol Age between 21 and 80 years.	Type 1 and 2 diabetes

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

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

Study	Characteristic	Skin Substitute	Skin Substitute	Control
Cazzell et al. 2017[48]	Number of patients (ITT population)	DermACELL (n=71)	GraftJacket (n=28)	SOC (n=69)
	Mean age ±SD (years)	59.1±12.76	58.5±9.83	56.9±10.86
	% male	80.3%	71.4%	73.9%
	Wound type	DFU	DFU	DFU
	Average wound size (cm^2) (range)	3.9±4.15	3.3±2.69	3.6±3.61
	Mean wound duration (weeks) (range)	40.0 (6.0–479.0)	36.8 (2.0-226.0)	36.4 (2.0–167.0)
	Wound severity	12 (16.9%) Grade 1 Wagner, 59 (83.1%) Grade 2 Wagner	5 (17.9%) Grade 1 Wagner, 23 (82.1%) Grade 2 Wagner	14 (20.3%) Grade 1 Wagner, 55 (79.7%) Grade 2 Wagner
	Comorbidities	4 (5.6%) type 1 DM, 64 (90.1%) type 2 DM, 11 (15.5%) current smokers	2 (7.1%) type 1 DM, 26 (92.9%) type 2 DM, 9 (13.0%) current smokers	2 (2.9%) type 1 DM, 67 (97.1%) type 2 DM, 2 (7.1%) current smokers
	Completion rate	75%	82.1%	81.1%

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

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

Study	Study Detail	Description
Cazzell et al. 2017[48]	Specific wound treatment comparison	DermACELL vs. GraftJacket vs. SOC
	Wound type	DFU
	Country	USA
	Institutes involved	13 centers in 9 states
	Method of patient recruitment	Patients presenting to the clinic for care of DFU
	Patients enrolled	203 enrolled, 168 randomly assigned
	Date range of study	NR
	Care setting	Outpatient wound care centers
	Use of run-in (length)	30 days
	Method of measuring wound condition at enrollment	Tracings
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	Yes
	Handling of dropouts	3 subjects were removed from the per-protocol population, including 1 subject who was withdrawn after missing 15 visits, 1 who was withdrawn after Week 7 for lung cancer, and a conventional care subject who withdrew consent at Week 3.
	Statistical power calculations	A power analysis determined 66 patients would be needed to be enrolled in the DermACELL and SOC arm to have an 80% chance of obtaining a statistically significant result. Statistical significance was not sought or expected for the GraftJacket arm so it was not included in the power analysis.
	Length of study	24 weeks
	Source of funding	LifeNet Health, manufacturer of DermACELL

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

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

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities
Ananian et al. 2018[32]	≥1 cm^2 and <15 cm^2	4 to 52 weeks	Extends through the dermis with no exposed muscle, tendon, bone, or joint capsule. ABI between 0.7 and 1.3 Toe brachial index of ≥0.5, or a Doppler waveform demonstrating biphasic or triphasic flow in the foot. No index ulcers that decreased ≥20% in size during the 1-week screening period.	Diagnosed with type 1 or 2 DM Aged between 18 years and 80 years	Type 1 and 2 DM, obesity, smoking use, heart disease, mild PAD

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities
Frykberg et al. 2016[34]	NR	≥4 weeks	Extends through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone, or joint capsule. Postdebridement, wound is free of necrotic debris and appears made up of healthy vascularized tissue. Adequate circulation to the study foot as evidenced by a Doppler measure ABI of ≥0.7 after 10 minutes of rest. No decrease in ulcer size by ≥30% during the screening period. No increase in ulcer size by ≥50% during the screening period. No ulcer has tunnels or sinus tracts that cannot be completely debrided.	Individuals with HbA1c <12%, no severe malnutrition (albumin <2.0 g/dl), and no random blood sugar reading >450 mg/dl.	Type 1 and 2 DM
Zelen et al. 2016[38]	≥1 cm^2 and <25 cm^2	≥4 weeks	No clinical signs of infection. Adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test ≥30 mmHg or ABI between 0.7 and 1.2 or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg. No index wound duration of >52 weeks without intermittent healing. No ulcer probing to tendon, muscle, capsule, or bone. No known or suspected malignancy of current ulcer. No wounds improving greater than 20% over the 2-week run-in period of the trial using standard of care dressing and Camboot offloading.	Type 1 or 2 diabetes, serum creatinine <3.0 mg/dl and HbA1c <12%. No diagnosis of autoimmune connective tissue disease, use of biomedical/topical growth factor within previous 30 days, pregnancy or breast feeding, taking medications considered to be immune system modulators, and taking Cox-2 inhibitors. Not currently receiving radiation or chemotherapy. No diagnosis of autoimmune connective tissue disease. No use of biomedical/topical growth factor in previous 30 days. Not pregnant or breast-feeding. Not taking medications considered to be immune system modulators. No allergy or known sensitivity to Gentamicin, Streptomycin, bovine collagen, or components of linear polysaccharide shipping medium. No use of Cox-2 inhibitors or planned use of Dakin's solution, Mafenide Acetate, Scarlet Red Dressing, Tincoban, Zinc Sulfate, Povidone-iodine solution, Mafenide Acetate, Polymyxin/Nystatin, or Chlorhexidine during trial.	Smoking use, hypertension, CAD, CHF, obesity

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

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

Study	Characteristic	Skin Substitute	Skin Substitute	Control
Ananian et al. 2018[32]	Number of patients	GrafixPrime (n=38)	Dermagraft (n=37)	N/A
	Mean age ±SD (years)	55.3±12.09	58.1±11.89	N/A
	% male	73.7%	86.5%	N/A
	Wound type	DFU	DFU	N/A
	Average wound size (cm^2) (range)	7.15	5.70	N/A
	Mean wound duration (days) (range)	199.32 days	146.32 days	N/A
	Wound severity	NR	NR	N/A
	Comorbidities	68.4% BMI ≥30, 13.2% type 1 DM, 86.8% type 2 DM, 10.5% current smoker, 92.1% heart disease, 55.3% prior amputation, 31.6% mild PAD	54.1% BMI ≥30, 2.7% type 1 DM, 97.3% type 2 DM, 5.4% current smoker, 94.6% heart disease, 54.1% prior amputation, 24.3% mild PAD	N/A
	Completion rate	86.8%	83.7%	N/A
Frykberg et al. 2016[34]	Number of patients	MatriStem MicroMatrix and MatriStem Wound Matrix (n=27)	Dermagraft (n=29)	N/A
	Mean age ±SD (years)	57.0±9.8	58.5±11.4	N/A
	% male	77.8%	75.9%	N/A
	Wound type	DFU	DFU	N/A
	Average wound size (cm^2) (range)	4.3±5.7	3.2±4.5	N/A
	Mean wound duration (days) (range)	263 days overall (range, 30 to 1095)	263 days overall (range, 30 to 1095)	N/A
	Wound severity (based on University of Texas Grade)	100% A1	93.1% A1, 6.9% >A1	N/A
	Comorbidities	11.1% type 1 DM, 88.9% type 2 DM	17.2% type 1 DM, 82.7% type 2 DM	N/A
	Completion rate	100%	100%	N/A
Zelen et al. 2016[38]	Number of patients	Apligraf (n=33)	EpiFix (n=32)	SC (n=35)
	Mean age ±SD (years)	63.8±11.86	63.3±12.25	60.6±11.55
	% male	13.9%	18.8%	21.8%
	Wound type	DFU	DFU	DFU
	Average wound size (cm^2) (range)	1.7 (range, 1.0 to 14.7)	1.7 (range, 1.0 to 16.9)	1.8 (range, 1.0 to 15.5)
	Mean wound duration (weeks) (range)	NR	NR	NR
	Wound severity	NR	NR	NR
	Comorbidities	% DM not reported, 18.2% smokers, 72.7% hypertension, 15.2% CAD, 15.2% CHF, 19.8% obese	% DM not reported, 28.1% smokers, 68.8% hypertension, 18.8% CAD, 6.3% CHF, 19.8% obese	% DM not reported, 34.3% smokers, 74.3% hypertension, 28.6% CAD, 8.6% CHF, 22.8% obese
	Completion rate	85.2%	91.4%	48%

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

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

Study	Study Detail	Description
Ananian et al. 2018[32]	Specific wound treatment comparison	GrafixPrime (n=38) vs. Dermagraft (n=37)
	Wound type	DFU
	Country	USA
	Institutes involved	7 centers
	Method of patient recruitment	NR
	Patients enrolled	105 screened, 75 randomly assigned
	Date range of study	January 2016 to May 2017
	Care setting	Wound clinics, medical centers
	Use of run-in (length)	1 week
	Method of measuring wound condition at enrollment	No
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Safety based on ITT, clinical outcomes based on per-protocol population
	Handling of dropouts	NR
	Statistical power calculations	"Powered to show that vCPM [GrafixPrime] is not inferior to hFDS [Dermagraft] for wound closure. A treatment effect difference of 20% for the non-inferiority (NI) test was used in this analysis based on published clinical outcomes of vCPM and hFDS. A conservative NI margin of 15% was used per U.S. FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness. Using these parameters, 74 patients was determined to be the sample size needed to meet the primary endpoint. In this analysis, noninferiority of vCPM compared to hFDS could be proven only if the lower bound of the Newcombe 90% confidence interval for the difference in the two proportions (difference = vCPM – hFDS) was greater than −15%."
	Length of study	9 weeks
	Source of funding	Osiris Therapeutics, Inc.
Frykberg et al. 2016[34]	Specific wound treatment comparison	MatriStem MicroMatrix and MatriStem Wound Matrix vs. Dermagraft
	Wound type	DFU
	Country	USA
	Institutes involved	13 unnamed
	Method of patient recruitment	NR
	Patients enrolled	95 enrolled, 56 randomly assigned
	Date range of study	NR
	Care setting	VA medical facilities (2), outpatient research clinics (4), private practice clinics (5), and hospital-based outpatient clinics (2)
	Use of run-in (length)	4 weeks
	Method of measuring wound condition at enrollment	Photos, tracings, and measurement of depth via Visitrak Depth Probe.
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	Yes
	Handling of dropouts	To account for a 10% dropout rate, the sample size was upwardly adjusted to 102 subjects.
	Statistical power calculations	92 subjects are needed for enrollment to have 90% power at a 10% noninferiority margin.

Study	Study Detail	Description
	Length of study	6 months
	Source of funding	NR: 1 author is chief scientific officer and stockholder in ACell, Inc. (commercializes MatriStem)
Zelen et al. 2016[38]	Specific wound treatment comparison	Apligraf vs. EpiFix vs. SOC
	Wound type	DFU
	Country	USA
	Institutes involved	3 centers (unspecified) in Virginia, 1 center (unspecified) in Oklahoma
	Method of patient recruitment	Presenting to the clinic with type 1 or 2 diabetes for care of a lower-extremity ulcer
	Patients enrolled	126 enrolled, 104 randomly assigned
	Date range of study	September 2013 to August 2015
	Care setting	Outpatient wound care centers
	Use of run-in (length)	2 weeks
	Method of measuring wound condition at enrollment	Photos and tracings
	Stratification of results (wound severity or comorbidities)	Hazard ratios were calculated using covariates of hypertension (vs. no hypertension), initial wound area (1.2 to 2.5 cm^2 and >2.5 vs. <1.2 cm^2), and location of DFU (forefoot, midfoot, rearfoot/ankle vs. toes).
	Use of intent-to-treat	Yes
	Handling of dropouts	LOCF
	Statistical power calculations	Sample size calculations (PASS 11) showed that group sample sizes of 23 in group 1 and 23 in group 2 could achieve 81% power to detect a difference between the group proportions of 0,4 (proportion healed); however, study enrollment continued until 100 patients meeting inclusion/exclusion criteria were recruited.
	Length of study	12 weeks
	Source of funding	NR

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

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

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities
Towler et al. 2018[30]	>1 cm^2 and <40 cm^2 and <5 mm deep	>30 days	ABI >0.5 or biphasic or triphasic Doppler signals in the dorsalis pedis and posterior tibial arteries of the affected extremity. No suspected gangrene or wound infection on any part of the affected limb. No leg ulcers secondary to a disease other than venous ulcers.	No history or end-stage renal disease, immunosuppression, severe malnutrition, severe liver disease, aplastic anemia, scleroderma, positive for AIDS or HIV, connective tissue disorder, sickle cell anemia, osteomyelitis, bone cancer or metastatic disease of the affected limb, irradiation of the affected extremity, and chemotherapy in the last 12 months. No hypersensitivity to bovine collagen or agarose (listed Apligraf directions for use). Has not received or currently receiving (within 30 days of randomization) or scheduled to receive a medication or treatment known to interfere with or affect the wound healing rate. Has not been treated with growth factors, engineered tissue, or skin substitutes within 30 days of randomization.	Diabetes, morbid obesity, peripheral vascular disease, smoking use, lymphedema, neuropathy

Study	Minimum Wound Surface Area	Minimum Wound Duration	Other Wound Characteristics	General Health, Prior Treatment and Age Requirements*	Comorbidities
Sanders et al. 2014[33]	>1 cm^2 and <10 cm^2.	>30 days	Minimum 2 cm margin between study ulcer and other ulcers. ABI >0.65 Toe pressure >50 mm Hg $tcPO_2$ >20 mm Hg No gangrene or wound infection of the foot.	Individuals with type 1 or 2 diabetes and HbA1c <12%. No end-stage renal disease, immunosuppression, aplastic anemia, scleroderma, AIDs or HIV-positive, severe malnutrition, liver disease, connective tissue disorders, or sickle cell anemia. No mental or physical incapacity that could interfere with adherence; substance abuse; excessive lymphedema, unstable or deformed Charcot foot; vasculitis, neoplasms, or hematologic disorders; cellulitis, osteomyelitis, or wound infection; history of bone cancer or metastatic disease. No hypersensitivity to bovine collagen and/or chondroitin. No hypersensitivity to gentamycin, vancomycin, or the reagents listed in the TheraSkin® Instructions for Use. No oral parenteral corticosteroids, immunosuppressive, or cytotoxic drugs with 12 months. Treatment with growth factors or bioengineered skin substitutes within 30 days.	Type 1 and 2 DM, neuropathy, PAD, smoking use

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

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

Study	Characteristic	Skin Substitute	Control
Towler et al. 2018[30]	Number of patients	Apligraf (n=12)	Theraskin (n=15)
	Mean age ±SD (years)	63.7±13.4	66.3±18.0
	% male	58.3%	66.7%
	Wound type	VLU	VLU
	Average wound size (cm^2) (mean±SD)	6.37±6.95	4.94±4.43
	Mean wound duration (weeks) (range)	NR	NR
	Wound severity	NR	NR
	Comorbidities	33.3% diabetes, 50% morbidly obese, 8.3% peripheral vascular disease, 25% daily smokers, 8.3% lymphedema, 16.7% neuropathy	46.7% diabetes, 66.7% morbidly obese, 33.3% peripheral vascular disease, 25% daily smokers, 13.3% lymphedema, 13.3% neuropathy
	Completion rate	92% overall (of 4 dropouts, 1 received Apligraf, 3 did not receive grafts)	100%
Sanders et al. 2014[33]	Number of patients	Dermagraft (n=12)	Theraskin (n=11)
	Mean age ±SD (years)	56.58±14.96	60.0±15.74
	% male	50%	45.45%
	Wound type	DFU	DFU
	Average wound size (cm^2) (range)	4.78 (0.86 to 14.45)	5.45 (0.50 to 18.02)
	Mean wound duration (weeks) (range)	11.71 (4 to 26.1)	43.58 (4 to 260)
	Wound severity	NR	NR
	Comorbidities	8.33% type 1 DM, 91.67% type 2 DM, 58.33% neuropathy, 16.67% PAD, 9.09% smokers	9.09% type 1 DM, 90.9% type 2 DM, 72.73% neuropathy, 0% PAD, 0% smokers
	Completion rate	100%	100%

