

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Skin Substitutes for Adults With Diabetic Foot Ulcers and Venous Leg Ulcers: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Wounds such as diabetic foot ulcers and venous leg ulcers can be difficult to heal. Diabetic foot ulcers are a common complication of diabetes. They form because of pressure or repetitive irritation to the skin tissue on the foot, which then breaks down, exposing the layers underneath. Venous leg ulcers are sores on the leg that are very slow to heal, usually because of impaired blood circulation in the veins of the leg.

Diabetic foot ulcers and venous leg ulcers are usually treated with traditional dressings (for example, absorbent dressings and antiseptic dressings). People with diabetic foot ulcers should also receive an offloading device (a device that relieves pressure on the foot, such as a cast or special shoe). People with venous leg ulcers should receive compression therapy (special stockings that provide support to the veins in the leg). Skin substitutes are a new treatment. They provide temporary or permanent coverage of open skin wounds. They can be beneficial when traditional dressings do not work well enough. Skin substitutes work by mimicking the properties of normal skin.

This health technology assessment looked at how safe, effective, and cost-effective skin substitutes are for adults with diabetic foot ulcers and venous leg ulcers. It also looked at the budget impact of publicly funding skin substitutes and at the experiences, preferences, and values of people with diabetic foot ulcers and venous leg ulcers.

What Did This Health Technology Assessment Find?

In adults with diabetic foot ulcers and venous leg ulcers that are difficult to heal, skin substitutes combined with standard care are more effective in promoting complete wound healing than standard care alone.

Compared with standard care alone, the cost-effectiveness of skin substitutes plus standard care is uncertain in people with diabetic foot ulcers and highly unlikely in people with venous leg ulcers. We estimate that publicly funding skin substitutes over the next 5 years would cost an additional \$0.17 million in year 1 to \$1.2 million in year 5 for people with diabetic foot ulcers, and from \$1 million in year 1 to \$7.7 million in year 5 for people with venous leg ulcers.

People with diabetic foot ulcers and venous leg ulcers we spoke with generally felt positively about the potential use of skin substitutes to heal their wounds. Barriers to access include the limited use of skin substitutes across Ontario, lack of knowledge of skin substitutes among people with these conditions, and cost.

Acknowledgments

This report was developed by a multidisciplinary team from Ontario Health. The primary clinical epidemiologist was Conrad Kabali, the primary medical librarian was Caroline Higgins, the primary health economist was Jennifer Guo, the secondary health economist was Chunmei Li, and the primary patient and public partnership analyst was Jigna Mistry.

The medical editors were Jeanne McKane and Kara Cowan. Others involved in the development and production of this report were Paul Kolodziej, Merissa Mohamed, Claude Soulodre, Susan Harrison, Saleemeh Abdolzahraei, Elisabeth Smitko, Sarah McDowell, Vivian Ng, David Wells, Andrée Mitchell, Charles de Mestral and Nancy Sikich.

We would like to thank the following people and organizations for lending their expertise to the development of this report:

- Afsaneh Alavi, Women's College Hospital
- Ann-Marie McLaren, St. Michael's Hospital
- Karen Cross, St. Michael's Hospital
- Laura Teague, Ontario Woundcare Interest Group
- Perry Mayer, The Mayer Institute
- Valerie Winberg, Ontario Woundcare Interest Group
- MiMedx

We also thank our lived experience participants who generously gave their time to share their stories with us for this report.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

Citation

Ontario Health. Skin substitutes for adults with diabetic foot ulcers and venous leg ulcers: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2021 June 21(7):1–165. Available from: <https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/skin-substitutes-for-adults-with-diabetic-foot-ulcers-and-venous-leg-ulcers>

Abstract

Background

Wounds may be caused in a variety of ways. Some wounds are difficult to heal, such as diabetic foot ulcers and venous leg ulcers. We conducted a health technology assessment of skin substitutes for adults with neuropathic diabetic foot ulcers and venous leg ulcers, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding skin substitutes, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Cochrane risk-of-bias tool for randomized studies (version 2), and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost–utility analysis with a 26-week time horizon from a public payer perspective. We also analyzed the budget impact of publicly funding skin substitutes in adults with diabetic foot ulcers and venous leg ulcers in Ontario. We explored the underlying values, needs, and priorities of those who have lived experience with diabetic leg ulcers and venous leg ulcers, as well as their preferences for and perceptions of skin substitutes.

Results

We included 40 studies in the clinical evidence review. Adults with difficult-to-heal neuropathic diabetic foot ulcers who used dermal (GRADE: High) or multi-layered (GRADE: Moderate) skin substitutes as an adjunct to standard care were more likely to experience complete wound healing than those who used standard care alone. Adults with difficult-to-heal venous leg ulcers who used dermal (GRADE: Moderate) or multi-layered (GRADE: High) skin substitutes as an adjunct to standard care were more likely to experience complete wound healing than those who used standard care alone. The evidence for the effectiveness of epidermal skin substitutes was inconclusive for venous leg ulcers because of the small size of the individual studies (GRADE: Very low). We found no studies on epidermal skin substitutes for diabetic foot ulcers. We could not evaluate the safety of skin substitutes versus standard care, because the number of adverse events was either very low or zero (because sample sizes were too small).

In our economic analysis, the use of skin substitutes as an adjunct to standard care was more costly and more effective than standard care alone for the treatment of difficult-to-heal diabetic foot ulcers and venous leg ulcers. For diabetic foot ulcers, the incremental cost-effectiveness ratio (ICER) of skin substitutes plus standard care compared with standard care alone was \$48,242 per quality-adjusted life-year (QALY), and the cost per ulcer-free week was \$158. For venous leg ulcers, the ICER was \$1,868,850 per QALY, and the cost per ulcer-free week was \$3,235. At the commonly used willingness-to-pay of \$50,000 per QALY, the cost-effectiveness of skin substitutes plus standard care versus standard care alone was uncertain (47% probability of being cost-effective) for diabetic foot ulcers and highly unlikely (0% probability of being cost-effective) for venous leg ulcers. At the commonly used willingness-to-pay of \$100,000 per QALY, the cost-effectiveness of skin substitutes plus standard care versus standard care alone was moderately likely (71% probability of cost-effectiveness) for people with diabetic foot ulcers and highly unlikely (0% probability of being cost-effective) for people with venous leg ulcers. The annual budget impact of publicly funding skin substitutes in Ontario over the next 5 years would range from an

additional \$0.17 million in year 1 to \$1.2 million in year 5 for people with diabetic foot ulcers, and from \$1 million in year 1 to \$7.7 million in year 5 for people with venous leg ulcers.

Direct patient engagement consisted of three participants for this assessment and 51 from previous health technology assessments that addressed interventions for diabetic foot ulcers and venous leg ulcers. Participants spoke of the negative impact on their quality of life with regard to mobility, employment, social activities, and emotional and mental health. No participants had direct experience using skin substitutes, but participants were open to this treatment option. Barriers to access included the limited use of skin substitutes across Ontario, lack of knowledge of skin substitutes among people with diabetic foot ulcers and venous leg ulcers, and cost.

Conclusions

Dermal and multi-layered skin substitutes, when used as an adjunct to standard care, were more effective than standard care alone in completely healing difficult-to-heal neuropathic diabetic foot ulcers and venous leg ulcers in adults. Using skin substitutes as an adjunct to standard care was more costly and more effective than standard care alone for the treatment of difficult-to-heal neuropathic diabetic foot ulcers and venous leg ulcers. For adults with diabetic foot ulcers, the likelihood of skin substitutes being cost-effective compared with standard care depends on the willingness to pay. The likelihood of skin substitutes being cost-effective compared with standard care is uncertain at \$50,000 per QALY and moderately likely at \$100,000 per QALY. For adults with venous leg ulcers, skin substitutes were highly unlikely to be cost-effective compared with standard care. We estimated that publicly funding skin substitutes in Ontario would result in additional costs of \$3 million and \$20 million over the next 5 years for people with diabetic foot ulcers and venous leg ulcers, respectively. The people with diabetic foot ulcers and venous leg ulcers we spoke with were open to using skin substitutes as a treatment option.