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

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

Study	Study Detail	Description
Towler et al. 2018[30]	Specific wound treatment comparison	Apligraf vs. Theraskin
	Wound type	VLU
	Country	USA
	Institutes involved	1, Bon Secours St Francis Wound Healing Center, Greenville, SC
	Method of patient recruitment	NR
	Patients enrolled	31 enrolled, 31 randomly assigned
	Date range of study	June 2013 to June 2016
	Care setting	Wound center
	Use of run-in (length)	Yes, 30 days
	Method of measuring wound condition at enrollment	Photos
	Stratification of results (wound severity or comorbidities)	No
	Use of intent-to-treat	NR
	Handling of dropouts	NR
	Statistical power calculations	Pilot study with a power calculation only to predict the risk of type 2 error
	Length of study	20 weeks
	Source of funding	No funding

Study	Study Detail	Description
Sanders et al. 2014[33]	Specific wound treatment comparison	Dermagraft vs. Theraskin
	Wound type	DFU
	Country	USA
	Institutes involved	Bon Secours Wound Care Clinic at Mary Immaculate Hospital (Newport News, VA) and Washington Hospital Wound Center (Washington, PA)
	Method of patient recruitment	NR
	Patients enrolled	23
	Date range of study	NR
	Care setting	2 hospital-based outpatient wound care centers
	Use of run-in (length)	No
	Method of measuring wound condition at enrollment	Photos, tracings,
	Stratification of results (wound severity or comorbidities)	NR
	Use of intent-to-treat	No
	Handling of drop outs	NR
	Statistical power calculations	Post-study calculation: 0.80 based on the closure rate of the wounds in each group
	Length of study	20 weeks
	Source of funding	Soluble Systems, LLC, and LifeNet Health

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

Table C-18. Assessment of wound closure in 17 RCTs

Study	Comparison	Wound Type	Primary Outcome(s)	Definition of a "Healed Wound"	Reported Assessment and Reassessment of Wound Closure	Blinding of Assessors
Ananian et al. 2018[32]	GrafixPrime vs. Dermagraft	DFU	Proportion of patients who achieved complete closure of the index wound by the end of treatment	100% reepithelialization	Weekly through week 9 or until wound healed. Reassessment not described.	NR
Bianchi et al. 2018[35]	EpiFix plus multilayer compression therapy vs. SOC	VLU	Time to complete wound closure, as assessed over a 12-week period from treatment initiation	100% reepithelialization without drainage	Weekly through week 12 with 1 followup visit at week 16. Individuals who achieved healing before 12 weeks were required to be seen weekly for all 12 visits and return at week 16 for reassessment of healed wounds.	Yes
Towler et al. 2018[30]	Apligraf vs. Theraskin	VLU	Complete wound closure, time to wound closure	100% epithelialization without drainage	Weekly through 12 weeks, followed until wound healed or up to 20 weeks. Reassessment not described.	NR
Zelen et al. 2018[44]	AlloPatch Pliable vs. SOC	DFU	Proportion (%) of ulcers healed at 6 weeks. Complete wound closure.	Complete (100%) reepithelialization without drainage and need for dressing	Weekly through 12 weeks or until wound healed. Reassessment not described.	Yes
Alvarez et al. 2017[40]	MatriStem Wound Matrix* vs. SOC	DFU	Incidence of complete wound closure by 16 weeks	Complete epithelialization without drainage or dressings required by 16 weeks	Weekly through 16 weeks. Healed wounds were reassessed once/monthly up to 1 year.	NR
Alvarez et al. 2017[49]	Hyalomatrix Wound Matrix plus compression vs. SOC	VLU	Incidence of wound healing at 12 and 16 weeks	NR	Weekly through week 16. Reassessment not described.	NR
Cazzell et al. 2017[48]	DermACELL vs. GraftJacket vs. SOC	DFU	To compare the proportion of chronic DFUs completely closed at the end of 12 weeks	100% reepithelialization without drainage or dressing requirements confirmed at 2 consecutive study visits 2 weeks apart	Weekly assessments until complete wound healing or until 24 weeks. Healed wounds were reassessed 4, 8, and 12 weeks after complete wound closure.	Yes
DiDomenico et al. 2016[45]	Amnioband vs. SOC	DFU	To compare the proportion of wounds healed at 6 weeks	Complete (100%) epithelialization without drainage and need for dressing	Weekly assessments until complete wound healing or until 12 weeks. Reassessment of healed wounds was scheduled 1 week after complete wound closure.	Yes

Study	Comparison	Wound Type	Primary Outcome(s)	Definition of a "Healed Wound"	Reported Assessment and Reassessment of Wound Closure	Blinding of Assessors
Frykberg et al. 2016[34]*	Matristem vs. Dermagraft	DFU	Complete wound closure with up to 8 weekly device applications (day 56)	Complete reepithelialization with no wound drainage present and no dressing required	Weekly assessments through wound closure or until subject received once/weekly (±3 days) treatment applications without complete wound closure, whichever came first. At 8 weeks, nonhealers received 3 additional SOC-only visits to determine delayed healing. Healed wounds (by day 70) were reassessed at 6 months.	Yes
Snyder et al. 2016[46]	AmnioExcel vs. SOC	DFU	Proportion of subjects with complete wound closure before or on week 6 after initiation of treatment	100% complete skin reepithelialization without drainage or dressing requirements	Weekly through week 6. No reported reassessment for closed wounds.	NR
Zelen et al. 2016[38]**	Apligraf vs. EpiFix vs. SOC	DFU	To compare healing characteristics between groups	Complete (100%) reepithelialization without drainage or need for dressing	Once every 7 days (±3 days) for up to 12 weeks or until 1 week after complete healing.	Yes
Driver et al. 2015[47]	Integra Dermal Regeneration Template vs. SOC	DFU	Percentage of subjects with complete closure of the study ulcer, as assessed by the investigator, during the treatment phase	100% reepithelialization of the wound surface with no discernable exudate and without drainage or dressing requirements	Weekly through 16 weeks or until wound closure. Reassessment of wound closure was 1 week later and a second consecutive study visit.	Yes
Lavery et al. 2014[39]	Grafix vs. SOC	DFU	Proportion of patients with complete wound closure by 12 weeks	100% reepithelialization with no wound drainage	Weekly for 12 weeks. Healed wounds were reassessed 2 weeks postclosure. The followup phase consisted of 2 visits during the first month and then monthly for 2 additional visits.	Yes
Sanders et al. 2014[33]	Dermagraft vs Theraskin	DFU	Complete wound closure, number of grafts required by week 12	100% epithelialization without drainage	Weekly assessments through 12 weeks, followed until wound healed or up to 20 weeks. Reassessment of a healed wound occurred in 1 "confirmatory visit"; timing not reported.	NR
Serena et al. 2014[37]	EpiFix plus MLCT vs. MLCT	VLU	Proportion of patients with ≥40% reduction of wound size at 4 weeks	100% epithelialization without drainage	Weekly assessments through week 4. Reassessment of a healed wound 1 week later.	NR
Harding et al. 2013[31]	Dermagraft plus f4-layer compression therapy vs. 4-layer compression therapy	VLU	Proportion of patients with completely healed study ulcers by 12 weeks	Full epithelialization of the wound with the absence of drainage for 2 consecutive weekly visits	Weekly assessments until complete wound healing or until 24 weeks. Healed wounds were reassessed in a consecutive week.	NR

Study	Comparison	Wound Type	Primary Outcome(s)	Definition of a "Healed Wound"	Reported Assessment and Reassessment of Wound Closure	Blinding of Assessors
Zelen et al. 2013[36]	EpiFix vs. SOC	DFU	Reduction of wound size and the proportion of ulcers completely healed after 4 and 6 weeks	Complete epithelialization of the open area of the wound	At time 0 and at least once every 7 days (±3 days) for up to 12 weeks or until complete healing, whichever occurred first.	NR

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

Table C-19. Definition of failure to heal during treatment phase in 17 RCTs

Study	Comparison	Wound Type	Failure to heal
Bianchi et al. 2018[35]	EpiFix plus multilayer compression therapy vs. multilayer compression therapy	VLU	Standard of care group subjects whose VLU wound area did not decrease in area by at least 40% by week 8 were classified as study failures and were allowed to receive advanced treatments
Zelen et al. 2018[44]	AlloPatch Pliable vs. SOC	DFU	Failed to decrease in size by 50% in 6 weeks
DiDomenico et al. 2016[45]	Amnioband vs. SOC	DFU	Failed to reduce in area by 50% or more
Zelen et al. 2016[38]	Apligraf vs. EpiFix vs. SOC	DFU	Failed to heal by ≥50% within the first 6 weeks of study enrollment.
Zelen et al. 2013[36]	EpiFix vs. SOC	DFU	Did not achieve 50% area reduction at 6 weeks

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

Table C-20. Description of treatments in 17 RCTs

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Ananian et al. 2018[32]	Cleaning and debriding at the investigator's discretion	Offloading with a standardized fixed ankle walker (plantar wounds) or standard postoperative shoe (dorsal wounds). Alternative offloading devices permitted.	GrafixPrime: up to 8 applications available in 5 cm x 5 cm and 2 cm x 3 cm. Covered with a nonadherent dressing and a secondary dressing.	Dermagraft: up to 8 applications available in a 5 cm x 7.5 cm size. Covered with a nonadherent dressing and a secondary dressing.	NR
Bianchi et al. 2018[35]	Moist dressings and multilayer compression	Cleaning, debridement, standard moist wound dressings (Adaptic Touch™ – primary wound contact layer and Tuekke® Max nonadhesive hydropolymer dressing – absorbent secondary dressing), and multilayer compression bandages	EpiFix® dehydrated human amnion/chorion membrane allograft (MiMedx Group, Inc., Marietta, GA): up to 12 weekly applications; nonadherent moist wound dressings placed over the allograft, followed by dry gauze wrap and multilayer compression.	SOC	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Towler et al. 2018[30]	Compression and local wound care	For 12 weeks, debridement; Dressing changes with a nonadherent contact layer (Mepilex transfer foam, Molnlycke Health Care, Norcross, GA; or Adaptic, Systagenix, Quincy, MA); Multilayer compression dressing. Highly exudate wounds received biweekly changes. Weeks 12 to 20 for nonhealers: multilayer compression therapy alone	Apligraf: Weekly evaluations by study investigators. Weekly grafts through week 12 unless repeat grafts were contraindicated, based on clinical assessment (i.e., infection) or if a graft was not available on the schedule date of application. Grafting continued until wound healing occurred or until further grafts were not covered or authorized by insurance. Grafts were covered with Mepilex transfer foam or Adaptic. Subjects were followed through week 20 or until the study wound was completely healed (100% epithelialization without drainage).	Theraskin: similar application as Apligraf	NR
Zelen et al. 2018[44]	Cleaned and surgically debrided	Irrigation with sterile normal saline, debrided, daily dressing changes with a collagen alginate (Fibracol, Systagenix, Gargrave, Yorkshire, UK), followed by a 3-layer padded generic dressing of gauze, soft roll, and a compressive wrap; offloading using a removable cast walker (Royce Medical, Inc., Camarillo, CA), total contact cast, or similar generic device	AlloPatch Pliable (human reticular acellular dermal matrix (HR-ADM)): Weekly applications of HR-ADM during the study period. Following immersion in sterile saline for 5 to 10 seconds, the graft was pie-crusted with a 15-scalpel blade, not greater than ×1.5 to ×1.0, and cut to size using sterile scissors and applied to the entire ulcer surface ensuring maximum surface contact. A nonadherent dressing (Adaptic Touch, Systagenix) was applied over the graft, followed by a moisture-retentive dressing (hydrogel bolster) and a padded 3-layer dressing (Dynaflex, Systagenix or equivalent) until complete closure.	SOC	Systemic antibiotics were administered until the infection was clinically resolved. Patients were withdrawn from the study if the infection worsened such that it interrupted HR-ADM treatment or interfered with study visits.

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Alvarez et al. 2017[40]	Extensive debridement	Nonadherent (siliconized) medical-grade foam (Mepilex Wound Dressing; Molnlycke Health Care, Norcross, GA), offloading with a total contact cast	MatriStem Wound Matrix* (urinary bladder matrix): weekly applications through week 16 or until healing was achieved. Trimmed to fit, then moistened with saline and applied directly to the wound bed. Secured with adhesive skin closure strips, then a secondary dressing.	SOC weekly for 16 weeks or until healing was achieved.	NR
Alvarez et al. 2017[49]	NR	Nonadherent silicone foam dressing and either 2-layer short-stretch compression bandage or 4-layer compression bandage	Hyalomatrix Wound Matrix: application not reported	SOC	NR
Cazzell et al. 2017[48]	Debridement	Debridement followed by moist-wound treatment with alginate, foam, or hydrogel dressings. Dressings covered the wound for at least 5 days, but no more than 9 days, (7 days±2 days) until the next study visit. Dressings were changed only by the study team.	DermACELL: meshed, 4 x 4 cm (thickness range, 0.5–1.0 mm) D-ADM was applied and covered with an appropriate nonadherent dressing. A second ADM application was allowed to be administered if determined medically necessary by the investigator, no fewer than 3 weeks but no longer than 12 weeks (Weeks 3–12) after the first application of ADM.	GraftJacket: meshed, 4 x 4 cm (thickness range, 0.38–1.02 mm) with similar application as DermACELL.	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
DiDomenico et al. 2016[45]	Debridement, offloading, collagen alginate and a 3-layer dressing	Saline irrigation, debridement	Amnioband (dehydrated human amnion and chorion allograft (dHACA)): cut to size, rinsed with sterile saline, and placed over the entire wound surface. Graft was covered with a nonadherent dressing (Adaptic Touch, Systagenix, Yorkshire, UK) topped with a moisture-retentive dressing (hydrogel bolster) and a padded 3-layer dressing (Dynaflex, Systagenix). Weekly applications of dHACA were allowed.	SOC: dressed daily with collagen alginate (Fibracol, Systagenix, Gargrave, Yorkshire, UK) by patients or their caregivers at home 6 days a week and by the site investigator 1 day a week.	Infection management: If suspected, both anaerobic and aerobic cultures were obtained from wound swabs and appropriate systemic antibiotic treatment was initiated and continued until the infection was clinically resolved. If the infection precluded dHACA application in the treatment group or caused problems with scheduled visits in either group, the patient was withdrawn from the trial and the treatment was considered a failure. Diabetes management: Individuals with poor metabolic control were referred to their primary care physician or endocrinologist to ensure adequate diabetes management.
Frykberg et al. 2016[34]	Debridement, saline irrigation, primary dressing, and offloading boot	Sharp debridement, saline irrigation, foot offloading	MatriStem MicroMatrix (MSMM) and MatriStem Wound Matrix (MSWM): A sheet of MSWM was placed over the wound area followed by a nonadherent dressing and hydrogel dressing. Weekly application of both MSMM and MSWM occurred until a service-level granulation tissue was observed. Subsequently on weekly visits, only Wound Matrix and hydrogel were applied. Up to 8 applications of Matristem were allowed. Healthcare provider applying grafts not reported.	Dermagraft: applied weekly per-product specifications. Up to 8 applications were allowed.	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Snyder et al. 2016[46]	Cleaned, debrided	Debridement, moist wound dressings, offloading with a DH Walker boot, infection surveillance, and management	AmnioExcel dehydrated amniotic membrane allograft (DAMA): cut to fit the DFU. Dressed with Adaptic (Systagenix, Gatwick, UK) and covered with a foam nonadhesive dressing. Wrapped with the conforming bandage and lightly secured. Cover dressing consisting of a compression dressing of the cohesive bandage wrap was applied. DAMA could be reapplied weekly upon the investigator's discretion.	SOC: in addition to SOC received by all patients, controls also received Xtra-Sorb foam nonadhesive dressing (Derma Sciences, Princeton, NJ). After hemostasis was achieved, the wound was wrapped with Duform Synthetic Conforming Bandage (Derma Sciences) and lightly secured. Lastly, a compression dressing (Duban Cohesive Bandage, Derma Sciences) was applied as a cover dressing.	"Infection surveillance and management"
Zelen et al. 2016[38]	Debridement, collagen-alginate dressings and gauze, offloading cast walker	Debridement, saline irrigation, collagen-alginate dressing, offloading	Apligraf: weekly application followed by a nonadherent dressing (Adaptic Touch, Systagenix, San Antonio, TX or equivalent), a moisture-retentive dressing (NuGel, Systagenix, San Antonio, TX, or equivalent) and a compressive dressing. Dressings were changed weekly. Healthcare provider applying grafts not reported.	EpiFix: similar application as Apligraf	NR
Driver et al. 2015[47]	See SOC	Sharp debridement, moist wound therapy consisting of 0.9% sodium chloride gel plus a secondary dressing (a nonadherent foam dressing, an outer gauze wrap, and an offloading/protective device [Active Offloading Walker boot and/or shoe]).	Integra Dermal Regeneration Template (IDRT): applied in the outpatient setting. Fenestrating and meshing of the IDRT was permitted to allow for drainage and in the presence of exudating wounds or hematomas. The IDRT was trimmed to size and secured with sutures or staples and covered with a secondary dressing. The silicone layer of IDRT was removed when the collagen layer was replaced by new tissue, typically 14–21 days after application. Reapplication of IDRT was performed at the investigator's discretion. The secondary dressing changes for the active treatment group were performed weekly by site personnel.	See SOC	NR

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Lavery et al. 2014[39]	NR	Surgical debridement, offloading and nonadherent dressings. All patients received a nonadherent dressing (Adaptic® (Systagenix, Gatwick, UK) and either saline-moistened gauze or Allevyn® (Smith & Nephew, London, UK) for moderately draining wounds. An outer dressing was then applied. Patients were provided walking boots or a post-op shoe depending on wound location. Custom offloading boots were also available.	Grafix: applied once a week (±3 days) for up to 84 days; the human viable wound matrix (hVWM) was placed to come in full contact with the wound and edges.	SOC: once a week (±3 days) for up to 84 days.	NR
Sanders et al. 2014[33]	NR	Saline irrigation, debridement offloading. Graft covered with dressing changes with either Mepitel or Polymem (Ferris Manufacturing Corp., Fort Worth, TX); weeks 12 to 20 for nonhealers: saline-moistened gauze and debridement.	Dermagraft: Weekly evaluations by study investigators. Weekly grafts through week 12. Grafts were covered with Mepilex or Polymem. Subjects were followed through week 20 or until the study wound was completely healed (100% epithelialization without drainage). One visit (timing not reported) was scheduled to confirm healed wound.	Theraskin: similar care except grafts were applied every other week.	NR
Serena et al. 2014[37]	Cleaned, debrided	Cleaned, debrided, MLCT bandage (Coban2, 3M St. Paul, MN) applied at every visit.	EpiFix (1 or 2 applications) plus MLCT: The dHACM was applied once in the 1 dHACM application treatment group at day 0 and applied twice in the 2 dHACM applications treatment group at day 0 and week 2.	MLCT: see SOC	Topical antimicrobials or oral antibiotics were permissible, but topical antibiotics were not.

Study	Prior Wound Therapy	Standard of Care	Skin Substitute Treatment	Control Wound Treatment	Comorbidities Treatment
Harding et al. 2013[31]	Debridement, saline rinse, and standard dressing regimen, including 4-layer compression bandaging. Wounds were covered with a nonadherent dressing (Dermanet®, DeRoyal, Powell, TN). Deeper ulcers received gauze on top of the Dermanet. Heavily exuding ulcers could receive additional absorbent dressings at the investigator's discretion. Dressings were changed weekly or earlier if clinically indicated.	Identical to prior wound therapy	Dermagraft plus 4-layer compression therapy: applied weeks 0, 1, 4, and 8. Cut to fit the shape of the ulcer (accommodating any epithelial islands) then placed into the wound bed with no overlap onto the intact skin surrounding the ulcer and smoothed to ensure that the entire piece of Dermagraft was in contact with the wound surface.	4-layer compression therapy: using the Profore™ 4-layer compression system (Smith & Nephew, Hull, UK)	NR
Zelen et al. 2013[36]	No	Debridement, appropriate moist wound therapy (Silvasorb gel and Aquacel AG), a compression dressing, and offloading with a removable cast walker (Active Offloading Walker; Darco, Huntington, WV)	EpiFix, a dehydrated amniotic membrane allograft: applied and covered with a nonadherent dressing (Adaptic®), followed by a moisture-retentive dressing (hydrogel bolster) and a compression dressing. Weekly dressing changes and EpiFix applications weeks 2, 4, 6, 8, and 10, if nonhealing ulcer.	See SOC	NR

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

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

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between Group Difference
Bianchi et al. 2018[35]	Wounds closed at 12 weeks (number, %)	100% reepithelialization without drainage	31/52 (60%) EpiFix plus multilayer compression therapy	20/57 (35%) SOC (dressings and multilayer compression therapy alone)	p=0.0128
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	37/52 (71%)	25/57 (44%)	p=0.00625
	Average time to wound closure (Kaplan-Meier analysis: time to heal within 12 weeks)	N/A	NR	NR	Significantly improved time to healing using EpiFix (log-rank p=0.0110)
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Zelen et al. 2018[44]	Wounds closed at 6 weeks (number, %)	Complete (100%) reepithelialization without drainage and need for dressing	27/40 (68%) AlloPatch Pliable (human reticular acellular dermal matrix)	6/40 (15%) SOC	$p=2.7 \times 10^{-6}$ (statistically significant)
	Wounds healed after 6 weeks (12 weeks) (number, %)	N/A	32/40 (80%)	12/40 (30%)	$p=8.4 \times 10^{-6}$ (statistically significant)
	Average time to wound closure at 6 weeks (days[95% CI])	N/A	27 days (95% CI: 23 to 32)	41 days (95% CI: 39 to 42)	$p=9.9 \times 10^{-7}$
	Average time to wound closure at 12 weeks (days[95% CI])	N/A	38 days (95% CI: 29 to 47)	72 days (95% CI: 66 to 79)	$p=3.9 \times 10^{-7}$ (statistically significant)
	Number of patients with infected wounds and increase in wound size	N/A	6/40 (15%) infections requiring hospitalization and IV antibiotic	2/40 (5%) infections requiring hospitalization and IV antibiotic	NR
	Other wound healing outcomes Average number of grafts at 6 weeks (weeks[SD])	N/A	3.4±2.1	N/A	N/A
	Average number of grafts at 12 weeks (weeks[SD])	N/A	4.7±3.4	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between Group Difference
	Hospitalization	N/A	3 from infection	5 from infection	NR
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Alvarez et al. 2017[40]	Wounds closed at 12 weeks (number, %)	Complete epithelialization without drainage or dressings required by 16 weeks.	10/11 (91%) MatriStem Wound Matrix*	2/6 (33%) SOC	p=0.041
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	11/11 (100%)	5/6 (83%)	p value NR
	Average time to wound closure (days[SD])	N/A	62.4 days	92.8 days	p=0.031
	Number of patients with infected wounds and increase in wound size	N/A	Local wound infection reported in 6 patients (arm unspecified)	Local wound infection reported in 6 patients (arm unspecified)	N/A
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence at 1 year	N/A	1/11 (10%)	3/6 (50%)	p value NR
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Alvarez et al. 2017[49]	Wounds closed at 12 weeks (number, %)	NR	66.6% Hyalomatrix Wound Matrix plus compression	14.2% SOC (nonadherent primary dressing plus a multilayer compression bandage)	p=0.066
	Wounds healed after 12 weeks (16 weeks) (number, %)	N/A	87.5%	42.8%	p=0.059
	Average time to wound closure (days)	N/A	41	104	p=0.029
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	NR	NR	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between Group Difference
DiDomenico et al. 2016[45]	Wounds closed at 6 weeks (number, %)	Complete (100%) epithelialization without drainage and need for dressing	14/20 (70%) Amnioband (dehydrated human amnion and chorion allograft)	3/20 (15%) SOC	p=0.001; Cohen's d: 1.3; OR 17, 95% CI: 3.1 to 93; p=0.001
	Wounds healed after 6 weeks (12 weeks) (number, %)	N/A	17/20 (85%)	5/20 (25%)	p value NR
	Average time to wound closure at 6 weeks (days[95% CI])	N/A	30 days (95% CI: 24 to 35)	40 days (95% CI: 37 to 43)	p=0.00073
	Average time to wound closure at 12 weeks (days[95% CI])	N/A	36 days (95% CI: 27 to 46)	70 days (95% CI: 59 to 81)	p=0.00073
	Number of patients with infected wounds and increase in wound size	N/A	1 (5%) infection only	1 (5%) infection only	N/A
	Other wound healing outcomes Average number of grafts per wound at 6 weeks	N/A	3.1±1.7	N/A	N/A
	Average number of grafts per wound at 12 weeks	N/A	3.8±2.2	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	0	2	NR
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Snyder et al. 2016[46]	Wounds closed at 6 weeks (number, %)	100% complete skin reepithelialization without drainage or dressing requirements	5/15 (35%) AmnioExcel dehydrated amniotic membrane allograft	0/14 (0%) SOC	p=0.0170, 95% CI of responder ratio: 25.0 to 46.4 AmnioExcel, 0.00 to 0.00 SOC; p=0.0407
	Wounds healed after 6 weeks (number, %)	N/A	NR	NR	N/A
	Average time to wound closure (weeks[SD])	N/A	NR	NR	Statistically significantly shorter time to closure with AmnioExcel (p<0.0001; Kaplan-Meier analysis)
	Number of patients with infected wounds and increase in wound size	N/A	1 (6.7%) wound infection	1 (7/1%) diabetic foot infection	N/A
	Other wound healing outcomes Total number of grafts (mean±SD)	N/A	4.3±1.7; 1 piece applied weekly (7.3±0.6 days)	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between Group Difference
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Driver et al. 2015[47]	Wounds closed at 12 weeks (number, %); 16 weeks was end of treatment phase	100% reepithelialization of the wound surface with no discernable exudate and without drainage or dressing requirements	70/154 (45%) Integra Dermal Regeneration Template (IDRT)	31/153 (20%) SOC	p<0.001 OR 3.3, 95% CI: 2.0 to 5.4; p<0.001
	Wounds healed after 12 weeks (16 weeks, end of treatment) (number, %)	N/A	79/154 (51%) IDRT	49/153 (32%) SOC	p=0.001 OR 2.2, 95% CI: 1.4 to 3.5; p=0.001
	Median time to wound closure (days)	N/A	43	78	NR
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	N/A
	Other wound healing outcomes Median number of grafts/patient	N/A	1 (range, 1 to 15)	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence at end of followup phase (28 weeks)	N/A	19%	26%	p=0.32
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	Significant difference in body pain favoring Integra (p=0.033)
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Lavery et al. 2014[39]	Wounds closed at 12 weeks (number, %)	100% reepithelialization with no wound drainage	31/50 (62.0%) Grafix	10/47 (21.3%) SOC	p=0.0001 OR 6.037, 95% CI: 2.449 to 14.882
	Wounds healed after 12 weeks (24 weeks) (number, %)	N/A	NR	NR	N/A
	Median time to wound closure (days)	N/A	42.0	69.5	p=0.019
	Probability of complete wound closure (Kaplan-Meier analysis)	N/A	67.1%	27.1%	Log-Rank, p<0.0001
	Number of patients with infected wounds and increase in wound size	N/A	9/50 (18.0%) infections only	17/47 (36.2%) infections only	p=0.044
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	NR	NR	N/A
	Amputation	N/A	0 (0%)	1 (2.1%)	NS

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control	Between Group Difference
	Recurrence	N/A	5/28 (17.8%); report 31 healed, provide data only on 28/31 patients	3/10 (30%)	p=0.42
	Hospitalizations related to infections	N/A	6%	15%	p=0.15
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	NR	NR	N/A
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A
Serena et al. 2014[37]	Wounds closed at 4 weeks (number, %)	100% epithelialization without drainage	6/53 (11.3%) EpiFix plus MLCT	4/51 (7.8%) MLCT	NR
	Wounds healed after 4 weeks (20 weeks) (number, %)	N/A	NR	NR	N/A
	Average time to wound closure (weeks[SD])	N/A	NR	NR	N/A
	Number of patients with infected wounds and increase in wound size	N/A	1 infection and increase drainage and abscess	2 infections only and 1 maceration around the wound with increased drainage	NR
	Other wound healing outcomes Average number of grafts (weeks[SD])	N/A	26 patients received 1 application of EpiFix at day 0. 27 patients received 2 applications of EpiFix at day 0 and week 2.	N/A	N/A
	Amputation	N/A	NR	NR	N/A
	Recurrence	N/A	NR	NR	N/A
	Hospitalization	N/A	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A
	Pain	N/A	Of 89.8% reporting pain at randomization, 79.5% reported a reduction	Of 75.0% reporting pain at randomization, 52.4% reported a reduction	NR
	Exudate	N/A	NR	NR	N/A
	Odor	N/A	NR	NR	N/A

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

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

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Bianchi et al. 2018[35]	EpiFix plus multilayer compression therapy (n=52)	0	0	0	0	0	Severe AE: 9 EpiFix, 4 SOC; p=0.140
	SOC (dressings and multilayer compression therapy alone) (n=57)	0	0	0	0	0	
Zelen et al. 2018[44]	AlloPatch Pliable (human reticular acellular dermal matrix) (n=40)	0	0	0	0	0	Serious AEs: 3 AlloPatch Pliable, 6 SOC 8 of the 9 SAEs were due to diabetic foot infections that required hospitalization and IV antibiotics. 1 SAE occurred in the SOC arm was due to an acute Charcot foot. 7 nonserious AEs also occurred but were not related to treatment.
	SOC (n=40)	0	0	0	0	0	
Alvarez et al. 2017[40]	MatriStem Wound Matrix* (n=11)	See general comments	0	See general comments	0	0	AEs included local wound infection (n=6), and dermatitis (n=4). Serious AEs included cellulitis (n=1), urinary tract infection (n=1), and congestive heart failure (n=1). Authors indicated no events were related to the intervention.
	SOC (n=6)	See general comments	0	See general comments	0	0	
Alvarez et al. 2017[49]	Hyalomatrix Wound Matrix plus compression (n=9)	NR	NR	NR	NR	NR	NR
	SOC (nonadherent primary dressing plus a multilayer compression bandage) (n=7)	NR	NR	NR	NR	NR	
DiDomenico et al. 2016[45]	Amnioband (dehydrated human amnion and chorion allograft) (n=20)	0	0	0	1	0	1 serious AE occurred in each arm. Both involved foot infection that progressed to osteomyelitis. 4 adverse events occurred (1 dHACA, 3 SOC).
	SOC (n=20)	0	0	0	1	0	
Snyder et al. 2016[46]	AmnioExcel dehydrated amniotic membrane allograft (n=15)	0	0	0	1 (6.7%)	0	1 wound infection (AmnioExcel), 1 diabetic foot infection (SOC), and 1 localized infection (AmnioExcel) were reported. Deep vein thrombosis occurred in 1 patient (SOC).
	SOC (n=14)	1 (7.1%)	0	0	0	0	
Driver et al. 2015[47]	Integra Dermal Regeneration Template (IDRT)	0	0	0	0	0	Significantly more severe AEs (15.6% IDRT vs. 26.8% SOC; p=0.016) and moderate AEs in SOC (31.8% IDRT vs. 42.5% SOC; p=0.053). Potentially study-related AEs were noted as similar (7/154 [4.5%] Integra vs. 8/153 [5.2%] SOC).
	SOC	0	0	0	0	0	
Lavery et al. 2014[39]	Grafix (n=50)	0	0	0	0	0	At least 1 AE occurred in fewer patients receiving Grafix (44% vs. 66%; p=0.031).
	SOC (n=47)	0	0	0	0	0	