Table of Contents

List of Tables	8
List of Figures	9
Objective.....	10
Background	10
Health Conditions	10
<i>Diabetic Foot Ulcers</i>	<i>10</i>
<i>Venous Leg Ulcers</i>	<i>10</i>
Clinical Need and Target Population	10
Health Technology Under Review	11
Regulatory Information	12
Ontario, Canadian, and International Context	13
Expert Consultation	13
PROSPERO Registration	13
Clinical Evidence.....	14
Research Question.....	14
Methods	14
<i>Clinical Literature Search</i>	<i>14</i>
<i>Eligibility Criteria.....</i>	<i>14</i>
<i>Literature Screening.....</i>	<i>15</i>
<i>Data Extraction</i>	<i>15</i>
<i>Statistical Analysis</i>	<i>15</i>
<i>Critical Appraisal of Evidence.....</i>	<i>16</i>
Results	16
<i>Clinical Literature Search</i>	<i>16</i>
<i>Characteristics of Included Studies</i>	<i>18</i>
<i>Risk of Bias in the Included Studies</i>	<i>23</i>
<i>Complete Wound Healing</i>	<i>23</i>
<i>Volume of Wound Healed</i>	<i>30</i>
<i>Quality of Life.....</i>	<i>30</i>
<i>Adverse Effects.....</i>	<i>30</i>
<i>Ongoing Studies</i>	<i>32</i>
Discussion	32
Conclusions.....	34
Economic Evidence	35
Research Questions	35
Methods	35
<i>Economic Literature Search</i>	<i>35</i>
<i>Eligibility Criteria.....</i>	<i>35</i>

<i>Literature Screening</i>	36
<i>Data Extraction</i>	36
<i>Study Applicability and Limitations</i>	36
Results	36
<i>Economic Literature Search</i>	36
<i>Overview of Included Economic Studies</i>	37
<i>Applicability and Limitations of the Included Studies</i>	39
Discussion	39
Conclusions	40
Primary Economic Evaluation	41
Research Questions	41
Methods	41
<i>Type of Analysis</i>	41
<i>Target Populations</i>	41
<i>Perspective</i>	42
<i>Intervention and Comparator</i>	42
<i>Time Horizon and Discounting</i>	43
<i>Main Assumptions</i>	43
<i>Model Structure—Diabetic Foot Ulcers</i>	44
<i>Model Structure—Venous Leg Ulcers</i>	51
<i>Internal Validation</i>	55
<i>Analysis</i>	55
Results	57
<i>Diabetic Foot Ulcers</i>	57
<i>Venous Leg Ulcers</i>	63
Discussion	67
Strengths and Limitations	68
Conclusions	69
Budget Impact Analysis	70
Research Questions	70
Methods	70
<i>Analytic Framework</i>	70
<i>Key Assumptions</i>	71
<i>Target Population</i>	71
<i>Uptake of the New Intervention</i>	72
<i>Current Intervention Mix</i>	73
<i>New Intervention Mix</i>	74
<i>Resources and Costs</i>	74
<i>Internal Validation</i>	74
<i>Analysis</i>	74
Results	75
<i>Budget Impact Analysis—Diabetic Foot Ulcers</i>	75

<i>Budget Impact Analysis—Venous Leg Ulcers</i>	79
Discussion	81
Strengths and Limitations	83
Conclusions	83
Preferences and Values Evidence	84
Objective	84
Background	84
Direct Patient Engagement	84
<i>Methods</i>	84
<i>Results</i>	86
<i>Discussion</i>	91
<i>Conclusions</i>	91
Conclusions of the Health Technology Assessment	92
Abbreviations	93
Glossary	94
Appendices	99
Appendix 1: Literature Search Strategies	99
<i>Clinical Evidence Search</i>	99
<i>Economic Evidence Search</i>	109
<i>Grey Literature Search</i>	117
Appendix 2: Forest Plots for EpiFix Studies in the Clinical Review That Were Used in the Economic Analysis	119
Appendix 3: Critical Appraisal of Clinical Evidence	120
Appendix 4: Selected Excluded Studies—Clinical Evidence	124
Appendix 5: R Code for Figures 2 to 5	127
Appendix 6: Results of Economic Literature Review	132
Appendix 7: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review	140
Appendix 8: Minor and Major Lower-Extremity Amputation Data Inputs	146
Appendix 9: Parameters Varied in the Economic Models	149
Appendix 10: Letter of Information	151
Appendix 11: Interview Guide	152
References	154

List of Tables

Table 1: Skin Substitutes With a Health Canada Licence	12
Table 2: Characteristics of Included Studies	19
Table 3: Risk Difference of Dermal Substitutes Versus Standard Care for Complete Wound Healing.....	24
Table 4: Effectiveness of Multi-layered (Bi-layered and Tri-layered) Skin Substitutes Versus Standard Care for Complete Wound Healing	26
Table 5: Effectiveness of Epidermal Skin Substitutes Versus Standard Care for Complete Wound Healing	27
Table 6: Adverse Effects.....	31
Table 7: Disease Intervention and Comparators Evaluated in the Primary Economic Models	42
Table 8: Natural History Inputs Used in the Economic Model—Diabetic Foot Ulcers.....	46
Table 9: Summary Estimates (Risk Difference) Used in the Economic Model—Diabetic Foot Ulcers.....	46
Table 10: Health State Utilities Used in the Economic Model—Diabetic Foot Ulcers	46
Table 11: Resource Use and Cost Parameters Used in the Economic Model—Diabetic Foot Ulcers.....	49
Table 12: Natural History Inputs Used in the Economic Model—Venous Leg Ulcers.....	53
Table 13: Summary Estimates (Risk Difference) Used in the Economic Model—Venous Leg Ulcers.....	53
Table 14: Health State Utilities Used in the Economic Model—Venous Leg Ulcers	53
Table 15: Resource Use and Cost Parameters Used in the Economic Model—Venous Leg Ulcers.....	54
Table 16: Reference Case Results—Diabetic Foot Ulcers	58
Table 17: Scenario Analysis Results—Diabetic Foot Ulcers	61
Table 18: Reference Case Analysis Results—Venous Leg Ulcers	63
Table 19: Scenario Analysis Results—Venous Leg Ulcers	66
Table 20: Input Parameters for Estimating Target Populations—Diabetic Foot Ulcers	72
Table 21: Input Parameters for Estimating Target Populations—Venous Leg Ulcers	72
Table 22: Target Population or Volume of Intervention—Diabetic Foot Ulcers	73
Table 23: Target Population or Volume of Intervention—Venous Leg Ulcers.....	73
Table 24: Budget Impact Results—Diabetic Foot Ulcers	76
Table 25: Scenario Analysis Results—Diabetic Foot Ulcers	77
Table 26: Budget Impact Results—Venous Leg Ulcers	79
Table 27: Scenario Analysis Results—Venous Leg Ulcers	80
Table A1: Risk of Bias ^a Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool Version 2)....	120
Table A2: GRADE Evidence Profile for the Comparison of Skin Substitutes and Standard Care	123
Table A3: Results of Economic Literature Review for Diabetic Foot Ulcers—Summary	132
Table A4: Results of Economic Literature Review for Venous Leg Ulcers—Summary	135
Table A5: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Skin Substitutes	140
Table A6: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Skin Substitutes	142
Table A7: Minor and Major Lower-Extremity Amputations as Defined in This Report	146
Table A8: Physician Fees for Minor and Major Lower-Extremity Amputations, by Amputation Type.....	147
Table A9: Physicians Fees for Initial Consultation and Follow-Up Visit Following Minor and Major Lower- Extremity Amputations	148
Table A10: Ontario Case Costing 2017/18 Hospitalization Costs Associated With Major Lower-Extremity Amputations	148
Table A11: Model Parameters Varied in the Probabilistic Analysis—Diabetic Foot Ulcers.....	149
Table A12: Model Parameters Varied in the Probabilistic Analysis—Venous Leg Ulcers.....	150

List of Figures

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy	17
Figure 2: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care— Stratified by Run-In Period.....	27
Figure 3: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care— Stratified by Duration of Follow-up	28
Figure 4: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care— Stratified by Class of Skin Substitute and Type of Dressing Used in Standard Care	28
Figure 5: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care— Stratified by Class of Skin Substitute	29
Figure 6: PRISMA Flow Diagram—Economic Search Strategy	37
Figure 7: Model Schematic—Diabetic Foot Ulcers	45
Figure 8: Model Schematic—Venous Leg Ulcers	52
Figure 9: Cost-Effectiveness Acceptability Curve—Diabetic Foot Ulcers.....	59
Figure 10: Cost-Effectiveness Acceptability Curve—Venous Leg Ulcers.....	64
Figure 11: Budget Impact Model Schematic.....	70
Figure A1: Complete Wound Healing—Studies Comparing EpiFix With Standard Care That Included Alginate Dressings.....	119
Figure A2: Proportion of Controls With Complete Wound Healing for Studies in Figure A1	119

Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of skin substitutes for adults with diabetic foot ulcers and venous leg ulcers. It also evaluates the budget impact of publicly funding skin substitutes and the experiences, preferences, and values of people with diabetic foot ulcers and venous leg ulcers.