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Serena et al. 2014[37]	EpiFix plus MLCT (n=53)	2	0	0	0	0	In EpiFix plus MLCT arm, 2 cases of cellulitis on the affected extremity, 1wound infection, and 1 wound with increased drainage and abscess. In MLCT arm, AEs of 5 patients included maceration around the wound with increased drainage and 2 wound infections.
	MLCT (n=51)	0	0	0	0	0	

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

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

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

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

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

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Harding et al. 2013[31]	Dermagraft plus 4-layer compression therapy (n=187)	12 (6.4%)	0	10 (5.3%)	0	13 (7%)	Study site infection: 43 (23%) Dermagraft plus 4-layer compression therapy, 46 (26%) 4-layer compression therapy Wound infection (purulence and/or odor): 55 (29.4%) Dermagraft plus 4-layer compression therapy, 43 (24.0%) 4-layer compression therapy Serious/severe AE: 24 Dermagraft plus 4-layer compression therapy, 33 four-layer compression therapy
	4-layer compression therapy (n=179)	18 (10.1%)	0	6 (3.4%)	0	5 (2.8%)	

AE = adverse event

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

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Skin Substitute	Control	Between Group Difference (versus SOC)
Cazzell et al. 2017[48]	Wounds closed at 16 weeks (number, %); ITT population	100% reepithelialization without drainage or dressing requirements confirmed at 2 consecutive study visits 2 weeks apart	66% DermACELL single-application	NR for GraftJacket	37.7% SOC	HR: 1.918, 95% CI: 1.139 to 3.23; p=0.0093 No significant differences for GraftJacket vs. SOC or DermACELL vs. GraftJacket (data not reported).**
	Wounds healed at 24 weeks (number, %); ITT population	N/A	70.0%	NR for GraftJacket	49.3%	HR 1.589; 95% CI: 0.9824 to 2.572; p=0.0442
	Average time to wound closure (weeks [SD])	N/A	NR	NR	NR	N/A
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR	NR	N/A
	Other wound healing outcomes Average number of grafts*	N/A	NR	NR	NR	N/A
	Amputation	N/A	NR	NR	NR	N/A
	Recurrence* (for ITT)	N/A	NR	NR	NR	N/A
	Hospitalization	N/A	NR	NR	NR	N/A
	Return to function or activities of daily living	N/A	NR	NR	NR	N/A
	Pain	N/A	NR	NR	NR	N/A
	Exudate	N/A	NR	NR	NR	N/A
	Odor	N/A	NR	NR	NR	N/A

*Data not included for average number of grafts and recurrence since they were based on the "per protocol population." For recurrence, data for percentage of healed wounds that remained closed at post-termination visits were missing for 48.5% of patients.
**Authors noted that statistical significance was not sought or expected for the GraftJacket arm.
CI = confidence interval; HR = hazard ratio: ITT = intent-to-treat; NR = not reported; SD = standard deviation; SOC = standard of care

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

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Cazzell et al. 2017[48]	DermACELL (n=71)	0	1*	0	5.6%	0	Serious treatment-related adverse events: 28.2% DermACELL, 28.6% Graftjacket, 27.9% SOC
	GraftJacket (n=28)	0	0	0	10.7%	0	
	SOC (n=68)	0	0	0	5.9%	0	

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

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

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Skin Substitute	Control	Between Group Difference
Ananian et al. 2018[32]	Wounds healed at 8 weeks (number, %) per protocol population	100% reepithelialization	15/31 (48.39%) GrafixPrime	12/31 (38.71%) Dermagraft	N/A	Estimated difference in percent: 9.68%, 90% CI: -10.67% to 28.94%*
	Wounds ≤5 cm^2 healed at 8 weeks (number, %) Per protocol population	N/A	13/16 (81.3%)	6/16 (37.5%)	N/A	p=0.0118
	Wounds >5 cm^2 healed at 8 weeks (number, %) Per protocol population	N/A	NR	NR	N/A	p=0.2148
	Average time to wound closure (days [SE]) Per protocol population	N/A	38	31	N/A	p=0.2016
	Number of patients with infected wounds and increase in wound size - ITT	N/A	5/38 (13.1%) osteomyelitis or cellulitis	2/37 (5.4%) infections (1 osteomyelitis and 1 cellulitis)	N/A	NR
	Other wound healing outcomes Average number of grafts	N/A	5.3	4.0	N/A	NR
	Amputation	N/A	NR	NR	N/A	N/A
	Recurrence	N/A	NR	NR	N/A	N/A
	Hospitalization	N/A	NR	NR	N/A	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A	N/A
	Pain	N/A	NR	NR	N/A	N/A
	Exudate	N/A	NR	NR	N/A	N/A
	Odor	N/A	NR	NR	N/A	N/A
Frykberg et al. 2016[34]	Wounds closed at day 56 (number, %)	Complete reepithelialization with no wound drainage present and no dressing required.	5 (18.5%) MatriStem	2 (6.9%) Dermagraft	N/A	p=0.244
	Wounds healed at day 70 (10 weeks) (number, %)	N/A	7 (25.9%)	9 (31.0%)	N/A	p=0.768
	Average time to wound closure (days [SE])	N/A	69.817±3.271	65.738±1.910	N/A	p=0.523
	Number of patients with infected wounds and increase in wound size	N/A	1 of 27 (3.7%) infected	2 of 29 (6.9%) infected	N/A	NR

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Skin Substitute	Control	Between Group Difference
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	NR	NR	N/A	N/A
	Other wound healing outcomes Change in wound size over 8 week treatment period (cm^2, 8 weeks)	N/A	-2.277	-0.792	N/A	p=0.762
	Amputation	N/A	NR	NR	N/A	N/A
	Recurrence at 6 months (10 patients reporting)	N/A	Of the 5 returning, 1 reoccurred (20%). Of the 7 healed at 70 days, 1 reoccurred (14.2%)	Of the 5 returning, 2 reoccurred (40%). Of the 9 healed at 70 days, 2 reoccurred (22.2%)	N/A	NS
	Hospitalization	N/A	NR	NR	N/A	N/A
	Return to function or activities of daily living	N/A	NR	NR	N/A	N/A
	Pain	N/A	NR	NR	N/A	N/A
	Exudate	N/A	NR	NR	N/A	N/A
	Odor	N/A	NR	NR	N/A	N/A
Zelen et al. 2016[38]	Wounds closed at 12 weeks (number, %)	Complete (100%) reepithelialization without drainage or need for dressing	24 (73%) Apligraf	31 (97%) EpiFix	18 (51%) SOC	Adjusted p=0.00019
	Wounds healed after 12 weeks (20 weeks)(number, %)	N/A	NR	NR	NR	N/A
	Average time to wound closure (days [95% CI])	N/A	47.9 (95% CI: 38.2 to 57.7)	23.6 (95% CI: 17.0 to 30.2)	57.4 (95% CI: 48.2 to 66.6)	Adjusted p=3.2×10^{-7}
	Number of patients with infected wounds and increase in wound size	N/A	7 overall infections were reported; 5 not attributed to a product	7 overall infections were reported; 5 not attributed to a product	2 infections	N/A
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	5.9±3.6	3.4±2.9	N/A	0.003
	Amputation	N/A	NR	NR	NR	N/A
	Recurrence	N/A	NR	NR	NR	N/A
	Hospitalization	N/A	1 unrelated to product	1 unrelated to product	2	N/A
	Return to function or activities of daily living	N/A	NR	NR	NR	N/A
	Pain	N/A	NR	NR	NR	N/A
	Exudate	N/A	NR	NR	NR	N/A
	Odor	N/A	NR	NR	NR	N/A

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

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

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Ananian et al. 2018[32]	GrafixPrime (n=38)	5 cellulitis and osteomyelitis	0	0	0	0	Serious AEs: 4 GrafixPrime, 7 Dermagraft Of SAEs, number index ulcer-related: 2 (50%) GrafixPrime, 6 (85.7%) Dermagraft
	Dermagraft (n=37)	1	0	0	1	0	
Frykberg et al. 2016[34]	MatriStem (n=27)	3 (11.1%)	0	0	1 (3.7%)	0	Wound infection: 1 (3.7%) MatriStem, 2 (6.9%) Dermagraft 1 death due to cerebrovascular accident was not considered product related. Overall incidence of AEs was reported as comparable (29.6% MatriStem, 34.5% Dermagraft), and none were reported as device- or procedure-related. Number of subjects with at least 1 AE: 8 (29.6%) MatriStem, 10 (34.5%) Dermagraft. AE severity was reported as mild (2 MatriStem, 5 Dermagraft), moderate (4 in each arm), and severe (2 MatriStem, 1 Dermagraft)
	Dermagraft (n=29)	1 (3.4%)	0	0	1 (3.4%)	0	
Zelen et al. 2016[38]	Apligraf (n=33)	0	0	0	0	0	7 wound/foot infections were reported; 2 in SOC arm. 4 serious AEs included 2 hospitalizations in SOC arm for wound infections (1 diagnosed with osteomyelitis later withdrew). 1 patient each was hospitalized for a urinary tract infection (Apligraf) and a car accident (EpiFix).
	EpiFix (n=32)	0	0	0	0	0	
	SOC (n=35)	0	0	0	1	0	

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

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

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Towler et al. 2018[30]	Wounds closed at 12 weeks (number, %)	100% epithelialization without drainage	75% Apligraf	93.3% Theraskin; p=0.294
	Wounds healed after 12 weeks (20 weeks) (number, %)	N/A	83.3%	93.3%; p=0.569
	Average time to wound closure (weeks [SD])	N/A	NR	NR
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR
	Other wound healing outcomes Average number of grafts (weeks [SD])	N/A	3.33	2.27; p=0.119
	Amputation	N/A	NR	NR
	Recurrence	N/A	NR	NR
	Hospitalization	N/A	NR	NR
	Return to function or activities of daily living	N/A	NR	NR
	Pain	N/A	NR	NR
	Exudate	N/A	NR	NR
	Odor	N/A	NR	NR

Study	Outcome	Definition and Method of Determining Outcome	Skin Substitute	Control
Sanders et al. 2014[33]	Wounds closed at 12 weeks (number, %)	100% epithelialization without drainage	4 (33.3%) Dermagraft	7 (63.6%) Theraskin; p=0.0498
	Wounds healed after 12 weeks (20 weeks) (number, %)	N/A	66.67%	90.91%; p=0.4282
	Average time to wound closure (weeks [SD])	N/A	12.5 (range, 7 to 20)	8.9 (range, 5 to 20); p=0.0323
	Number of patients with infected wounds and increase in wound size	N/A	NR	NR
	Other wound healing outcomes Average number of grafts (weeks [SD]): healing wounds	N/A	8.92 (range, 6 to 12)	4.36 (range, 2 to 7); p<0.0001, SE 0.77584
	Average number of grafts (weeks [SD]): non-healing wounds	N/A	12	6
	Amputation	N/A	NR	NR
	Recurrence	N/A	NR	NR
	Hospitalization	N/A	NR	NR
	Return to function or activities of daily living	N/A	NR	NR
	Pain	N/A	NR	NR
	Exudate	N/A	NR	NR
	Odor	N/A	NR	NR

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

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

Study	Group	Cellulitis	Death	Dermatitis	Osteomyelitis	Peripheral Edema	General Comments
Towler et al. 2018[30]	Apligraf (n=12)	0	0	0	0	0	None
	Theraskin (n=15)	0	0	0	0	0	
Sanders et al. 2014[33]	Dermagraft (n=12)	0	0	0	0	0	Dermagraft: maceration around the wound (2 patients) Theraskin: erythema (1 patient)
	Theraskin (n=11)	0	0	0	0	0	

Table C-31. Risk-of-bias assessments for 17 primary studies (rated as low, moderate, or high risk)

Study	1	2	3	4	5	6	7	8	9	10	Risk of Bias
Ananian et al. 2018[32]	Y	N	Y	N	N	N	N	N	Y	Y	Moderate
Bianchi et al. 2018[35]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Low
Towler et al. 2018[30]	Y	Y	N	N	N	Y	N	N	Y	Y	Moderate
Zelen et al. 2018[44]	Y	Y	N	N	N	Y	Y	N	Y	Y	Moderate
Alvarez et al. 2017[40]	N	N	N	N	N	Y	N	Y	Y	Y	Moderate
Alvarez et al. 2017[49]	N	N	N	Y	N	Y	N	N	Y	Y	Moderate
Cazzell et al. 2017[48]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Low
DiDomenico et al. 2016[45]	Y	Y	N	N	N	Y	Y	N	Y	Y	Moderate
Frykberg et al. 2016[34]	N	N	N	N	N	Y	Y	Y	Y	Y	Moderate
Snyder et al. 2016[46]	Y	Y	N	N	N	Y	N	N	Y	Y	Moderate
Zelen et al. 2016[38]	Y	Y	N	Y	N	Y	Y	N	Y	Y	Low

Study	1	2	3	4	5	6	7	8	9	10	Risk of Bias
Driver et al. 2015[47]	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Low
Lavery et al. 2014[39]	N	N	N	Y	Y	Y	Y	Y	Y	Y	Low
Sanders et al. 2014[33]	Y	Y	N	N	N	Y	N	N	Y	Y	Moderate
Serena et al. 2014[37]	Y	Y	N	Y	Y	Y	N	N	Y	Y	Low
Harding et al. 2013[31]	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Low
Zelen et al. 2013[36]	N	N	N	Y	Y	Y	N	N	Y	Y	Moderate

N = no; Y = yes

Appendix D. Commercially Available Skin Substitutes Products

Table D-1. Acellular/Dermal replacement from human cadaver dermis (13 products in this category)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
AlloPatch HD® Acellular Dermal Matrix	Musculoskeletal Transplant Foundation - MTF Biologics Edison, NJ, USA	AlloPatch HD is human allograft skin minimally processed to remove epidermal and dermal cells. The process preserves the extracellular matrix of the dermis. AlloPatch HD is aseptically processed and is not terminally sterilized. AlloPatch HD is processed to remove cells while maintaining the integrity of the matrix to address the issues of the specific and nonspecific inflammatory responses. It is used to replace damaged or inadequate integumental tissue or to repair, reinforce, or supplement soft-tissue defects.	"Allopatch HD is minimally processed, which better preserves and maintains the graft's natural biomechanical and biochemical properties. Unlike other ECMs [extracellular membranes] that need to be hydrated for 60 minutes or more before being used, delaying procedure completion and prolonging OR time, Allopatch HD requires no refrigeration or hydration and is ready to use off the shelf almost immediately." 3-year shelf life at ambient temperature.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
AlloPatch® Pliable	Musculoskeletal Transplant Foundation - MTF Biologics	AlloPatch Pliable is an aseptically processed human reticular dermal tissue for use as a chronic or acute wound covering.	"AlloPatch Pliable tissue is processed from deep cut tissue from which the epidermal layer has been physically removed. The process utilized preserves the extracellular matrix of the dermis. The resulting allograft serves as a framework to support cellular repopulation and vascularization at the surgical site. Open tissue architecture optimal for cell infiltration and host tissue remodeling." 3-year shelf life at ambient temperature.	Regulated by FDA as human tissue for transplantation. in accordance with the FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Alloskin™ AC Acellular Dermal Matrix	AlloSource, Centennial, CO, USA	AlloSkin AC is a meshed dermis-only human skin graft that has been decellularized while preserving the natural biologic components and structure of the dermal matrix.	"The graft provides a favorable microenvironment for bio-ingrowth to begin revascularization and cellular repopulation. Single application often sufficient to potentially help stimulate the wound healing process. Ready-to-use off the shelf. Pliable and stretchable for contouring to wound topography and maintenance of wound bed contact. Robust enough to suture or staple. Meshed (1:1) encouraging fluid drainage from wound" Ready-to-use, shelf-stable graft with room temperature storage, eliminating the need for costly cryo freezers	Regulated by FDA as human tissue for transplantation. in accordance with the FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
AlloSkin™ RT	AlloSource	AlloSkin RT meshed human dermal graft is a sterile skin graft with broad clinical applications for acute and chronic wound therapy.	"Skin allografts mechanically protect the wound and provide biologic factors native to human skin, which may help stimulate the wound healing process. AlloSource's process uses electron beam irradiation to yield a ready-to-use, shelf-stable graft with room temperature storage, eliminating the need for costly cryo freezers. Pliable and stretchable, AlloSkin RT allows graft contouring to wound topography, yet is robust enough to suture or staple graft without tearing. In addition, 1:1 meshing encourages exudate drainage from wound, allowing the graft to be secure to the surface and avoid 'floating'." Ready-to-use, shelf-stable graft with room temperature storage, eliminating the need for costly cryo freezers	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Dermacell® Human Acellular Dermal Matrix. Dermacell AWM is intended for chronic wounds.	LifeNet Health®, Virginia Beach, VA, USA	Dermacell is a technologically advanced human acellular dermal matrix. Dermacell is decellularized using Matracell®, a proprietary and patented technology that removes ≥97% of donor DNA without compromising the graft's desired biomechanical or biochemical properties and allows for rapid cellular infiltration and revascularization.	"Dermacell is ready to use out of the package and stored at room temperature, eliminating the need for refrigeration and rehydrating processes. As a final step, all Dermacell grafts are terminally sterilized - rendering the graft sterile to medical device-grade standards with a SAL of 10-6." "Facilitates cell proliferation and migration, critical for wound management." Ready-to-use, room temperature storage,	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Dermapure®	Tissue Regenix Group, San Antonio, TX, USA	DermaPure is a decellurized human dermis product. DermaPure works by taking human, cadaveric skin and removing the nucleated cells and cellular debris, using the patented dCELL® Technology process to create a natural biological scaffold that is up to 99% DNA-free.	"The decellularized dermal allograft aids the natural healing process by providing an environment that supports cell migration to facilitate the body's repair, or replacement, of damaged or inadequate integumental tissue. DermaPure maintains the structure and biochemical characteristics of native dermis, fully integrating into the wound bed after application. It provides a scaffold into which the recipient's cells can grow, becoming vascularized and supporting the generation of a new epithelial layer, ultimately regenerating native skin." Ambient temperature storage.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
DermaSpan™ Acellular Dermal Matrix	Zimmer Biomet. (manufactured by Biomet Orthopedics, Warsaw, IN, USA)	DermaSpan Acellular Dermal Matrix is derived from allograft human skin and carefully processed to offer biocompatibility as well as biomechanical strength. DermaSpan ACD can be used in various practices, including orthopedics, plastic surgery, and general surgery, to repair or replace damaged or inadequate integumental tissue (wound coverage).	"DermaSpan Acellular Dermal Matrix is very carefully processed to offer biocompatibility as well as biomechanical strength in tendon coverage or reinforcement and wound coverage procedures. DermaSpan Acellular Dermal Matrix has the added advantage of being supplied sterile…unlike many other dermal allograft products." Does not need refrigeration.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
FlowerDerm™	Flower Orthopedics, Horsham, PA, USA	FlowerDerm is a meshed dermis-only decellularized human skin graft that preserves the natural biologic components and structure of the dermal matrix. The graft provides a favorable environment for revascularization and cellular repopulation.	"A single application of this product is often sufficient to stimulate the wound healing process. The pliable, flexible material adheres to wound topography and maintains contact with the wound bed. It's also durable enough to suture or staple and has a mesh construction to encourage fluid drainage. FlowerDerm is ready for use right off the shelf." Stored at room temperature, 2-year shelf life.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
GammaGraft™	Promethean LifeSciences, Inc., Pittsburgh, PA, USA	GammaGraft is an irradiated human skin allograft storable at room temperature. Used as a temporary skin graft on burns and chronic wounds.	"GammaGraft has unrivalled ease of use and safety and provides one of the easiest biological grafts for patient compliance. Promethean's proprietary technology sterilizes and preserves the tissues. This technique leads to safer grafts as well as ones that are easier to handle and use. Many doctors and nurses are skeptical that GammaGraft can be used without any other wound coverings after the GammaGraft has dried on the wound. This is possible because GammaGraft has a natural keratin layer that acts as a vapor barrier for the wound. This allows for moist wound healing and a moist wound bed, even though the GammaGraft is dry." Stored at ambient temperature	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
GraftJacket™ RTM	Wright Medical Group N.V., Memphis, TN, USA	GraftJacket Matrix is used to provide supplemental support, protection, and reinforcement of tendon and ligamentous tissue; to be used as a periosteal patch or covering; or for protection and support of bone and tendons in foot and ankle and hand surgery. It is a human dermal collagen matrix that is readily incorporated into the body. The matrix undergoes a patented process that renders the material essentially acellular and is freeze-dried with a proprietary process that prevents the formation of ice crystals to preserve the intact matrix, including vascular channels.	"The Graftjacket Matrix provides a scaffold for host cell repopulation, revascularization and, ultimately, conversion to host tissue. Coupled with excellent tensile and suture retention strength, the biological characteristics of the Graftjacket Matrix make it an excellent scaffold to reinforce primary soft-tissue repairs throughout the body while eliminating morbidity associated with harvesting autograft." Stored at room temperature, 2-year shelf life.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
hMatrix® ADM	Bacterin International, Inc., Belgrade, MT, USA	hMatrix ADM is an allograft derived from donated human skin. The dermis is processed using a proprietary method to remove the cells to maximize graft incorporation. The natural collagen and elastin matrix is ideal for neovascularization and cellular proliferation and has the potential to expedite the healing process. hMatrix ADM is provided as a sterile product with a device-level (SAL) of 10-6.	"The successful treatment of deep wounds often requires the use of a dermoconductive graft material to facilitate formation of granulation tissue and aid in wound closure. One such graft material used for this purpose is allograft-derived acellular dermis. ADM are used as a primary grafting material that can replace damaged or inadequate dermal tissue while helping to reduce the size of the wound and providing protection to the site of injury. • Superior suture retention strength. • Flexible matrix for precise placement. • Lower inflammatory response vs. competitors. • Distributed as a frozen product. • Sterility assurance level (SAL) 10-6 • 5 year shelf life • Frozen storage"	Regulated by the FDA as human tissue for transplantation. in accordance with the FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
IntegoPly®	Aziyo Biologics, Silver Spring, MD, USA	IntegoPly is human ACD processed to maintain the biologic and structural integrity of the tissue's extracellular matrix components, while delivering a SAL of 10^{-6}. Promoted for treating chronic wounds.	"Supports the repair or replacement of integumental tissue, as well as closure of chronic diabetic foot ulcers, venous leg ulcers and pressure wounds." • "Intact extracellular matrix that promotes tissue remodeling • Superior safety profile – over 20,000 applications with no adverse reactions reported"	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Matrix HD® Allograft	RTI Surgical, Alachua, FL, USA	Matrix HD allograft is an acellular human dermis allograft sterilized using the Tutoplast™ Tissue Sterilization process. This proprietary process retains the 3-dimensional intertwined multidirectional fibers and mechanical properties of the native dermis tissue.	"The Matrix HD graft provides a natural scaffold to support the body's regenerative process." "Sterile - Terminally sterilized to a SAL of $^{10-6}$. Validated viral inactivation. Biocompatible: Preserved vascular channels. Preserved key components of the native matrix." "Convenient: Room temperature storage. Five year shelf life. Simple, single-step rehydration."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

21 CFR = Code of Federal Regulations Title 21; ACD = acellular dermal matrix; ADM = acellular dermal matrix; FDA = U.S. Food and Drug Administration; OR = operating room; SAL = sterility assurance level

Table D-2. Acellular/Dermal replacement from human amniotic membrane (26 products in this category)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
AlloWrap®	AlloSource, Centennial, CO, USA	AlloWrap is a human amniotic membrane containing bioactive proteins that support wound healing.	"Strong, pliable tissue conforms to wound topography. Amniotic tissue is naturally rich in growth factors to support the healing process, and provides an immune-privileged barrier to support the patient's body in preventing inflammation and scar tissue generation. Available in a moist configuration (AlloWrap DS) or dry (AlloWrap Dry) designed for ease of handling in wound care placements. Room temperature storage, with two-year shelf life, no need for expensive cryo freezer storage."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
AltiPlast®	Aziyo Biologics, Silver Spring, MD, USA	AltiPlast is a cryopreserved placental matrix derived from human amniotic and chorionic membranes.	"AltiPlast provides a universal approach to treating complex, chronic wounds. Whether an irregular, tunneling or undermining wound, AltiPlast finds its way, reaching deep into the wound to treat hidden fissures. The matrix components intimately contact the wound bed to support closure. AltiPlast is adaptable and ready to integrate into your treatment approach." Frozen	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
AmnioBand® Allograft Placental Matrix	MTF Biologics, Edison, NJ, USA	AmnioBand is a minimally processed human allograft that retains the structural properties of the extracellular matrix. The resulting dehydrated allograft serves as a wound covering.	"Maintains inherent growth factors and matrix proteins essential to wound healing and host tissue remodeling. Aseptic processing preserves tissue's natural structure. Ready, right out of the package. Can be used in the hydrated or dehydrated state. Shelf life of three years at ambient temperature. Conforms to anatomy and maintains surface contact."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Amnioexcel®	Integra LifeSciences Corp. acquired Derma Sciences, Plainsboro, NJ, USA	Amnioexcel is dehydrated human amnion-derived tissue allograft with intact extracellular matrix intended for homologous use as a wound covering to aid in closing chronic wounds.	"The membrane forms a protective covering over the wound while providing the key components found in human amnion including an intact ECM, cytokines and other growth factors. It easily integrates into the wound and helps provide the optimal environment to repair, reconstruct and replace wound tissue." Room-temperature stable for 2 years	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
AmnioFill® Human Placental Tissue Allograft	MiMedx Group, Inc., Marietta, GA, USA	AmnioFill is a minimally manipulated, nonviable cellular tissue matrix allograft that contains multiple extracellular matrix proteins, growth factors, cytokines, and other specialty proteins present in placental tissue to help enhance healing.	"Human collagen matrix. Contains growth factors that modulate inflammation, reduce scarring, and enhance healing. Versatile tissue form provides a scaffold for ingrowth in acute and chronic wounds. Terminally sterilized for enhanced patient safety. PURION® processed to provide an effective allograft with excellent handling characteristics. 5 year shelf life stored at ambient conditions."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
AmnioFix® Amnion/Chorion Membrane Allograft	MiMedx Group	AmnioFix is a bioactive tissue matrix allograft composed of dehydrated human amnion/chorion membrane (dHACM) that preserves and contains multiple extracellular matrix proteins, growth factors, cytokines, and other specialty proteins. AmnioFix is intended for homologous use to reduce scar tissue formation, modulate inflammation, enhance surgical wound healing, and act as a barrier membrane.	"Acts as a barrier membrane. Reduces scar tissue formation. Modulates inflammation. Enhances healing. Terminally sterilized for enhanced patient safety. PURION® processed to provide an effective allograft with excellent handling characteristics. 5 year shelf life stored at ambient conditions."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Amniomatrix® Human Amniotic Suspension Allograft	Integra LifeSciences Corp. acquired Derma Sciences	Amniomatrix is a cryopreserved suspension allograft derived from the amniotic membrane and components of the amniotic fluid. It is cryopreserved using the patented CryoPrime™ processing method that preserves the structural properties of the collagen, cytokines, growth factors, ECM, and viable cellular materials. Amniomatrix is intended for homologous use to help supplement the recipient's tissue and aid in the closing of chronic wounds.	"The liquid based suspension is especially suited to help repair wounds where membrane products might not be as effective (i.e. tunneling or deep wounds)." Should be stored at -60°C or below	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products) AMNIOMATRIX® Human Amniotic Suspension Allograft is used for treating acute and chronic wounds, including diabetic foot ulcers, venous leg ulcers, arterial ulcers, pressure ulcers, inflammatory ulcers, and burns. See FDA letter June 2015.
Artacent® Wound	Tides Medical, Lafayette, LA, USA	Wound-specific, dual-layer amniotic tissue graft designed for enhanced efficacy and ease-of-use. Intended for chronic wounds.	"Artacent Wound is the only wound-specific amniotic patch that can be applied with either side facing the wound. Amniotic tissues are safe, natural biologic barriers, with native membranes supplying a wide array of growth factors. The unique design of Artacent Wound allows for easy manipulation and repositioning, making it a flexible, dependable option for a variety of wound covering applications." Dehydrated, storage at room temperature, shelf life greater than 2 years.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
BioDFactor® Viable Tissue Matrix	Integra LifeSciences Corp., originally BioD, LLC	BioDFactor Viable Tissue Matrix is a flowable tissue allograft derived from morselized amniotic tissue and components of the amniotic fluid.	"BioDFactor® Viable Tissue Matrix is a cryopreserved allograft derived from the human placental tissues. It has been developed for use as a wound covering in the treatment of localized tissue defects or areas of inflammation. Placental tissues are a rich source of collagen, elastin, fibronectin, and growth factors to support tissue repair and regeneration. Additionally, amniotic tissue has anti-adhesive and anti-microbial properties important in the treatment of soft tissue injuries." Maintain the product at -65°C or colder until immediately prior to use, 2 year shelf life	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products) See FDA letter June 2015.