Background

Health Conditions

Wounds may be caused in a variety of ways. Some wounds are difficult to heal (chronic), including diabetic foot ulcers and venous leg ulcers. Difficult-to-heal wounds can cause severe emotional and physical stress and create a substantial economic burden for families and for the health care system.¹

Diabetic Foot Ulcers

Diabetic foot ulcers are a common complication of diabetes. Diabetic foot ulcers occur as a result of various factors, such as neuropathy (nerve damage or dysfunction) and peripheral arterial disease (which may lead to ischemia, a restriction in blood flow).² Neuropathy, characterized by a loss of protective sensation in the foot, often coupled with restricted blood flow from peripheral arterial disease, places people with diabetes at risk for minor foot injuries and slow wound healing.^{2,3} If they are not healed, diabetic foot ulcers may become infected and lead to amputation. Treatments for diabetic foot ulcers include debridement (the removal of dead, damaged, infected tissue or foreign objects from the wound), treatment of arterial insufficiency, wound dressing, the use of offloading devices, good blood glucose management, proper nutrition, and antibiotics if the ulcer is infected.³⁻⁵

Venous Leg Ulcers

Venous leg ulcers occur when the veins in the legs are unable to push blood back up to the heart as well as they should.⁶ As a result, blood accumulates in the veins, building up pressure.⁶ Pressure buildup then impedes the flow of nutrients and oxygen to the tissues, causing cell death and tissue damage, eventually leading to the formation of a wound. Most venous leg ulcers occur above the ankle and are slow to heal without treatment.⁶ A venous duplex ultrasound is used to establish the cause (thrombosis or valvulopathy) and extent (superficial or deep) of underlying venous insufficiency in people with venous leg ulcers. The pedal pulse examination and ankle-brachial pressure index are common tests used to rule out concurrent peripheral arterial disease and help determine appropriate treatment.⁷ Treatments for venous leg ulcers include debridement, proper wound dressing, compression therapy, lifestyle changes such as exercise and smoking cessation, and antibiotics if the ulcer is infected.^{7,8}

Clinical Need and Target Population

In 2016, about 11 million Canadians were living with type 1 diabetes, type 2 diabetes, or prediabetes.⁹ In 2013, approximately 1.53 million people in Ontario were living with diabetes.¹⁰ The lifetime risk for diabetic foot ulcers in people with diabetes is up to 25%. From 2011 through 2012, more than 2,000 amputations related to diabetic foot ulcers were conducted across Canada.¹¹ The cost of amputations can be 10 to 40 times greater than the initiatives to prevent them.¹¹ As well, diabetic foot ulcers can increase the length of hospital stay in people hospitalized with diabetes.¹²

Venous leg ulcers constitute 80% to 90% of all leg ulcers.⁷ The prevalence of venous leg ulcers ranges from 0.8 to 1 per 1,000 population.¹³ Approximately 30% of venous leg ulcers remain unhealed 6 months after occurrence.¹⁴ Of venous leg ulcers that have healed, 60% to 70% will recur, most within a year.¹⁴ Rates of venous leg ulcers in Ontario have increased over time; the average increase in hospital discharges for venous leg ulcers across the 14 local health integration networks between 2012 and 2014 was 11%.⁷ Complications of venous leg ulcers include recurrent cellulitis (a type of severe bacterial infection), osteomyelitis (an infection in the bone), and lymphedema (swelling in the legs).¹⁵

Health Technology Under Review

Skin substitutes are biologic, synthetic, or biosynthetic materials that provide temporary or permanent coverage of open skin wounds.¹⁶ The aim of skin substitutes is to replicate the properties of normal skin.¹⁷ The use of skin grafts to treat wounds originated in India around 1500 BCE^{16,18} and first appeared in Western literature around the 15th century.¹⁸ Although natural skin grafts are clinically useful, they have several limitations, including the availability of a donor site, immune rejection (in the case of skin grafts from another person), pain, scarring, slow healing, and infection.¹⁹ Skin substitutes were introduced in 1880 to regenerate damaged skin without the need for a natural skin graft.¹⁹ Since then, many advances in skin substitutes have been made. Natural skin grafts may be made from the epidermis (the outermost layer of skin), the dermis (the layer of skin beneath the epidermis), and the hypodermis (a layer of tissue that lies below the dermis).

Skin substitutes can be classified in many ways²⁰:

- Cellular or acellular
- Autologous (from one's own cells), allogeneic (from another person), or xenogeneic (from a different species)
- Single layer (epidermal only or dermal only), bi-layer (composed of both epidermal and dermal), or tri-layer (composed of epidermal, dermal, and hypodermal)
- Natural, synthetic, or a hybrid of both
- Temporary (degradable), permanent (not degradable), or semi-permanent

For ease of categorization, we have used the layering classification in this health technology assessment, although any classification system could be used.

Dermal skin substitutes fulfill the functions of the cutaneous dermal layer: control of pain and scarring. They act as matrices or scaffolds, promoting new tissue growth and enhancing wound healing with enhanced pliability and a more favourable scar.²¹ Epidermal skin substitutes are usually made of cultured autologous keratinocytes (cells grown from a patient's own skin sample).²¹ The keratinocytes are grown to create layers representing the epidermis.²² Bi-layered skin substitutes consist of keratinocytes (or a removable silicone epidermal layer) and fibroblast-containing dermal substitutes.²³ The skin cells (keratinocytes and fibroblasts) can be autologous or allogeneic and are integrated into scaffolds.²³ Bi-layered skin substitutes can be split-thickness (containing the epidermis and a portion of the dermis) or full-thickness (consisting of the epidermis and entire dermis). In tri-layered skin substitutes, a scaffold (e.g., hydrogel) is added to the hypodermis.²⁴ Throughout this health technology assessment, we have used the term "multi-layer" to refer to either bi- or tri-layer skin substitutes.

At present, all commercialized skin substitutes are free of several cellular components such as melanocytes (cells that produce a dark pigment primarily responsible for skin colour), Langerhans cells (cells in the skin's immune system that specialize in antigen presentation), and structures such as hair follicles, sebaceous and sweat glands, nerves, and lymphatic and blood capillaries/vessels, although research is being conducted to develop skin substitutes that contain these elements.²² One brand of skin substitute manufactured by Systagenix (Promogran Prisma²⁵) contains silver, which is known to have antimicrobial properties and is used to treat infected wounds.

There is no clear guidance on the exact indications for the use of skin substitutes because of heterogeneity in comorbidities and a lack of comparative studies in this area.²⁶

Regulatory Information

Some skin substitutes are classified by Health Canada under the Cells, Tissues, and Organs category, and others under the Devices category. Table 1 shows the brands of skin substitutes that have received a Health Canada licence.

Table 1: Skin Substitutes With a Health Canada Licence

Product	Company, Location	Licence No.	Layering	Replaced Region	Materials Used
AlloDerm	LifeCell, Branchburg, NJ, United States	100128 (CTO)	Single-layer	Dermis	Natural: acellular dermis from cadaver
Biobrane	UDL Laboratories, Inc., Rockford, IL, United States	98343 (Devices)	Multi-layer	Epidermis and dermis (full-thickness)	Natural and synthetic: silicone, nylon mesh, porcine collagen
EpiFix	MiMedx, Marietta, GA, United States	100204 (CTO)	Single-layer	Dermis	Natural: dehydrated human amnion/chorion membrane
Integra Dermal Regeneration Template	Integra LifeSciences Corporation, Plainsboro, NJ, United States	229 (Devices)	Multi-layer	Epidermis and dermis (full-thickness)	Natural and synthetic: silicone, bovine collagen type I, chondroitin-6-sulphate
Integra Flowable Wound Matrix	Integra LifeSciences Corporation, Plainsboro, NJ, United States	96660 (Devices)	Multi-layer	Epidermis and dermis (partial- and full-thickness)	Natural and synthetic: granulated cross-linked bovine tendon collagen and glycosaminoglycan
Nanoderm	Axcelon Biopolymers Corp., London, ON	93631 (Devices)	Single-layer	Dermis	Natural: bacterial cellulose

Product	Company, Location	Licence No.	Layering	Replaced Region	Materials Used
Oasis Wound Matrix	Healthpoint, Fort Worth, TX, United States	13352 (Devices)	Single-layer	Dermis	Natural: acellular extracellular matrix (porcine small intestine submucosa)
PriMatrix	Tei Biosciences Inc., Boston, MA, United States (now acquired by Integra LifeSciences)	86784 (Devices)	Single-layer	Dermis	Natural: collagen

Abbreviation: CTO, Cells, Tissues, and Organs.

Ontario, Canadian, and International Context

In Ontario, skin substitutes are occasionally used to treat wounds that are otherwise difficult to heal with simple conventional dressings, such as moisture-retentive dressings and dressings with antiseptics (L. Teague, PhD, phone communication, August 2019). Usually, treatment is done in an outpatient setting, unless there are other complications of the diabetic foot ulcer or venous leg ulcer that require hospital admission (A. Alavi, MD, email communication, October 2019).

Skin substitutes are not publicly funded in Ontario: people must pay out of pocket to receive these treatments (L. Teague, PhD, phone communication, August 2019). The cost of a skin substitute varies depending on the brand and the size of the wound. For example, AlloDerm and Integra Dermal Regeneration Template cost about \$20 to \$40 per square centimetre,²⁷ whereas EpiDerm is sold in kits of 24 individual tissues that cost about \$1,300.²⁸ Skin substitutes are available in only a few clinics (L. Teague, PhD, phone communication, August 2019).

Expert Consultation

We engaged with experts in the specialty areas of wounds, chiropody, and dermatology to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42020162767), available at <https://www.crd.york.ac.uk/PROSPERO>.

Clinical Evidence

Research Question

What are the effectiveness and safety of skin substitutes as an adjunct to standard care, compared with standard care alone, for the treatment of adults with diabetic foot ulcers and venous leg ulcers in adults?