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Biodfence®	Integra LifeSciences Corp., originally BioD, LLC	BioDFence® G3 and BioDDryFlex® are membrane allografts derived from the human placental tissues for use as a tissue barrier that covers and protects the underlying tissues. BioDFence G3 is a multilayer amnion and chorion allograft providing enhanced handling characteristics. BioDDryFlex is a single-layer amniotic allograft for applications in which bulk may not be optimal.	Website does not list any specific benefits for chronic wounds. Ambient temperature storage, terminally sterilized with a 5-year shelf life	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Biovance® Amniotic Membrane Allograft	Alliqua Biomedical, Langhorne, PA, USA	Biovance® is a decellularized, dehydrated human amniotic membrane (DDHAM) with a preserved natural epithelial basement membrane and an intact extracellular matrix structure with its biochemical components. The epithelial basement membrane and extracellular matrix of this allograft provide a natural scaffold that allows cellular attachment or infiltration and growth factor storage. Biovance provides a protective cover and supports the body's wound healing processes. Biovance is an allograft intended for use as a biological membrane covering that provides the extracellular matrix while supporting the repair of damaged tissue. It is intended for chronic wounds.	"The easy-to-use human amniotic membrane allograft with 5-year off-the-shelf convenience ease of application and wound visualization. The progenerative power of the amniotic membrane supports the body's natural ability to restore tissue to a pre-wound state. The natural function of the amniotic membrane brings protection and support to the wound it covers. BIOVANCE contains natural substances found in amniotic membrane tissue that support the body's ability to heal."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Cellasta Amniotic Membrane	Ventris Medical, Newport Beach, CA, USA	Cellesta Amniotic Membrane is a minimally manipulated, placental allograft product. The single-layered allografts are affixed to a poly mesh backing and can be sutured, glued, or laid over the desired tissue. Only the poly mesh is removed; either side of the graft may be applied to the target tissue. This natural human tissue scaffold with relevant, inherent characteristics can be used for therapeutic solutions.	"Cellesta is a natural human tissue scaffold that protects and cushions, just as it does in utero. Made up of growth factors, hyaluronic acid, cytokines, amino acids, and extracellular matrix proteins, it makes an attractive wound material." Store at ambient temperature.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Cygnus® Amnion Patch Allografts	Vivex Biomedical, Atlanta, GA, USA	Cygnus is applied as an anatomic barrier that helps provide mechanical protection while supporting healing with endogenous growth factors. The Cygnus proprietary process preserves the natural healing properties of amniotic tissue, maintaining inherent levels of key extracellular matrix molecules, growth factors, and cytokines.	"Requires no up-front preparation, and hydrates rapidly in the surgical site • Stored at ambient temperature with a 5-year shelf-life • Orientation stickers and notch in the upper left hand corner allow placement of the patch epithelial side up and stromal side down • E-Beam sterilization provides sterility assurance level (SAL) of 10-6."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Dermavest® and Plurivest® Human Placental Connective Tissue Matrix	Aedicell, Inc., Honeoye Falls, NY, USA	"Dermavest Human Placental Tissue Matrix (HPTM) is comprised of donated human placental tissue (placenta disc, amnion/chorion and umbilical cord) that has been particularized, processed to remove cells, cellular material and contamination, freeze-dried to remove moisture, pressed into a sheet then E-beam irradiated at a minimum 17.5 kGy with a validated sterilization process."	"Dermavest provides a scaffold to replace damaged or inadequate integumental tissue." Store at room temperature. 3-year shelf life.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Epicord®	MiMedx	"Epicord is a minimally manipulated, dehydrated, non-viable cellular umbilical cord allograft for homologous use. … EpiCord is processed using the PURION® PLUS process, a unique approach that provides an easy to use allograft stored at ambient conditions."	"EpiCord provides a protective environment for the healing process. Provides a connective tissue matrix to replace or supplement damaged or inadequate integumental tissue. 5 year shelf life stored at ambient conditions."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Epifix®	MiMedx	Epifix is a dehydrated human amnion/chorion membrane (dHACM) allograft. EpiFix is a bioactive tissue matrix allograft composed of dHACM that preserves and contains multiple extracellular matrix proteins, growth factors, cytokines, and other specialty proteins. Promoted to treat diabetic foot ulcers and venous leg ulcers.	• "Acts as a barrier membrane • Reduces scar tissue formation • Modulates inflammation • Enhances healing • Terminally sterilized for enhanced patient safety • Purion processed to provide an effective allograft with excellent handling characteristics • 5 year shelf life stored at ambient conditions"	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Floweramniopatch™ and Floweramnioflo™	Flower Orthopedics, Horsham, PA, USA	FlowerAmnioPatch is a dual-layer amniotic membrane allograft and FlowerAmnioFlo is a flowable amnion tissue allograft.	"FlowerAmnioPatch is a Ready-for-Surgery™, dual-layer amniotic membrane allograft with excellent handling characteristics. • Safe, natural covering that improves wound healing • Reduces inflammation • Adhesion barrier • Reduces scarring at surgical site • Decreases post-operative pain" Stored at room temperature	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Integra® BioFix® Amniotic Membrane Allograft	Integra LifeSciences	Integra BioFix and Integra BioFix Plus (BioFix) are sterile, human tissue allografts derived from allogeneic dehydrated and decellularized amniotic membrane. BioFix is intended for homologous use as a wound covering for surgical sites, voids, and tissue defects.	"BioFix Amniotic Allografts are carefully processed using HydraTek® technology, a proprietary process designed to preserve the natural structure and biological properties of the tissue, to provide ideal graft handling, strength, and performance." "Features & Benefits: • Omnidirectional Placement – Membranes can be implanted on either side to provide an effective covering and gliding surface over the tissue. • Foundation for Regeneration – The Extracellular Matrix contains collagen and other fibrous proteins that provide a structural scaffold to support cellular migration. Naturally occurring growth factors, fibronectin, integrins, laminins, and hyaluronic acid play a key role in cell proliferation, differentiation, and adherence to the scaffold." Store at ambient temperature.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Integra BioFix Flow Placental Tissue Matrix Allograft	Integra LifeSciences	Integra BioFix Flow is a sterile, human tissue allograft derived from decellularized particulate human placental connective tissue matrix. It is intended for homologous use as a connective tissue matrix.	"Features & Benefits: • Off-the-Shelf Storage – BioFix Flow can be stored at an ambient temperature for 5 years. • Reduces Inflammation, Scarring, and Pain – Amniotic tissues may reduce inflammation, fibrous tissue growth, and potential scar tissue formation. • Flexible Application ¬– BioFix Flow is ready to implant and precisely targets defects using a range of needle gauges for ease of implantation."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Interfyl™ Human Connective Tissue Matrix	Alliqua Biomedical, Langhorne, PA, USA	Interfyl is connective tissue matrix filler derived from the placenta of a healthy, full-term pregnancy. Available in flowable and particulate formulations.	"Support tissue regeneration in complex surgical spaces." "An adaptable filler of decellularized connective tissue matrix • Able to completely fill irregular spaces or soft tissue voids resulting from trauma, surgery, or aging • Allows for cell adherence and growth during tissue repair • Consists of natural human structural and biochemical extracellular matrix components • Adapts to local mechanical forces • Provides structural support while maintaining elasticity." Store in its original packaging in a clean, dry environment at an ambient room temperature.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Neox® Wound Allografts	Amniox Medical, Inc., Miami, FL, USA	Neox Wound Matrix is human Umbilical Cord and Amniotic Membrane, preserved to maintain the innate physical and biological properties of these tissues. Neox Wound Allograft is indicated for use as a wound covering for dermal ulcers and defects.	"The regenerative healing properties of Umbilical Cord and Amniotic Membrane delivered in a 1 mm thick allograft for superior handling and fixation, preserved using our patented Cryotek® process." Shelf life is two years from date of manufacture. Can be stored in a standard refrigerator or freezer at specified temperatures and specified times.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
NuShield®	Organogenesis, Inc., Canton, MA, USA	NuShield is a dehydrated placental allograft designed to protect and support healing in a variety of wound sizes and types.	"Organogenesis' proprietary BioLoc™ processing method results in less manipulation than other dehydrated amniotic allografts. This process preserves the native structure of the amnion and chorion membranes, and maintains the spongy/intermediate layer, which is an abundant source of proteoglycans, glycoproteins and hyaluronic acid. Through this process, NuShield is also optimized to provide excellent strength, flexibility, and handling." Five-year shelf life	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
PalinGen® Membrane & Hydromembrane	Amnio Technology LLC, Phoenix, AZ, USA	PalinGen Membrane and Hydromembrane are human allografts processed from healthy placental tissue. Placental tissue and membrane contain collagen substrates, growth factors, and extracellular matrix proteins recognized as part of the complex wound healing process.	• "Resorbable • Chorion free • Amnion membrane • Growth Factors • Cytokines • Amino Acids • Extracellular Matrix Proteins • Hyaluronic Acid • Available in a variety of sizes • Sterile • Room temperature (15° C to 30° C)"	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Revita®	StimLabs, LLC, Roswell, GA, USA	Revita is an intact human placental membrane allograft that preserves all layers of the biologic tissue and maintains the physiologic 3D architecture of the natural barrier membrane. Revita provides the complete intact human placental membrane that is the physiologic tissue barrier naturally found in the body. This complete barrier containing amnion, intermediate layer and chorion retains many of the cytokines, growth factors, extracellular components, and cell communication signals the body uses to heal, protect, and grow tissues.	"Using the Clearify™ processing method, Revita preserves all three layers of the amniotic membrane architecture." • "Freeze-dried • Never delaminated • Preserves intermediate layer which contains hyaluronic acid and additional proteins." "Revita contains many essential cytokines and growth factors."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
WoundEx® Membrane and WoundEx Flow	Skye Biologics, Inc., El Segundo, CA, USA	WoundEx Membrane is a FastActing® dehydrated amniotic membrane skin substitute, available in thin amnion-only WoundEx® 45 and thick chorion-based WoundEx 200. WoundEx Flow is a flowable human placental connective tissue matrix skin substitute. It is provided as a concentrated fluid in the vial and can be extended with saline or anesthetic to provide greater coverage throughout the entire wound.	"WoundEx® Membrane Product Benefits: Provides a native human placental BioActive® ECM, Various sizes minimize graft waste & cost, Adheres to wound bed without fixation, FastActing® Technology improves biologic response." Room temperature storage.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Xwrap® Amniotic Membrane-Derived Allograft	Applied Biologics™, Scottsdale, AZ, USA	Xwrap is a Chorion-Free amniotic membrane wrap, cover or patch.	"Xwrap ECM is a chorion-free, non-crosslinked soft-tissue wound covering which acts as a natural scaffold for cellular migration, attachment, and proliferation. It is a natural alternative to cadaveric or animal-derived products." "Xwrap® ECM is carefully processed to preserve the structural qualities of the amniotic membrane. Amnion is a native source of collagen types III, IV, V, and VII, as well as and fibronectin and laminin. It also contains fibroblasts and growth factors, modulates, cytokine and growth factor levels, and has been shown to have unique properties, including the ability to suppress pain, fibrosis, and bacteria, and to promote wound healing."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

21 CFR = Code of Federal Regulations Title 21; ECM = extracellular matrix; FDA = U.S. Food and Drug Administration; kGy = kilogray