Methods

Clinical Literature Search

We performed a clinical literature search on November 26, 2019, using methodological filters to retrieve systematic reviews, meta-analyses, health technology assessments, and randomized controlled trials published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database, and the National Health Service Economic Evaluation Database (NHS EED). We used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.²⁹

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until the search date
- Randomized controlled trials
- Systematic reviews, meta-analyses, health technology assessments

Exclusion Criteria

- Animal and in vitro studies
- Reviews, abstracts, editorials, letters, case reports, and commentaries

PARTICIPANTS

- Adults (≥ 18 years old) with diabetic foot ulcers
- Adults (≥ 18 years old) with venous leg ulcers

INTERVENTIONS

- Skin substitutes as an adjunct to standard care

COMPARATORS

- Any standard care that included conventional dressings such as paraffin gauze, film dressings, antiseptic dressings, foam dressings, hydrocolloids, hydrogels, alginates, polysaccharide pastes, granules, or beads

OUTCOME MEASURES

- Complete wound healing
- Volume of wound healed
- Quality of life
- Adverse effects

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence³⁰ and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. A single reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

Statistical Analysis

Owing to variations in the format used to present the risk measures of effect across studies, we converted all measures to risk difference for ease of comparison. For studies with large cell counts (i.e., those in which the expected number of observations for each combination of treatment and outcome was ≥ 5), we used the normal approximation to compute confidence intervals. When at least one cell count was too small (< 5), we used the exact method of Shan and Wang.³¹ Because of substantial

heterogeneity in the types of skin substitute and the modes of standard care used, we did not conduct a meta-analysis; rather, we used graphs to summarize information.

Appendix 2 provides two forest plots of the findings for one brand of skin substitutes (EpiFix) used in the economic analysis. The two studies were similar enough in terms of treatments and population characteristics to allow pooling. We analyzed the data using R version 3.5.0,³² and SAS version 9.4.³³

Critical Appraisal of Evidence

We assessed risk of bias using the Cochrane risk-of-bias tool for randomized trials, version 2 (Appendix 3).³⁴ The risk of bias was assessed based on the following domains: randomization process, deviation from intended intervention (effect of adhering to intervention), deviation from intended intervention (effect of assignment to intervention), missing outcome data, measurement of selected outcomes, and selection of reported results.

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook*.³⁵ The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The database search of the clinical literature yielded 1,294 citations published from database inception until November 26, 2019. We identified 16 additional studies from other sources, for a total of 716 citations after removing duplicates. We found six systematic reviews, meta-analyses, or health technology assessments that partially addressed our research question but were excluded from this review because their scope was either too narrow or too broad for the population, interventions, or comparators we were interested in.³⁶⁻⁴¹ Nonetheless, we did use them to identify any randomized controlled trials that might have been missed by our search strategy; we have briefly mentioned these reviews in the Discussion section. In total, we identified 40 randomized controlled trials that met our inclusion criteria. See Appendix 4 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

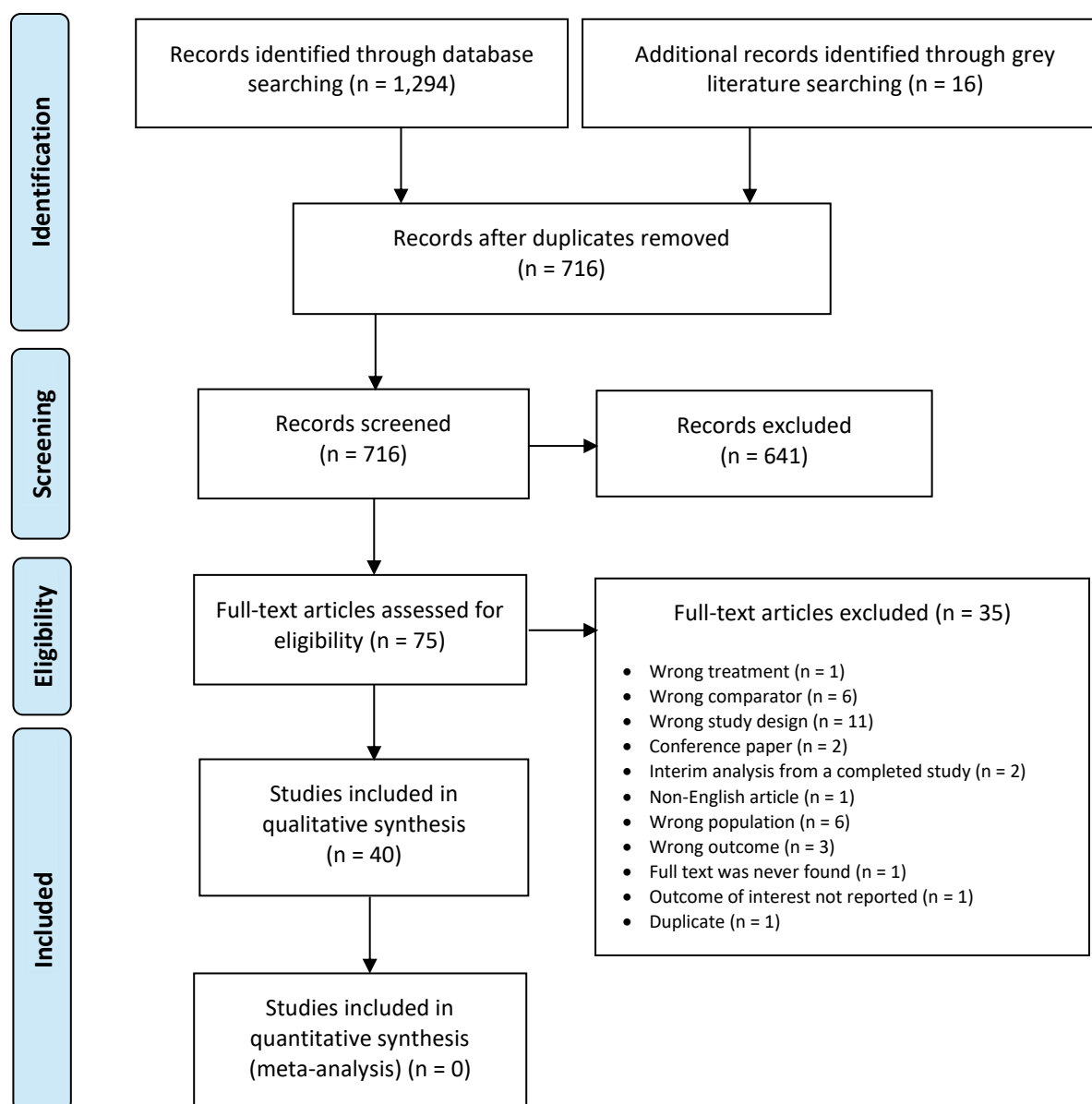


Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Moher et al.⁴²

Characteristics of Included Studies

Of the 40 eligible studies, 26 evaluated dermal substitutes,⁴³⁻⁶⁸ 12 evaluated multi-layered substitutes,^{61,69-79} and three focused on epidermal substitutes (Table 2).⁸⁰⁻⁸² The run-in period (the screening period to confirm that the wound was difficult to heal) was reported in 27 studies and ranged from 1 to 2 weeks. Twenty-nine studies assessed the effectiveness of skin substitutes in adults with neuropathic diabetic foot ulcers and 12 in adults with venous leg ulcers. The duration of follow-up ranged from 4 to 24 weeks for diabetic foot ulcers and 4 to 26 weeks for venous leg ulcers. The types of wound dressing used in standard care varied widely across studies.

With the exception of Veves et al,⁷⁴ who evaluated the effectiveness of Promogran (which is indicated for infected wounds), all other studies excluded wounds with infections (i.e., they evaluated skin substitutes contraindicated for infected wounds). In most studies, to be eligible, the wound area had to be 1 cm² to 25 cm². Other eligibility criteria for diabetic foot ulcer studies included a glycated hemoglobin (A1C) level of less than 12%, adequate circulation to the affected foot, Wagner ulcer classification (a classification system for diabetic foot ulcers) grade of 1 or 2, and the ability to comply with offloading and dressing-change requirements. For venous leg ulcer studies, other eligibility criteria were an ankle-brachial pressure index of greater than 0.75, adequate circulation to the affected foot, and the ability to comply with offloading and dressing-change requirements.

Table 2: Characteristics of Included Studies

Study, Year (Country)	Intervention (Brand), ^a Class	Control ^b	Patients, n	Run-in Period, wk ^c	Follow-up, wk
Neuropathic Diabetic Foot Ulcers					
Alvarez et al, 2017 ⁶⁹ (United States) ^d	Porcine urinary bladder–derived extracellular matrix (Cytal), multi-layered	Standard care	17	NR	16
Brigido et al, 2004 ⁴³ (United States) ^d	Human dermis acellular matrix (Graftjacket), dermal	Standard care	40	NR	4
Brigido, 2006 ⁴⁴ (United States) ^d	Human dermis acellular matrix (Graftjacket), dermal	Standard care	28	NR	16
Campitiello et al, 2017 ⁶⁵ (Italy)	Bovine tendon collagen and glycosaminoglycan dermal matrix (Integra Flowable Wound Matrix), dermal	Standard care	46	NR	6
Caravaggi et al, 2003 ⁴⁵ (Italy) ^d	Autologous dermal matrix (Hyalograft 3D plus Laserskin), dermal	Standard care	79	2	12
Cazzell et al, 2015 ⁷⁰ (United States) ^d	Porcine small intestine submucosa tri-layered matrix (Oasis), multi-layered	Standard care	82	NR	16
Cazzell et al, 2017 ⁴⁶ (United States) ^d	Acellular human tissue dermal matrix (Dermacell), dermal	Standard care	168	NR	24
DiDomenico et al, 2016 ⁴⁷ (United States) ^d	Dehydrated human amnion/chorion membrane (AmnioBand), dermal	Standard care	80	2	12
Di Mauro et al, 1991 ⁸³ (Italy)	Lyophilized type I collagen, dermal	Standard care	20	NR	NR
Edmonds et al, 2009 ⁷¹ (Sweden, United Kingdom, Austria, Finland, Australia) ^d	Living cell human–bovine bi-layered matrix (Apligraf), multi-layered	Standard care	154	2	12
Gentzkow et al, 1996 ⁴⁸ (United States) ^d	Cryopreserved human dermal substitute (Dermagraft), dermal	Standard care	50	NR	12
Hanft and Surprenant, 2002 ⁴⁹ (United States) ^d	Cryopreserved human dermal substitute (Dermagraft), dermal	Standard care	46	2	12

Study, Year (Country)	Intervention (Brand), ^a Class	Control ^b	Patients, n	Run-in Period, wk ^c	Follow-up, wk
Lavery et al, 2014 ⁵⁰ (United States) ^d	Cryopreserved human amniotic membrane (Graftix), dermal	Standard care	97	1	12
Lipkin et al, 2003 ⁷² (United States)	Human bi-layered cellular matrix (Orcel), multi-layered	Standard care	28	2	12
Marston et al, 2003 ⁵¹ (United States) ^d	Cryopreserved human dermal substitute (Dermagraft), dermal	Standard care	245	2	12
Mohajeri-Tehrani et al, 2016 ⁵² (Iran)	Acellular human amniotic collagen membrane (LifePatch), dermal	Standard care	57	NR	6
Pollak et al, 1997 ⁵³ (United States) ^d	Cryopreserved human dermal substitute (Dermagraft), dermal	Standard care	281	2	32
Serena et al, 2020 ⁵⁴ (United States) ^d	Hypothermically stored amniotic membrane, dermal	Standard care	76	2	16
Snyder et al, 2016 ⁵⁵ (United States) ^d	Dehydrated human amniotic membrane allograft (Amnioexcel), dermal	Standard care	29	2	6
Tettelbach et al, 2019 ⁵⁶ (United States) ^d	Dehydrated human umbilical cord (EpiCord), dermal	Standard care	155	2	12
Tettelbach et al, 2019 ⁵⁷ (United States) ^d	Dehydrated human amnion/chorion membrane (EpiFix), dermal	Standard care	110	2	12
Uccioli et al, 2011 ⁵⁸ (Italy) ^d	Dermal autologous graft (Hyalograft-3D), dermal	Standard care	160	2	12
Veves et al, 2001 ⁷³ (United States) ^d	Bi-layered human living cell substitute (Graftskin), multi-layered	Standard care	208	1	12
Veves et al, 2002 ⁷⁴ (United States) ^d	Freeze-dried collagen matrix (Promogran), multi-layered	Standard care	276	NR	12
Zelen, 2013 ⁵⁹ (United States)	Dehydrated human amnion/chorion membrane (EpiFix), dermal	Standard care	25	NR	12

Study, Year (Country)	Intervention (Brand), ^a Class	Control ^b	Patients, n	Run-in Period, wk ^c	Follow-up, wk
Zelen et al, 2014 ⁶⁰ (United States) ^d	Dehydrated human amnion/chorion membrane (EpiFix), dermal Bi-layered human living cell substitute (Apligraf), multi-layered	Standard care	60	2	6
Zelen et al, 2016 ⁶² (United States)	Dehydrated human amnion/chorion membrane (EpiFix), dermal Bi-layered human living cell substitute (Apligraf), multi-layered	Standard care	100	2	12
Zelen et al, 2017 ⁶¹ (United States)	Acellular human dermal matrix (AlloPatch), dermal	Standard care	40	2	12
Zelen et al, 2018 ⁶³ (United States)	Acellular human dermal matrix (AlloPatch), dermal	Standard care	80	2	12
Venous Leg Ulcers					
Bianchi et al, 2019 ⁶⁴ (United States) ^d	Dehydrated human amnion/chorion membrane (EpiFix), dermal	Standard care	128	2	16
Cazzell, 2019 ⁶⁶ (United States) ^d	Acellular human dermal matrix (Dermacell), dermal	Standard care	28	NR	24
Demling et al, 2004 ⁷⁶ (United States, Canada) ^d	Porcine small intestinal submucosa wound matrix (Oasis), multi-layered	Standard care	84	2	12
Falanga and Sabolinski, 1999 ⁷⁸ (United States) ^d	Living cell human–bovine bi-layered matrix (Apligraf), multi-layered	Standard care	120	NR	24
Falanga et al, 1998 ⁷⁷ (United States) ^d	Bi-layered allogeneic human skin equivalent (not commercialized), multi-layered	Standard care	293	NR	26
Harding et al, 2005 ⁸⁰ (Belgium, United Kingdom, Germany, Poland) ^d	Freeze-dried cultured allogeneic epidermal substitute (LyphoDerm), epidermal	Standard care	194	4	24
Harding et al, 2013 ⁶⁷ (United Kingdom, United States, Canada) ^d	Cryopreserved human dermal substitute (Dermagraft), dermal	Standard care	366	2	12

Study, Year (Country)	Intervention (Brand), ^a Class	Control ^b	Patients, n	Run-in Period, wk ^c	Follow-up, wk
Krishnamoorthy et al, 2003 ⁶⁸ (United Kingdom, Canada) ^d	Cryopreserved human dermal substitute (Dermagraft), dermal	Standard care	53	2	12
Mostow et al, 2005 ⁷⁹ (United States, United Kingdom, Canada) ^d	Porcine small-intestine submucosa wound matrix (Oasis), multi-layered	Standard care	120	2	12
Teepe et al, 1993 ⁸¹ (Netherlands, Belgium)	Cultured cryopreserved epidermal allografts (not commercialized), epidermal	Standard care	47	2	6
Wille et al, 2011 ⁸² (United States) ^d	A living serum-free cultured epidermal autograft (not commercialized), epidermal	Standard care	15	NR	12

Abbreviations: DFU, diabetic foot ulcer; NR, not reported; VLU, venous leg ulcer.

^aAll interventions included standard care. For commercialized products, the trade name is in parentheses.

^bStandard care included conventional wound dressings; the type of conventional dressings varied across studies.

^cScreening period to confirm that the wound was unhealed.

^dDisclosed that the study was industry sponsored.

Risk of Bias in the Included Studies

For most studies, the risk of bias was low. We noted a high risk of bias in only one study on venous leg ulcers, in which the dropout rate was high. We were unable to predict the direction of this bias.

There were some concerns about risk of bias in a few studies. For studies focusing on diabetic foot ulcers, the concerns were mainly related to the randomization process (n = 8), deviation from the intended intervention in terms of the effect of adhering to the intervention (n = 2), and deviation from the intended intervention in terms of the effect of assignment to intervention (n = 2). For studies on venous leg ulcers, concerns were mainly related to the randomization process (n = 1), deviation from the intended intervention in terms of the effect of adhering to the intervention (n = 2), deviation from the intended intervention in terms of the effect of assignment to intervention (n = 1), and selection of reported results (n = 1). See Appendix 2 for more details.

Complete Wound Healing

Of the 40 studies evaluated, all assessed the outcome of complete wound healing. Of those, 26 studies evaluated the effectiveness of dermal substitutes (Table 3), 12 evaluated the effectiveness of multi-layered substitutes (Table 4), and three evaluated the effectiveness of epidermal substitutes (Table 5).

We also calculated the risk difference for complete wound healing compared to standard care, stratified by study run-in period (Figure 2), follow-up period (Figure 3), class of skin substitute and type of dressing used in standard care (Figure 4), and class of skin substitute only (Figure 5).