Table D-3. Acellular/Dermal replacement from animal tissue source (22 products in this category)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Architect® stabilized collagen matrix	Harbor MedTech, Inc., Irvine, CA, USA	According to the company Architect is made from a widely available Xenograft commonly used in modern tissue heart valves and many other medical products. This tissue is homogeneous (over 95% type 1 collagen), durable, and porous. According to the 510(k) clearance document, Architect is made from decellularized equine pericardial tissue.	"Architect is the only ECM stabilized by the BriDGE® process which prevents premature degradation by the excess MMPs and other proteases found in chronic wounds. Because Architect® remains intact, its ECM healing properties remain intact, including: Helping to deactivate the inflammatory phase (which results in a reduction of MMPs, elastase, and other proteases). Helping to promote the proliferative/healing phase. Preserving cell signaling factors to trigger and accelerate healing. Providing an intact, durable scaffold for uninterrupted support of cellular growth and regeneration of native tissue." Freeze dried, stored at room temperature, long shelf life (actual length not reported)	Received 510(k) clearance as Architect Px Extracellular Collagen Matrix. Indicated for the local management of moderately to heavily exuding wounds including diabetic, venous, and pressure ulcers. Product code KGN. (K140367)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Bio-ConneKt® Wound Matrix	MLM Biologics, Inc., Alachua, FL, USA	Bio-ConneKt Wound Matrix is a collagen-based wound dressing for the local management of moderately to heavily exuding wounds. It is composed of reconstituted type I collagen that is stabilized, sterilized to SAL 10^{-6}, and stored at room temperature. Bio-ConneKt Wound Matrix is a sterile, conformable, and porous wound dressing made of reconstituted collagen derived from equine tendon. It is chemically crosslinked to provide resistance to enzymatic degradation. The dressing is provided sterile for single use only.	"bio-ConneKt Wound Matrix is succeeding at chronic wound resolution when other treatments fail. Its unique properties deliver a robust medical solution that handles several complications of the chronic wound environment such as senescent cells, corrupt scaffolding, poor oxygen and blood supply in addition to incessant infection and abnormal inflammatory response."	For the local management of moderately to heavily exuding wounds, including partial and full-thickness wounds, draining wounds, tunneling wounds, pressure sores/ulcer, venous ulcers, chronic vascular ulcers, diabetic ulcers. Product code KGN. (K140456)
Colla-pad	CoreLeader Biotech, New Taipei City, Taiwan	Colla-pad is made through lyophilization with bovine sourced collagen from Australia. It is type I collagen-enriched sponge.	"Biocompatible Australian bovine source Physical cross-linked Low risk of allergy More cost effective Free from chemical contamination"	Indicated for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers. Product code KGN. (K102946)
CollaSorb® collagen dressing	Hartmann USA, Rock Hill, SC, USA	CollaSorb is composed of 90% native collagen and 10% calcium alginate. • Sterile, noncytotoxic bovine-derived collagen. • Absorbs exudate up to 30 times its weight. • Reportedly easy to cut and apply.	Indicated for managing acute and chronic wounds	Indicated for management of full- and partial-thickness wounds including pressure, diabetic, and venous leg ulcers. Product code KGN (K091338)
CollaWound collagen sponge	Collamatrix Co., Ltd., Miaoli County, Taiwan	CollaWound wound dressing is a sterile, single-use, disposable wound dressing composed of cross-linked porous collagen matrix with yellow to off-yellow appearance and is supplied in sponge configuration. It forms a layer of thin film at the wound site and provides a biodegradable scaffold for the cell invasion and capillary growth (description from FDA 510[k] documents). Earlier 510(k) states the collagen is derived from porcine (K061474).	Collawound collagen sponge website provides no information on the device.	Used for the management of partial- and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds, first and second-degree bums, surgical wounds, draining wounds and trauma wounds. Product code KGN (K090894)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Collexa®	Innocoll Pharmaceuticals, Ireland	Collexa is a collagen matrix sponge with a polyurethane foam backing intended for topical use on wounds. The polyurethane foam is absorbent and acts as a reservoir for wound exudates (description in FDA 510(k). According to Innocoll their collagen products are made from bovine and equine Achilles tendons.	No product information on website.	Intended for management of wounds including diabetic, venous, and pressure ulcers. Product code KGN. (K100574)
Cytal® wound matrix	Acell, Inc., Columbia, MD, USA	Cytal is composed of porcine urinary bladder matrix (UBM). These products maintain an intact epithelial basement membrane. Cytal devices are appropriate for acute wounds and chronic wounds.	ACell's wound management products are medical devices that maintain and support a healing environment by facilitating remodeling of site-appropriate, functional tissue. Store in a clean, dry environment between 15°C-35°C (59°F-95°F) in unopened and undamaged package.	Intended for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, and diabetic ulcers. Product code KGN (K152721)
Endoform™ dermal template	Hollister Wound Care, Libertyville, IL, USA	Endoform Dermal Template contains a naturally derived ovine collagen ECM that is terminally sterilized and may be considered more culturally acceptable than other animal-derived sources.	"Broad spectrum MMP reduction • Advanced care accessible to all clinicians • Cost efficiency through weekly applications" Should be stored between 15ºC/59ºF–40ºC/104ºF in a clean and dry area.	Intended for single use treating the following wounds: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers. Product code KGN (K092096)
Excellagen®	Taxus Cardium Pharmaceuticals Group, San Diego, CA, USA	Excellagen is collagen gel composed of formulated, 2.6% (26 mg/mL) fibrillar bovine dermal collagen (type 1) that is topically applied directly to the wound surface.	"Excellagen is a flowable, formulated homogenate of purified bovine Type I dermal collagen with collagen's natural 3-dimensional fibrillar structure. Excelllagen promotes chemotaxis, cellular adhesion, migration and proliferation to stimulate granulation tissue formation. Excellagen is indicated for non-healing lower extremity ulcers in diabetic patients, and other dermal wounds and is intended for physician use during debridement procedures, which are used to promote and stimulate wound healing." Refrigerated 35-46°F (2-8°C) storage required	Intended for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers. Product code KGN (K110318)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
EZ Derm®	Mölnlycke Health Care, Norcross, GA, USA	EZ Derm is a porcine xenograft for partial skin loss injuries or as temporary cover.	"EZ Derm can be used for partial thickness skin loss injuries. EZ Derm can also be used as a temporary cover, or test graft, prior to autografting and as a protective covering over meshed autografts. EZ Derm maintains a protected moist wound environment during the healing process and aids the natural healing of the wound. It assists in controlling early wound exudates and assist in restoring water vapour function and heat loss. EZ Derm allows reepithelialization and growth of granulation tissue and reduces pain and fluid loss. It is a protective barrier by physical means and provide protection of the wound." Stored at room temperature	Product code KGN. No summary available online. (K935189)
Helicoll™	EnColl Corp., Fremont, CA, USA	Helicoll is an acellular collagen matrix free of contaminants. The product comes from USDA-approved bovine sources with FDA-required regulatory documentation to maintain and monitor the safety and quality of the procured animal derived raw materials.	Helicoll reduces wound pain, accelerates the healing rate, reduces scarring, reduces hospital stay, and reduces treatment cost. Shelf life of 3 years at room temperature.	Indicated for partial- and full-thickness wounds, pressure ulcers, venous ulcer, diabetic ulcer, etc. Product code KGN (K040314)
Integra® Matrix Wound Dressing; originally Avagen wound dressing.	Integra LifeSciences Corp., Plainsboro, NJ, USA	Integra Wound Matrix is a wound care device composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth. Integra Wound Matrix provides coverage over exposed bone, tendon, cartilage, and joints.	"A single layer collagen matrix that supports a healing environment for wounds." Room temperature storage with a 24-month shelf life.	Indicated for management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers. Product code KGN. (K022127)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
MicroMatrix®	ACell, Inc., Columbia, MD, USA	MicroMatrix is composed of a porcine-derived extracellular matrix known as urinary bladder matrix. The device is supplied in a particle form in units up to 1000 mg and packaged in a glass vial and peel-open pouch. The device is terminally sterilized using electron beam irradiation. ACell's Wound Management Products are medical devices that maintain and support a healing environment by facilitating remodeling of site-appropriate, functional tissue. Composed of naturally occurring urinary bladder matrix (UBM), MicroMatrix maintains an epithelial basement membrane and is appropriate for acute wounds and chronic wounds.	"ACell's Wound Devices: • Contain epithelial basement membrane • and numerous collagens • •Non-crosslinked wound management scaffold • Complement standard of care." Store in a clean, dry environment between 15°C-35°C (59°F-95°F)	Intended for the management of topical wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, and chronic vascular ulcers. Product code KGN (K153574)
Miroderm®	Miromatrix Medical, Inc., Eden Prairie, MN, USA	Miroderm is a non-crosslinked acellular wound matrix derived from porcine liver for the management of wounds. 1 surface of Miroderm retains the native liver capsule (an epithelial basement membrane), and the opposite surface is composed of open liver matrix. Originally Miromatrix Wound Matrix.	"The first-and-only wound matrix derived from porcine liver, Miroderm® retains an intact extracellular matrix with unique properties." Stored at room temperature.	Intended for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, and chronic vascular ulcers. Product code KGN (K140510)
ologen™ Collagen Matrix	Aeon Astron Europe B.V.	ologen Collagen Matrix is a dry scaffold containing a connected porous structure of 10–300 µm diameter made of cross-linked lyophilized porcine type I atelocollagen (≥90%) and glycosaminoglycans (GAG) (≤10%).	No website is devoted to this product for treating chronic wounds. Stored at room temperature with a shelf life of 36 months.	Intended 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, oral wounds and sores. Product code KGN (K173223)
Kerecis™ Omega3 Wound (originally Merigen wound dressing)	Kerecis, Arlington, VA, USA	Kerecis MariGen Wound Dressing is processed fish dermal matrix composed of fish collagen and is supplied as a sterile, intact, or meshed sheet.	"Kerecis produces tissue-based, skin-substitute products for use in surgery and for treating wounds. Compared to other tissue-transplant products, the Kerecis Omega3 fish skin is cost-effective, offers improved clinical performance, reduces the risk of disease transfer, and has no cultural constraints on usage." Store at 25°C (no more than 40°C).	Indicated for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, and diabetic ulcers. Product code KGN (K132343)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Oasis® Wound Matrix	Smith & Nephew, Inc., Fort Worth, TX, USA	Oasis Matrix products are naturally derived scaffolds of ECM, composed of porcine small intestinal submucosa (SIS), which help support the body's own wound closure mechanisms.	"Provides pathways for cellular migration and vascular growth." Storage at room temperature with a shelf life of 2 years.	Indicated for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, and chronic vascular ulcers. Product code KGN (K061711)
PriMatrix® Dermal Repair Scaffold	Integra LifeSciences Corp., Plainsboro, NJ, USA	According to the compary PriMatrix Dermal Repair Scaffold is a unique scaffold for the management of wounds. Derived from fetal bovine dermis, the acellular dermal matrix is designed to provide an environment to support cellular repopulation and revascularization processes for wound healing. PriMatrix contains type III collagen found in fetal dermis and believed to be active in developing and healing tissues.	"The PriMatrix proprietary processing technology preserves the beneficial properties of the natural dermal collagen fibers and generates a tissue matrix free of contaminants and artificial chemical crosslinks. When applied to the patient's wound PriMatrix rapidly fills with blood, binding both cells and growth factors. The enriched dermal collagen fibers support cellular repopulation and revascularization processes critical in wound healing." Store at room temperature.	Intended for the management of wounds that include: partial- and full-thickness wounds; Pressure, diabetic, and venous ulcers. Product code KGN (K083440)
Puracol® and Puracol® Plus Collagen Wound Dressings	Medline Industries, Northfield, IL, USA	Composed of 100% bovine collagen.	"Our Puracol wound dressings (Puracol Plus, Puracol Plus Ag+ and Puracol Ultra Powder) promote natural healing with type I 100% native collagen. Our exclusive, gentle manufacturing technology preserves the collagen's natural structure, resulting in dressings that provide more collagen to a wound for a longer period of time." "Native collagen wound dressings can be used to manage chronic wounds. The addition of collagen to the wound bed may reduce excess MMP activity to promote the wound healing cycle."	Indicated for the management of full-thickness and partial-thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, and diabetic foot ulcers. Product code FRO (K071552)
PuraPly® Antimicrobial (PuraPly® AM) Wound Matrix (formally called FortaDerm)	Organogenesis, Inc., Canton, MA, USA	PuraPly Antimicrobial Wound Matrix (PuraPly AM) consists of a collagen sheet coated with 0.1% polyhex-methylenebiguanide hydrochloride (PHMB) intended for the management of wounds. PuraPly AM is supplied dry in sheet form. The device is packaged in sterile, sealed single pouches. According to FDA 510(k) clearance document: "FortaDerm Antimicrobial PHMB Wound Dressing consists of two layers, crosslinked sheet of fenestrated sheet of porcine intestinal collagen coated with 0.1 % [PHMB]."	"PuraPly AM utilizes a purified native collagen matrix embedded with the antimicrobial [PHMB], a broad spectrum antimicrobial. It is this combination of native collagen and PHMB that helps manage the reformation of biofilm while supporting healing across a wide variety of wound types, regardless of severity or duration." Stored in a clean, dry location at room temperature.	The FortaDerm Antimicrobial PHMB Wound Dressing is intended for the management of wounds and as an effective barrier to resist microbial colonization n the dressing and reduce microbes penetrating through the dressing. May be used for the management of partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, and chronic vascular ulcers. Product code KMF (K051647)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Talymed®	Marine Polymer Technologies, Inc., Burlington, MA, USA	Talymed advanced matrix is composed of shortened fibers of poly-N-acetyl glucosamine isolated from microalgae.	• "86% of patients experienced complete wound healing. • Non-immunogenic. • Easy to apply. • Store at room temperature for up to 3 years."	Indicated for the management of wounds, including diabetic ulcers, venous ulcers, pressure wounds, ulcers caused by mixed vascular etiologies, full-thickness wounds, and partial-thickness wounds. Product code FRO (K102002)
TheraForm™ Standard/Sheet Absorbable Collagen Membrane	Sewon Cellontech Co., Seoul, Korea	TheraForm is an absorbable and biocompatible implant to enhance tissue regeneration and can be used with human cell or tissue-specific ingredients. It is a sterile, pliable, porous scaffold made of biocollagen for wound dressing, soft-tissue regeneration scaffold agent, periodontal tissue repair agent, and the control of bleeding. TheraForm Standard Sheet Absorbable Collagen Membrane is a sterile, pliable porous wound dressing made of highly purified collagen derived from porcine. TheraForm Standard / Sheet is completely absorbable and highly biocompatible, according to FDA 510(k) document.	"Absorbable collagen membrane is a sterile, pliable, porous surgical wound dressing. Standard and Sheet types are ideal wound healing biomatrix."	Intended for the management of wounds, including partial- and full-thickness wound, pressure ulcers, venous ulcers, diabetic ulcers, and chronic ulcers. Product code KGN (K090812)

21 CFR = Code of Federal Regulations Title 21; ECM = extracellular matrix; FDA = U.S. Food and Drug Administration

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

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Hyalomatrix® tissue reconstruction matrix	Anika Therapeutics, Bedford, MA, USA	Hyalomatrix is a bilayered, sterile, and flexible advanced wound care device. It is ideally suited for a range of wounds that include pressure ulcers, diabetic foot ulcers, and deep second-degree burns. Hyalomatrix is a nonwoven pad composed of a wound contact layer made of a derivative of hyaluronic acid (HA) in fibrous form with an outer layer composed of a semipermeable silicone membrane. The wound contact layer is biodegradable, and it acts as a 3D scaffold for cellular invasion and capillary growth. The silicone layer controls water vapor loss and provides protective coverage of the wound.	"The Hyalomatrix Advantage: Conveniently conformable to a variety of wound sizes. Minimizes risk of bacterial contamination with protective and flexible covering. Simplifies monitoring – wound can be inspected without matrix removal. Controls water vapor loss with semipermeable layer." Store at room temperature.	Indicated for the management of wounds, including partial- and full-thickness wounds, second-degree burns, pressure ulcers, venous ulcers, diabetic ulcers, and chronic vascular ulcers. Product code FRO (K073251)
Restrata™	Acera Surgical Inc., St. Louis, MO, USA	Restrata is a fully synthetic electrospun wound dressing composed of randomly oriented nanofibers that create a highly porous scaffold for cellular infiltration and vascularization during wound repair. Its structure was engineered to be similar to that of native extracellular matrix, 1 of the key building blocks of newly forming tissue. The fibers comprising Restrata Wound Matrix are produced from polyglactin 910 and polydioxanone, both bioabsorbable polymers.	Product website not available	Intended for use in the management of wounds, including partial- and full-thickness wounds, pressure sores/ ulcers, venous ulcers, diabetic ulcers, and chronic vascular ulcers. Product code FRO (K170300)

Table D-5. Acellular/Dermal replacement from combined natural and synthetic materials (3 products in this category)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Integra® Bilayer Matrix Wound Dressing	Integra LifeSciences Corp., Plainsboro, NJ, USA	Integra Bilayer Wound Matrix is an advanced wound care device composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone layer). Promoted for inpatient use.	"The semi-permeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth." Room temperature with a 24-month shelf life.	Indicated for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, and chronic vascular ulcers. Product code FRO (K021792)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Integra® Dermal Regeneration Template and Integra Omnigraft Regeneration Template	Integra LifeSciences	Integra Dermal Regeneration Template (Integra Template) has 2 layers: a thin outer layer of silicone and a thick inner matrix layer of pure bovine collagen and glycosaminoglycan (GAG). Both collagen and GAG are normal components of human skin. In Integra, the collagen is obtained from bovine tendon collagen, and the glycosaminoglycan is obtained from shark cartilage.	"Silicone layer: Enables immediate wound closure. Controls fluid loss. Provides mechanical protection. Provides a bacterial barrier. Water vapor transmission rate similar to that of normal skin." "3-Dimensional matrix layer: Cross-linked collagen and glycosaminoglycan. Functions as an extracellular matrix. Promotes cellular growth and collagen synthesis. Biodegrades while being replaced by autologous dermal tissue." Room temperature with a 24-month shelf life.	Approval for the Integra omnigraft dermal regeneration matrix (a.k.a. omnigraft) and Integra dermal regeneration template. Integra omnigraft dermal regeneration matrix is indicated for treating partial- and full-thickness neuropathic diabetic foot ulcers greater than 6-weeks in duration, with no capsule, tendon, or bone exposed, when used in conjunction with standard diabetic ulcer care. (P900033 S042)
Integra® Flowable Wound Matrix	Integra LifeSciences	Integra Flowable Wound Matrix is an advanced wound care matrix composed of granulated cross-linked bovine tendon collagen and glycosaminoglycan. The granulated collagen-glycosaminoglycan is hydrated with sterile saline and applied in difficult-to-access wound sites and tunneled wounds.	"It provides a scaffold for cellular invasion and capillary growth. When a wound is found to 'tunnel' into deep soft tissue and has an irregular geometry, grafting with a sheet form will not be adequate. In order to effectively correct the defect, one must obtain contact with the wound bed and fill the wound. This can be accomplished with Integra Flowable Wound Matrix, which is administered through a syringe with a flexible injector. This composition and method of administration allows for complete coverage in deep creviced wounds in a minimally invasive manner." Room temperature with an 18-month shelf life.	Indicated for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, and chronic vascular ulcers. Product code KGN (K072113)

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

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
AltiPly®	Aziyo Biologics, Silver Spring, MD, USA	Lyophilized Placental Membrane. The growth factor-rich matrix, with an outer basement membrane and epithelial layer, immediately serves as a scaffold for reepithelialization.	"AltiPly is opaque, and thicker than other grafts. The dry graft is flexible and easy to handle. What you can't see is the benefit of our proprietary processing on preserving the quality of the matrix. The growth factor-rich matrix, with an outer basement membrane and epithelial layer, immediately serves as a scaffold for reepithelialization." "Supports wound closure of chronic diabetic foot ulcers (DFU), venous leg ulcers (VLU) and pressure wounds." "Proprietary processing improves growth factor levels over dehydration methods."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

21 CFR = Code of Federal Regulations Title 21; FDA = U.S. Food and Drug Administration

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

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Affinity® Human Amniotic Allograft	Organogenesis, Inc., Canton, MA, USA	Affinity is a fresh amniotic membrane aseptically processed and hypothermically preserved using AlloFresh®, a proprietary storage system. The product is not dehydrated or frozen. Affinity can be applied to chronic wounds, such as diabetic foot ulcers, venous leg ulcers, and pressure ulcers.	"Affinity is the only fresh amniotic membrane that contains: viable cells (including stromal cells, fibroblasts, and epithelial cells), angiogenenic, regenerative and anti-inflammatory growth factors and cytokines, and a native extracellular matrix and multiple important [extracellular matrix] proteins." "Organogenesis' proprietary AlloFresh processing method allows for the fresh, hypothermic storage of the amniotic tissue while retaining its structural integrity, viability, and native benefits." All fresh allografts must be maintained at refrigerated temperature (between 1°C and 10°C) during storage.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
FlōGraft® Amniotic Fluid-Derived Allograft	Applied Biologics, Scottsdale, AZ, USA	FlōGraft is chorion-free allograft composed of amnion and amniotic fluid derived from prescreened, live, healthy donors. Amniotic membrane and fluid act as a biologic system that ensures symmetrical structure development and growth, cushions and protects the embryo, has a significant defensive role as a part of the innate immune system, and protects the fetus by maintaining consistent pressure and temperature. FlōGraft retains this protective function as a versatile and manageable liquid allograft and is indicated as an additive in several general surgical applications, including soft-tissue defects, soft-tissue trauma, tendinitis, tendinosis, chronic wounds, and localized inflammation.	FlōGraft is carefully processed to preserve the structural qualities of the amniotic membrane yet allow for the allograft to be implanted using a 22-23 gauge needle. Amnion is a native source of collagen types III, IV, V, and VII, as well as and fibronectin and laminin. It also contains fibroblasts and growth factors, modulates, cytokine, and growth factor levels, and has been shown to have unique properties, including the ability to suppress pain, fibrosis, and bacteria and to promote wound healing. These qualities may provide an ancillary benefit to the primary purpose of FlōGraft human allograft as a soft-tissue defect filler.	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
Grafix®	Osiris Therapeutics, Inc., Columbia, MD, USA	Grafix is a cryopreserved placental membrane composed of an ECM rich in collagen, growth factors, fibroblasts, mesenchymal stem cells, and epithelial cells native to the tissue.	"Designed for application directly to acute and chronic wounds. Flexible, conforming cover that adheres to complex anatomies." Minimum two year shelf life and should be stored frozen at -75°C to -85°C (-103°F to -121°F).	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)
GrafixPL Prime	Osiris Therapeutics	GrafixPL Prime is a lyopreserved placental amniotic membrane that is stored at room temperature. Suitable for a wide variety of hard-to-treat acute and chronic wounds.	"Both cryopreserved and lyopreserved products [Grafix Prime and GrafixPL Prime] retain the viable epithelial cells, fibroblasts, and mesenchymal stem cells found in fresh placental amnion. The extracellular matrix, including collagen, elastin, fibronectin, and laminin, is preserved in the native architecture within both products. The cytokines and growth factors for fresh amnion are preserved in both." Stored at room temperature	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