Table 3: Risk Difference of Dermal Substitutes Versus Standard Care for Complete Wound Healing

Study, Year	Complete Wound Healing		
	Intervention (n/Total)	Standard Care (n/Total)	Risk Difference (95% CI) ^a
Neuropathic Diabetic Foot Ulcers			
Brigido et al, 2004 ⁴³	Graftjacket (14/14)	Debridement, Curasol wound gel with gauze dressings, standardized offloading (4/14)	0.71 (0.406 to 0.919)
Brigido, 2006 ⁴⁴	Graftjacket (12/14)	Debridement, moist dressing, offloading (4/14)	0.57 (0.180 to 0.834)
Caravaggi et al, 2003 ⁴⁵	Hyalograft 3D (28/43)	Sterile saline-moistened gauze (18/36)	0.15 (−0.076 to 0.379)
Cazzell et al, 2017 ⁴⁶	Dermacell (50/71)	Debridement followed by moist wound treatment with alginate, foam, or hydrogel dressings (34/69)	0.21 (0.048 to 0.392)
DiDomenico et al, 2016 ⁴⁷	AmnioBand (27/40)	Collagen-alginate (8/40)	0.48 (0.284 to 0.666)
Gentzkow et al, 1996 ⁴⁸	Dermagraft (6/12)	Debridement, dressings, and pressure relief (1/13)	0.42 (0.063 to 0.712)
Hanft and Surprenant, 2002 ⁴⁹	Dermagraft (12/24)	Nonadherent interface, saline-moistened gauze, dry gauze, and adhesive tape; in addition, shoe gear with custom-moulded inserts to relieve pressure at the ulcer site (6/22)	0.23 (−0.072 to 0.489)
Lavery et al, 2014 ⁵⁰	Grafix (31/50)	Surgical debridement, offloading and nonadherent dressings (10/47)	0.41 (0.229 to 0.586)
Marston et al, 2003 ⁵¹	Dermagraft (39/130)	Nonadherent interface, saline-moistened gauze, dry gauze, and adhesive fixation sheets (Hypafix) (21/115)	0.12 (0.001 to 0.235)
Mohajeri-Tehrani et al, 2016 ⁵²	LifePatch (11/27)	Wet dressing (5/30)	0.24 (−0.028 to 0.482)
Pollak et al, 1997 ⁵³	Dermagraft (54/139)	Debridement, moist dressings, and pressure relief (45/142)	0.07 (−0.040 to 0.183)
Serena et al, 2020 ⁵⁴	Hypothermically stored amniotic membrane, not commercialized (24/38)	Sharp debridement, moist primary wound contact dressings, and total contact casting (14/38)	0.26 (0.046 to 0.480)
Snyder et al, 2016 ⁵⁵	Amnioexcel (5/15)	Debridement, moist wound dressings, offloading (0/14)	0.33 (0.070 to 0.619)
Tettelbach et al, 2019 ⁵⁶	EpiCord (71/101)	Debridement, alginate wound, nonadherent silicone dressing (26/54)	0.22 (0.061 to 0.382)

Study, Year	Complete Wound Healing		
	Intervention (n/Total)	Standard Care (n/Total)	Risk Difference (95% CI) ^a
Tettelbach et al, 2019 ⁵⁷	EpiFix (38/54)	Alginate dressings, absorbent nonadhesive hydropolymer secondary dressings, gauze (28/56)	0.20 (0.025 to 0.383)
Uccioli et al, 2011 ⁵⁸	Hyalograft-3D (19/37)	Nonadherent paraffin gauze (17/47)	0.15 (−0.060 to 0.364)
Zelen et al, 2013 ⁵⁹	EpiFix (12/13)	Moist wound therapy (1/12)	0.84 (0.478 to 0.973)
Zelen et al, 2014 ⁶⁰	EpiFix (19/20)	Debridement, collagen-alginate (7/20)	0.60 (0.330 to 0.796)
Zelen et al, 2016 ⁶²	EpiFix (31/32)	Collagen-alginate dressings (18/35)	0.45 (0.267 to 0.623)
Zelen et al, 2017 ⁶¹	AlloPatch (13/20)	Dressing with collagen-alginate (1/20)	0.60 (0.330 to 0.796)
Zelen et al, 2018 ⁶³	AlloPatch (34/40)	Dressing with collagen-alginate (12/40)	0.55 (0.343 to 0.710)
Venous Leg Ulcers			
Bianchi et al, 2019 ⁶⁴	EpiFix (38/64)	Moist dressings and multi-layer compression (25/64)	0.20 (0.034 to 0.373)
Campitiello et al, 2017 ⁶⁵	Integra Flowable Wound Matrix (20/23)	Wet dressing (12/23)	0.35 (0.081 to 0.577)
Cazzell, 2019 ⁶⁶	Dermacell (5/17)	Debridement and dressings with alginates, foams, or hydrogels (3/9)	−0.04 (−0.425 to 0.323)
Harding et al, 2013 ⁶⁷	Dermagraft (35/95)	Dressing with hydrocolloid and compression therapy (26/98)	0.12 (−0.009 to 0.246)
Krishnamoorthy et al, 2003 ⁶⁸	Dermagraft(5/13)	Compression bandaging (2/13)	0.23 (−0.131 to 0.575)

Abbreviations: CI, confidence interval; DFU, diabetic foot ulcer; VLU, venous leg ulcer.

^aComputed by the authors of this health technology assessment; for sparse data, we used the method of Shan and Wang.³¹

Table 4: Effectiveness of Multi-layered (Bi-layered and Tri-layered) Skin Substitutes Versus Standard Care for Complete Wound Healing

Study, Year	Complete Wound Healing		
	Intervention (n/Total)	Standard Care (n/Total)	Risk Difference (95% CI) ^a
Neuropathic Diabetic Foot Ulcers			
Alvarez et al, 2017 ⁶⁹	Cytal (11/11)	Nonadherent dressing plus a total contact cast (5/6)	0.17 (−0.148 to 0.641)
Cazzell et al, 2015 ⁷⁰	Oasis (22/41)	Debridement, saline-moistened dressing (13/41)	0.23 (−0.008 to 0.446)
Edmonds et al, 2009 ⁷¹	Apligraf (17/33)	Debridement, saline-moistened dressings, and a non-weight bearing regimen (10/39)	0.26 (0.040 to 0.478)
Lipkin et al, 2003 ⁷²	Orcel (5/15)	Sharp wound debridement, moist saline gauze with a layer of transparent adhesive dressing (3/13)	0.10 (−0.253 to 0.446)
Veves et al, 2001 ⁷³	Graftskin (63/112)	Saline-moistened gauze (36/96)	0.19 (0.054 to 0.321)
Veves et al, 2002 ⁷⁴	Promogran (51/138)	Debridement, moistened gauze, and a secondary dressing (39/138)	0.09 (−0.023 to 0.197)
Zelen et al, 2015 ^{75b}	Apligraf (7/20)	Debridement, collagen-alginate dressings, gauze, and an offloading cast walker (6/20)	0.05 (−0.270 to 0.332)
Zelen et al, 2017 ⁶¹	Apligraf (24/33)	Collagen-alginate dressing (18/35)	0.21 (−0.012 to 0.438)
Venous Leg Ulcers			
Demling et al, 2004 ⁷⁶	Oasis (32/45)	Cleansing, debridement, nonadherent dressing, and compression therapy (18/39)	0.25 (0.045 to 0.455)
Falanga and Sabolinski, 1999 ⁷⁸	Apligraf (11/48)	Standard multi-layer compression therapy (8/72)	0.12 (−0.021 to 0.257)
Falanga et al, 1998 ⁷⁷	Bi-layered allogeneic human skin equivalent, not commercialized (92/146)	Nonadherent dressing gauze bolster, zinc-oxide-impregnated paste bandage, and self adherent plastic wrap (63/129)	0.14 (0.025 to 0.258)
Mostow et al, 2005 ⁷⁹	Oasis (34/62)	Nonadherent dressing and compression therapy (20/58)	0.20 (0.030 to 0.378)

Abbreviations: CI, confidence interval; DFU, diabetic foot ulcer; VLU, venous leg ulcer.

^aComputed by the authors of this health technology assessment; for sparse data, we used the method of Shan and Wang.³¹

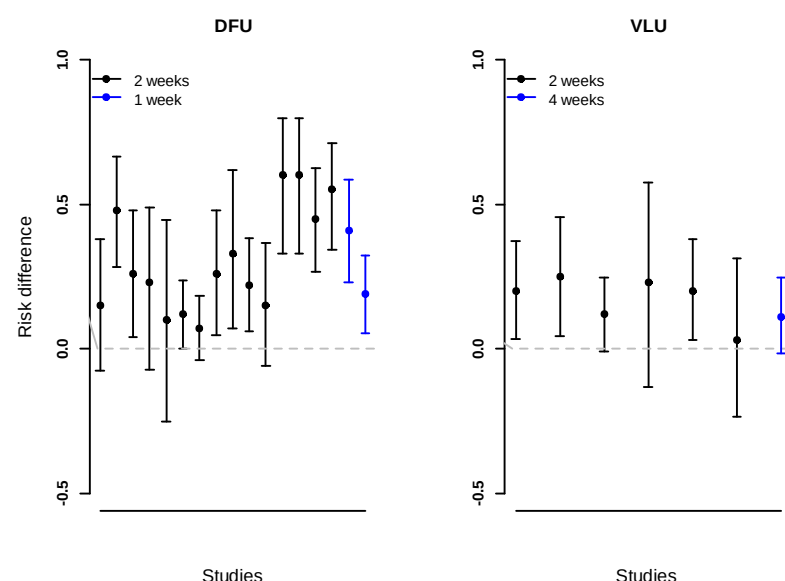
^bInterim analysis of Zelen et al, 2017.⁶¹

Table 5: Effectiveness of Epidermal Skin Substitutes Versus Standard Care for Complete Wound Healing

Study, Year	Complete Wound Healing		
	Intervention (n/Total)	Standard Care (n/Total)	Risk Difference (95% CI) ^a
Venous Leg Ulcers			
Harding et al, 2005 ⁸⁰	LyphoDerm (36/95)	Hydrocolloid dressings and compression therapy (26/98)	0.11 (–0.017 to 0.245)
Teepe et al, 1993 ⁸¹	Cultured cryopreserved epidermal allografts, not commercialized (6/22)	Hydrocolloid dressings (5/21)	0.03 (–0.237 to 0.311)
Wille et al, 2011 ⁸²	A living serum-free cultured epidermal autograft, not commercialized (8/10)	Debridement, saline dressing, and compression therapy (1/5)	0.60 (0.019 to 0.905)

Abbreviations: CI, confidence interval; VLU, venous leg ulcer.

^aComputed by the authors of this health technology assessment; for sparse data, we used the method of Shan and Wang.³¹

**Figure 2: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care—Stratified by Run-In Period**

Abbreviations: DFU, diabetic foot ulcer; VLU, venous leg ulcer.

Note: Studies that did not report the run-in period are not included in the plots.

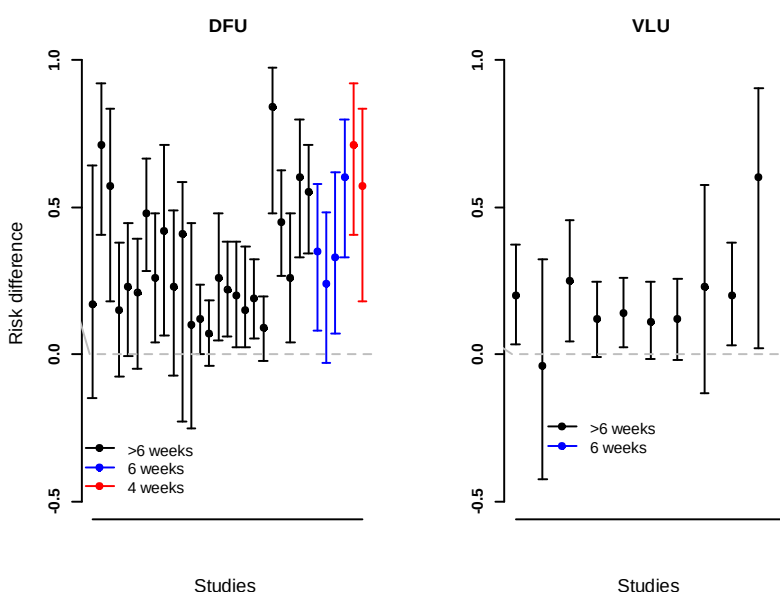


Figure 3: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care—Stratified by Duration of Follow-up

Abbreviations: DFU, diabetic foot ulcer; VLU, venous leg ulcer.

Note: Studies that did not report the duration of follow-up are not included in the plots.

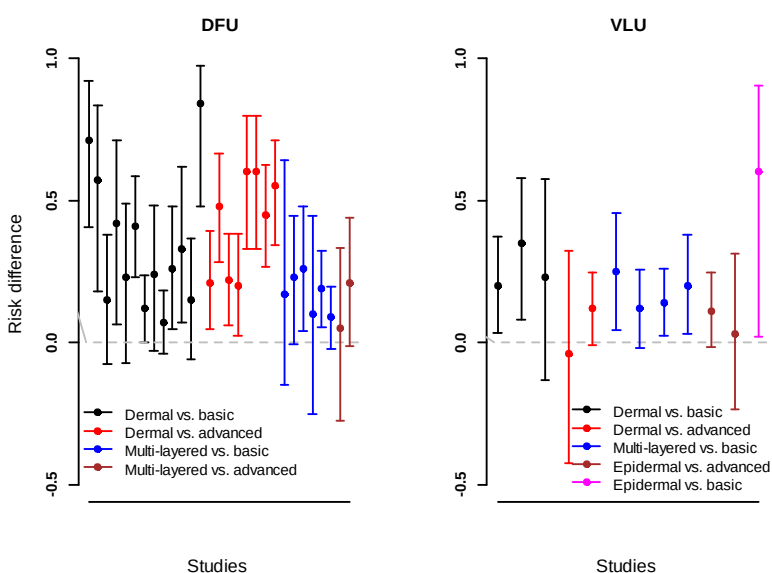


Figure 4: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care—Stratified by Class of Skin Substitute and Type of Dressing Used in Standard Care

Abbreviations: DFU, diabetic foot ulcer; VLU, venous leg ulcer.

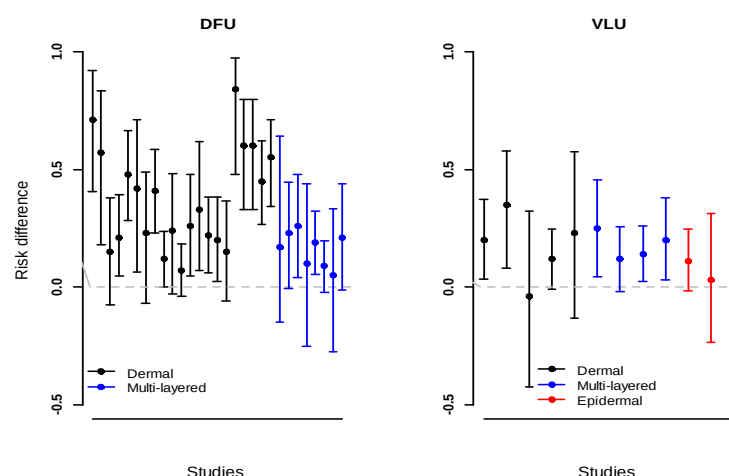


Figure 5: Risk Difference for Complete Wound Healing Between Skin Substitutes and Standard Care—Stratified by Class of Skin Substitute

Abbreviations: DFU, diabetic foot ulcer; VLU, venous leg ulcer.

DIABETIC FOOT ULCERS

Twenty-one of 29 studies (72%) disclosed that they were industry sponsored. Most dermal substitutes demonstrated complete healing for adults with neuropathic diabetic foot ulcers. The GRADE rating of our certainty in the evidence for this outcome was High (Tables A1 and A2).

Evidence of complete healing for multi-layered substitutes was clear in two^{71,73} of seven studies. All point estimates from the other five studies^{61,69,72,73,74} favoured multi-layered substitutes, but the confidence intervals were too wide. As a result, we downgraded the GRADE rating of our certainty in the evidence for this outcome to Moderate because of imprecision.

VENOUS LEG ULCERS

Eleven of 12 studies (92%) disclosed that they were industry sponsored. Evidence of complete wound healing for dermal substitutes in adults with venous leg ulcers was clearly demonstrated in two^{64,65} of five studies. The remaining three studies reported point estimates that were imprecise; two^{67,68} favoured dermal substitutes and one⁶⁶ favoured standard care. As a result, we downgraded the GRADE rating of our certainty in the evidence for this outcome to Moderate because of imprecision.

Evidence of complete healing for multi-layered substitutes was clearly demonstrated in three^{76,77,79} of four studies. The GRADE rating of our certainty in the evidence for this outcome was High.

Three studies^{80,81,82} evaluated epidermal substitutes. All three focused primarily on the outcome of complete wound healing. Although all three studies reported point estimates in favour of epidermal substitutes, the confidence intervals were too wide. As a result, we downgraded the GRADE rating of our certainty in the evidence for this outcome to Very low.

We also noted that, for dermal and epidermal substitutes, the point estimates tended to be higher when basic wound dressings (e.g., paraffin gauze) were part of standard care, rather than advanced dressings

(e.g., hydrocolloids; Figure 4). We found no studies for venous leg ulcers on multi-layered substitutes versus standard care involving advanced dressings.

Volume of Wound Healed

Only one study assessed the volume of wound healed.⁴⁴ Although the authors presented the findings for this outcome in graph form only, there seemed to be no difference in the percentage volume of wound healed between the treatment and control groups after 17 weeks of follow-up.

We did not perform a GRADE assessment on this outcome because no information was presented that would have allowed us to evaluate precision.

Quality of Life

No studies evaluated quality of life.

Adverse Effects

Of the 40 included studies, 30 evaluated adverse effects (Table 6). Because adverse effects occurred sporadically and sample sizes were small, no studies conducted a formal safety comparison between skin substitutes and standard care. For the few adverse effects that were reported, dryness, inflammation, ischemia, injury, poisoning, and procedural complications were most commonly observed for dermal substitutes; maceration was most commonly observed for multi-layered substitutes; and general disorders and administrative site conditions were most commonly observed for epidermal substitutes.