21 CFR = Code of Federal Regulations Title 21; FDA = U.S. Food and Drug Administration

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

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Dermagraft®	Organogenesis Inc., Canton, MA, USA	"Dermagraft is a cryopreserved human fibroblast derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold. Dermagraft is manufactured from human fibroblast cells derived from donated newborn foreskin tissue. During the manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a three-dimensional human dermal substitute containing metabolically active, living cells. Dermagraft does not contain macrophages, lymphocytes, blood vessels, or hair follicles."	"Dermagraft helps to restore the compromised DFU [diabetic foot ulcer] dermal bed to facilitate healing by providing a substrate over which the patient's own epithelial cells can migrate to close the wound." Must be stored continuously at -75°C ±10°C.	Approval for Dermagraft. "The device is indicated for use in the treatment of full-thickness diabetic foot ulcers greater than 6-weeks duration that 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 who have adequate blood supply to the involved foot." (P000036)

DFU = diabetic foot ulcer

Table D-9. Cellular/Epidermal and Dermal replacement from human cadaver skin (1 product in this category)

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Theraskin®	LifeNet Health, Virginia Beach, VA, USA (procurement and processing) Solsys Medical, Newport News, VA, USA (distribution)	TheraSkin is a human, living split-thickness allograft. TheraSkin contains all the relevant human biological components (growth factors, cytokines, fibroblasts, keratinocytes, and collagen types) required to close and replace damaged skin in hard-to heal wounds.	"Application of TheraSkin — a real human skin allograft — can replace damaged skin and can assist in healing most chronic wounds, even wounds that have not progressed for many months and have failed to heal with other therapies." "TheraSkin is a biologically active, cryopreserved human skin allograft, composed of living cells, fibroblasts and keratinocytes, and a fully developed extracellular matrix (ECM) in its epidermal and dermal layers. TheraSkin provides, upon application, a supply of growth factors/cytokines, and a robust collagen scaffold to jumpstart healing in a chronic wound."	Regulated by FDA as human tissue for transplantation. in accordance with FDA's requirements for banked human tissue (21 CFR, Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products)

21 CFR = Code of Federal Regulations Title 21; FDA = U.S. Food and Drug Administration

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

Device	Manufacturer	Product Description	Manufacturer Claims	Regulatory Information
Apligraf®	Organogenesis Inc., Canton, MA, USA	Apligraf is a living cell-based product for chronic venous leg ulcers and diabetic foot ulcers. Apligraf is supplied as a living, bi-layered skin substitute. The lower dermal layer combines bovine type 1 collagen and human fibroblasts (dermal cells), which produce additional matrix proteins. The upper epidermal layer is formed by promoting human keratinocytes (epidermal cells) first to multiply and then to differentiate to replicate the architecture of the human epidermis. See also prescribing information.	"Apligraf is the only living, bi-layered cell based product FDA approved to heal both Diabetic Foot Ulcers and Venous Leg Ulcers." "Apligraf plays an active role in healing by providing to the wound living cells, proteins produced by the cells, and collagen, which are important for healing." Should be kept in its tray on the medium in the sealed bag under controlled temperature 68°F-73°F (20°C-23°C) until ready for use	"This device is indicated 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." (P950032) "Approval 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." (P950032S016)

FDA = U.S. Food and Drug Administration

Appendix E. Ongoing Clinical Trials

Table E-1. Ongoing clinical trials

Clinicaltrials.gov Identifier	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT03010319*	Integra LifeSciences Corp.	To evaluate the efficacy of PriMatrix Dermal Repair Scaffold in the management of DFUs in subjects with diabetes mellitus vs. SOC	Acellular dermal, natural material – animal	DFU	June 2020	204	Recruiting	Complete wound closure up to 12 weeks
NCT03476876*	Baylor College of Medicine with LifeNet Health	To compare outcomes of DermACell acellular dermal matrix with Integra® Bilayer Matrix Wound Dressing	Acellular dermal, natural material – human dermis compared with acellular dermal, natural, and synthetic materials	DFU	June 15, 2020	50	Recruiting	Wound size change from baseline to 8 weeks and 16 weeks; time to reach successful granulation from baseline to 16 weeks; incidence from complication from baseline to 16 weeks; change in skin perfusion from baseline to 16 weeks; duration of application
NCT02322554**	U.S. Wound Registry	Hospital-based outpatient wound centers participating in the U.S. Wound Registry will provide comparative-effectiveness data for patients with chronic wounds and ulcers being treated with cellular and/or tissue-based products to help understand whether clinical practice guidelines are being followed	Multiple categories	DFU, pressure ulcer, venous leg ulcer	January 2020	50,000	Recruiting	Healing at 12 months
NCT03285698*	Georgetown University with LifeNet Health	To compare clinical outcomes for DermACELL® versus Integra® Bilayer Wound Matrix	Acellular dermal, natural materials – human dermis compared with acellular dermal, natural and synthetic materials	Chronic wounds	October 1, 2019	100	Recruiting	Time to heal for split-thickness graft application up to 160 days

Clinicaltrials.gov Identifier	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT02632929	Boise VA Medical Center with Integra LifeSciences Corp.	To determine whether the use of Amnioexcel® improves healing and reduces the need to amputate all or part of a leg in high-risk patients who have diabetes and foot sores	Acellular dermal, natural material – human amniotic/placental membrane	DFU	September 2019	20	Active, not recruiting	Limb salvage 1-month posthealing
NCT03547635*	Integra LifeSciences Corporation	To compare the outcomes associated with the use of Amnioexcel Plus Placental Allograft Membrane, a marketed comparator (Apligraf®) and SOC alone in the management of DFUs	Acellular dermal, natural materials – human amniotic/placental membrane compared with Cellular epidermal and dermal, natural materials – human and animal	DFU	August 31, 2019	114	Enrolling by invitation	Incidence of complete wound closure, as assessed by the investigator at or before week 12 of the treatment phase, which is confirmed closed 2 weeks later
NCT03205436	SerenaGroup, Inc., with NuTech Medical, Inc.	Extension of the randomized controlled trial NT-DFU-AFF-01. Subjects that were randomly assigned to the SOC group can cross over to the NT-DFU-AFF-02 trial and receive Affinity human amniotic membrane if they meet certain criteria.	Cellular dermal, natural material – human amniotic/placental membrane	DFU	August 2019	20	Recruiting	Time to initial closure up to 12 weeks
NCT02657876	Stratatech	To assess the safety and tolerability of ExpressGraft-C9T1 skin tissue in the treatment of DFU	Cellular epidermal and dermal, natural material – human	DFU	May 2019	6	Recruiting	Safety and tolerability of ExpressGraft-C9T1 skin tissue evaluated by adverse events, clinically significant vital signs, blood chemistry, safety laboratory values, and incidence of treatment site infection through study completion up to an average of 1 year

Clinicaltrials.gov Identifier	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT03230175	Tissue Tech, Inc.	Human placental umbilical cord tissue (TTAX01)	Acellular dermal, natural materials – human amniotic/placental membrane	DFU	March 2019	32	Active, not recruiting	Complete wound healing at 16 weeks Just in discussion: Confirmation of wound closure 2 weeks later
NCT03502824*	Organogenesis	To demonstrate how PuraPly® Antimicrobial Wound Matrix performs against SOC in Stage II-IV pressure ulcers	Acellular dermal, natural materials – animal	Pressure ulcer	March 2019	50	Recruiting	Reduction in size of ulcer area between groups up to 24 weeks, improvement in wound bed condition between groups
NCT03286452**	Organogenesis	To assess the impact of PuraPly™ Antimicrobial Wound Matrix on the management of wounds in real-world clinical settings as it leads to improvement in wound bed condition	Acellular dermal, natural materials – animal	DFU, pressure ulcer, venous leg ulcer	February 15, 2019	310	Active, not recruiting	Reduction in wound area, time to complete wound closure, and improvement in wound bed condition at 24 weeks
NCT02929056*	Greenville Health System with Clemson University and BioDlogics	To evaluate an amniotic membrane (AmnioExCel) dressing and compression therapy vs. SOC alginate dressing and compression to manage venous leg ulcers	Acellular dermal, natural materials – human amniotic/placental membrane	Venous leg ulcer	January 2019	40	Enrolling by invitation	Reduction in wound area at 4, 8, and 12 weeks
NCT02880592*	SerenaGroup, Inc. with NuTech Medical, Inc.	To evaluate the use of fresh hypothermically stored human amniotic membrane (Affinity: fHSAM) to determine whether addition of fHSAM to SOC results in faster healing of Wagner grade 1 and 2 serious foot ulcers compared to SOC alone	Cellular dermal, natural materials - human amniotic/placental membrane	DFU	January 2019	100	Recruiting	Time to initial closure up to 12 weeks

Clinicaltrials.gov Identifier	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT03283787*	Acell, Inc.	To evaluate incidence of complete epithelialization in stage 3/4 pressure ulcers using ACell products (primary comparison: MicroMatrix® plus Cytal™ vs. NPWT; secondary comparison: MicroMatrix plus Cytal plus NPWT vs. NPWT)	Acellular dermal, natural materials – animal (both)	Pressure ulcer	December 2018	60	Recruiting	Time to complete wound epithelialization at 12 weeks
NCT02609594*	SerenaGroup, Inc. with Musculoskeletal Transplant Foundation	To evaluate the safety and effectiveness of Amnioband Dehydrated Human Amniotic Membrane plus multi-layer compression therapy (MLCT) vs. MLCT alone to heal venous leg ulcer (also comparing weekly and biweekly applications of Amnioband)	Acellular dermal, natural materials – human amniotic/placental membrane	Venous leg ulcer	December 2018	240	Recruiting	Time to complete wound closure at 12 weeks
NCT02838784*	Tides Medical	To evaluate the efficacy of Artacent™ Human Amniotic Membrane vs. SOC in the treatment of diabetic and vascular lower-extremity ulcers	Acellular dermal, natural materials – human amniotic/placental membrane	DFU, venous leg ulcer	December 2018	134	Recruiting	Wound closure and time to wound closure at 12 weeks, ulcer recurrence at 6 months
NCT03044132	LifeNet Health	To explore the use of DermACELL (human acellular dermal matrix) in the treatment of chronic Wagner Grade 3/4 DFUs	Acellular dermal, natural material – human dermis	DFU	December 31, 2018	50	Recruiting	Time (days) required for wound bed preparation (granular bed after placement of DermACELL AWM up to 112 days
NCT03529578	MiMedx Group, Inc.	To investigate the safety of dehydrated amnion/chorion membrane (dHACM) in the treatment of patients with stage II/III pressure ulcers and decubitus ulcers	Acellular dermal, natural materials – human amniotic/placental membrane	Pressure ulcer	October 1, 2018	20	Enrolling by invitation	Percentage of subjects with complete wound closure at 8 weeks

Clinicaltrials.gov Identifier	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT02844660*	MiMedx Group, Inc.	To determine the safety and effectiveness of a dehydrated human umbilical cord allograft (EpiCord) compared to SOC for the treatment of chronic, nonhealing DFUs	Acellular dermal, natural materials – human amniotic/placental membrane	DFU	September 2018	130	Active, not recruiting	Complete ulcer closure and proportion of product-related adverse events at 12 weeks Secondary: recurrence
NCT03232333	Miromatrix Medical Inc.	To determine the number of successful complete wound closures within 12 weeks of treatment with Miroderm Fenestrated Biological Wound Matrix	Acellular dermal, natural material - animal	DFU	September 20, 2018	54	Completed	Healed ulcers at 12 weeks
NCT03312595*	Acera Surgical, Inc.	To determine the outcomes of patients who receive a certain type of skin substitute called Restrata™ Wound Matrix (Restrata)	Acellular dermal, synthetic material	DFU	July 30, 2018	30	Completed	Percent of wound closed up to 14 weeks
NCT01693133*	MiMedx Group, Inc.	To evaluate the percentage of patients with complete DFU closure following up to 12 weeks of treatment with either EpiFix dHACM plus SOC or SOC alone	Acellular dermal, natural material – human amniotic/placental membrane	DFU	June 2018	132	Completed	Percentage of subjects with complete closure at week 12 Secondary: Recurrence at week 16
NCT02870816*	Professional Education and Research Institute with Musculoskeletal Transplant Foundation	To determine whether amnion membrane grafts are more effective than another tissue engineered skin substitute (not specified)	Acellular dermal, natural material – human amniotic/placental membrane	DFU	May 2018	60	Recruiting	Complete healing at 6 weeks
NCT02707406*	Tissue Tech Inc.	To evaluate the safety, incidence and rate of wound closure with Neox ® Cord 1K, a cryopreserved human umbilical cord allograft, versus SOC	Acellular dermal, natural materials – human amniotic/placental membrane	DFU	April 2018	114	Active, not recruiting	Incidence of adverse events up to 16 weeks

Clinicaltrials.gov Identifier	Sponsor	Purpose	Skin Substitute Category for Mapping	Wound Type of Interest	Expected Completion Date	Estimated Enrollment	Status	Primary Outcome(s)
NCT02506452*	Alliqua BioMedical, Inc.	To compare the wound closure outcomes of subjects receiving DFU treatment with a dehydrated decullarized human amniotic membrane allograft (Biovance®) vs. SOC	Acellular dermal, natural materials – human amniotic/placental membrane	DFU	December 2017	51	Active, not recruiting	Wound closure at up to 12 weeks following baseline visit defined as 100% reepithelialization without drainage confirmed at 2 weeks following initial observation of closure
NCT02184455	Dr. Paul F. Gratzer, DeCell Technologies, Inc.	To perform a limited pilot study to determine the safety and feasibility of DermGEN (decellularized dermal matrix) in the treatment of nonhealing DFU	Acellular dermal, natural materials – human	DFU	December 2017	20	Unknown	Mean and median wound size at 4 weeks Secondary: recurrence at 20 weeks
NCT02344329*	University of North Dakota	To compare total contact casting using human amnion allograft (AmnioExcel) vs. total contact casting and SOC to treat DFU	Acellular dermal, natural materials – human amniotic/placental membrane	DFU	November 2017	12	Active, not recruiting	Time to closure up to 12 weeks
NCT03037970*	Lynch Biologics LLC	To investigate the safety and efficacy of Absolve Biologic Wound Matrix vs. placebo. Absolve is a combination of highly purified recombinant human platelet-derived growth factor BB homodimer combined with a biocompatible, collagen resorbable wound dressing	Not enough product information to determine category	DFU	October 15, 2017	40	Recruiting	Incidence of treatment-emergent adverse events up to week 24; successful wound healing for at least 2 consecutive measurements – first measurement at week 12
NCT02399826*	Lower Extremity Institute for Research and Therapy with Musculoskeletal Transplant Foundation	To compare the proportion of ulcers completely healed by use of an amniotic membrane graft (Amnioband) vs. SOC in patients with diabetes with a DFU with adequate arterial perfusion, for wound healing to the affected limb	Acellular dermal, natural materials – human amniotic/placental membrane	DFU	January 2017	40	Unknown	Proportion of ulcers completely healed at 6 weeks

*Randomized controlled trial **Patient registry
DFU = diabetic foot ulcer; MLCT = multi-layer compression therapy; NPWT = negative pressure wound therapy; SOC = standard of care