Table 6: Adverse Effects

Study, Year	Class of Skin Substitute (Brand)	Adverse Effects (Number of People)	
		Intervention	Standard Care
Neuropathic Diabetic Foot Ulcers			
Brigido et al, 2004 ⁴³	Dermal (Graftjacket)	Dryness (5), seroma (1)	None
Brigido, 2006 ⁴⁴	Dermal (Graftjacket)	Seroma (1), dryness (4)	NR
Caravaggi et al, 2003 ⁴⁵	Dermal (Hyalograft 3D and Laserskin)	Inflammation ischemia (7)	Inflammation ischemia (7)
Cazzell et al, 2015 ⁷⁰	Multi-layered (Oasis)	Maceration (26)	Maceration (26)
Cazzell et al, 2017 ⁴⁶	Dermal (Dermacell)	None	None
DiDomenico et al, 2016 ⁴⁷	Dermal (AmnioBand)	None	None
Edmonds et al, 2009 ⁷¹	Multi-layered (Apligraf)	None	None
Gentzkow et al, 1996 ⁴⁸	Dermal (Dermagraft)	None	None
Hanft and Surprenant, 2002 ⁴⁹	Dermal (Dermagraft)	None	None
Lavery et al, 2014 ⁵⁰	Dermal (Grafix)	Injury, poisoning, procedural complications (5)	Injury, poisoning, procedural complications (7)
Lipkin et al, 2003 ⁷²	Multi-layered (Orcel)	None	None
Marston et al, 2003 ⁵¹	Dermal (Dermagraft)	None	None
Serena et al, 2020 ⁵⁴	Dermal	Maceration (1)	None
Snyder et al, 2016 ⁵⁵	Dermal (Amnioexcel)	None	None
Tettelbach et al, 2019 ⁵⁶	Dermal (EpiCord)	None	None
Tettelbach et al, 2019 ⁵⁶	Dermal (EpiFix)	Maceration (1), wound cultures (2)	None
Uccioli et al, 2011 ⁵⁸	Dermal (Hyalograft-3D)	None	None
Veves et al, 2001 ⁷³	Multi-layered (Graftskin)	None	None
Veves et al, 2002 ⁷⁴	Multi-layered (Promogran)	None	None
Zelen et al, 2013 ⁸⁴	Dermal (EpiFix)	None	None
Zelen et al, 2014 ⁶⁰	Dermal (EpiFix)	None	None
Zelen et al, 2016 ⁶²	Dermal (EpiFix)	None	None
Zelen et al, 2018 ⁶³	Dermal (AlloPatch)	None	None

Study, Year	Class of Skin Substitute (Brand)	Adverse Effects (Number of People)	
		Intervention	Standard Care
Venous Leg Ulcers			
Bianchi et al, 2019 ⁶⁴	Dermal (EpiFix)	Not broken down; could not isolate adverse effects from adverse events	Not broken down; could not isolate adverse effects from adverse events
Falanga and Sabolinski, 1999 ⁷⁸	Multi-layered (Apligraf)	None	None
Harding et al, 2005 ⁸⁰	Epidermal (LyphoDerm)	General disorders and reactions at the site where dressing were applied (4)	General disorders and reactions at the site where dressing were applied (3)
Harding et al, 2013 ⁶⁷	Dermal (Dermagraft)	Not broken down; could not isolate adverse effects from adverse events	Not broken down; could not isolate adverse effects from adverse events
Krishnamoorthy et al, 2003 ⁶⁸	Dermal (Dermagraft)	Treatment-related infection (1)	None
Mostow et al, 2005 ⁷⁹	Multi-layered (Oasis)	Allergic reaction or intolerance to secondary dressing (3)	Allergic reaction or intolerance to secondary dressing (3), seroma (1)
Wille et al, 2011 ⁸²	Epidermal (uncommercialized)	None	None

Abbreviations: DFU, diabetic foot ulcer, NR, not reported; VLU, venous leg ulcer.

Ongoing Studies

We are aware of two ongoing randomized controlled trials on diabetic foot ulcers registered in clinicaltrials.gov, which were estimated to be completed in February 2017 (identifier: NCT02081352) and May 2018 (identifier: NCT02870816), but the current status of both is unknown.

Discussion

All studies eligible for this review were restricted to difficult-to-heal diabetic foot ulcers and venous leg ulcers. We encountered heterogeneity in the types of intervention, duration of follow-up, definitions of difficult-to-heal wound, and definition of standard care across the included studies. Despite this heterogeneity, studies consistently reported point estimates in favour of skin substitutes over standard care. However, not all studies reported point estimates precise enough to conclude that skin substitutes are effective. Thus, our conclusions with moderate or high certainty in the evidence for treatment effectiveness relied largely on studies with both precise estimates and low risk of bias.

Because the wound dressings used in standard care could have varying degrees of potency, caution should be exercised when interpreting effect sizes, because the effect size depends not only on the potency of the skin substitute but also on the potency of the standard care. For example, if advanced wound dressings such as hydrocolloids, alginates, foams, hydrogels, and films are more effective than

basic dressings such paraffin gauze (as reported in some studies),²² it would not be surprising to observe smaller effect sizes in studies of skin substitutes that used advanced dressings as controls. In cases in which a small risk difference was reported, it was difficult to determine whether this reflected low potency of the skin substitute. Most studies were industry sponsored. However, based on the information provided by these studies, it was impossible to determine if the source of funding had any bearing on the reported findings.

This health technology assessment focused on tissue-based therapies; therapies based on cells, such as stem cells or platelets, were out of scope. Tissue-based skin substitutes are usually made of components derived from extracellular matrix (a network of extracellular macromolecules that coordinate communication between cells) or placental-based allografts. Currently, most commercialized skin substitutes are not indicated for infected wounds, because they lack immunoregulatory cells such as Langerhans cells.²² For this reason, almost all studies excluded people with infected wounds. However, research on integrating immunological components into skin substitutes is ongoing.

This clinical evidence review identified no studies that evaluated quality of life. The short follow-up adopted in eligible studies (4 to 26 weeks) could explain why quality of life was not assessed. Furthermore, diabetic foot ulcers usually manifest at an advanced stage of diabetes, which includes other complications, so quality of life associated with diabetic foot ulcers could have been masked by the effects of these complications. As well, we did not assess the effect of skin substitutes on wound recurrence, because recurrence could be explained by the failure to manage the underlying cause of the ulcer, such as diabetic neuropathy or inadequate use of protective footwear. Most studies restricted their populations to those who were most likely to adhere to treatment, so treatment effects reported in these studies may overestimate real-world experience. Adverse effects were rare or nonexistent, and studies were not adequately powered to evaluate this outcome. Thus, we did not conduct a formal safety comparison between skin substitutes and standard care. The main strength of this clinical evidence review was the availability of many studies of fairly good quality.

We found several systematic reviews and/or meta-analyses that assessed the benefits of skin substitutes but focused on a different research question or a population different from ours. The United States Agency for Healthcare Research and Quality³⁶ conducted a health technology assessment on commercialized skin substitutes used in the United States to treat all types of wounds but did not make a general statement about the evidence for the effectiveness of these products. The Canadian Agency for Drugs and Technologies in Health³⁷ conducted a health technology assessment on the effectiveness and safety of bioengineered skin substitutes in treating any difficult-to-heal wounds. They found that bioengineered skin substitutes, when used in conjunction with standard care, can promote wound closure, resulting in more frequent and more rapid healing of difficult-to-heal diabetic foot ulcers. However, the evidence for venous leg ulcers was limited. Santema et al³⁸ conducted a Cochrane review on the effectiveness and safety of skin substitutes in treating diabetic foot ulcers. They concluded that skin substitutes, when used in conjunction with standard care, show an increase in the healing rate of diabetic foot ulcers and slightly fewer amputations compared with standard care alone. Similarly, systematic reviews and meta-analyses by Guo et al³⁹ and Haugh et al⁴⁰ found that acellular and placenta-based skin substitutes were effective in improving healing rates in diabetic foot ulcers. In contrast, a systematic review by Paggiaro et al⁴¹ did not find evidence of effectiveness of placenta-based skin substitutes for diabetic foot ulcers.

Conclusions

Dermal skin substitutes, when used as an adjunct to standard care, are more effective than standard care alone in promoting complete wound healing for adults with difficult-to-heal neuropathic diabetic foot ulcers (GRADE: High) and venous leg ulcers (GRADE: Moderate). Multi-layered skin substitutes, when used as an adjunct to standard care, are more effective than standard care alone in promoting complete wound healing for adults with neuropathic difficult-to-heal diabetic foot ulcers (GRADE: Moderate) and venous leg ulcers (GRADE: High). The effectiveness of epidermal skin substitutes for complete wound healing could not be determined for neuropathic diabetic foot ulcers (no studies), and evidence was uncertain for venous leg ulcers (GRADE: Very low). Finally, we were unable to form conclusions about the safety of skin substitutes versus standard care because of an insufficient number of events.

Economic Evidence

Research Questions

1. What is the cost-effectiveness of skin substitutes as an adjunct to standard care, compared with standard care alone, for the treatment of adults with diabetic foot ulcers?
2. What is the cost-effectiveness of skin substitutes as an adjunct to standard care, compared with standard care alone, for the treatment of adults with venous leg ulcers?

Methods

Economic Literature Search

We performed an economic literature search on November 28, 2019, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied. We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until the search date
- Cost–benefit analyses, cost-effectiveness analyses, cost–utility analyses

Exclusion Criteria

- Narrative reviews, editorials, case reports, commentaries, abstracts

POPULATION

- Adults (≥ 18 years old) with diabetic foot ulcers
- Adults (≥ 18 years old) with venous leg ulcers

INTERVENTIONS

- Skin substitutes as an adjunct to standard care

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence³⁰ and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.⁸⁵ We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly applicable.

Results

Economic Literature Search

The database search of the economic literature yielded 482 citations published from database inception until November 28, 2019. We identified two additional studies from other sources, for a total of 310 citations after removing duplicates. In total, we identified 14 studies that met our inclusion criteria. Figure 6 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

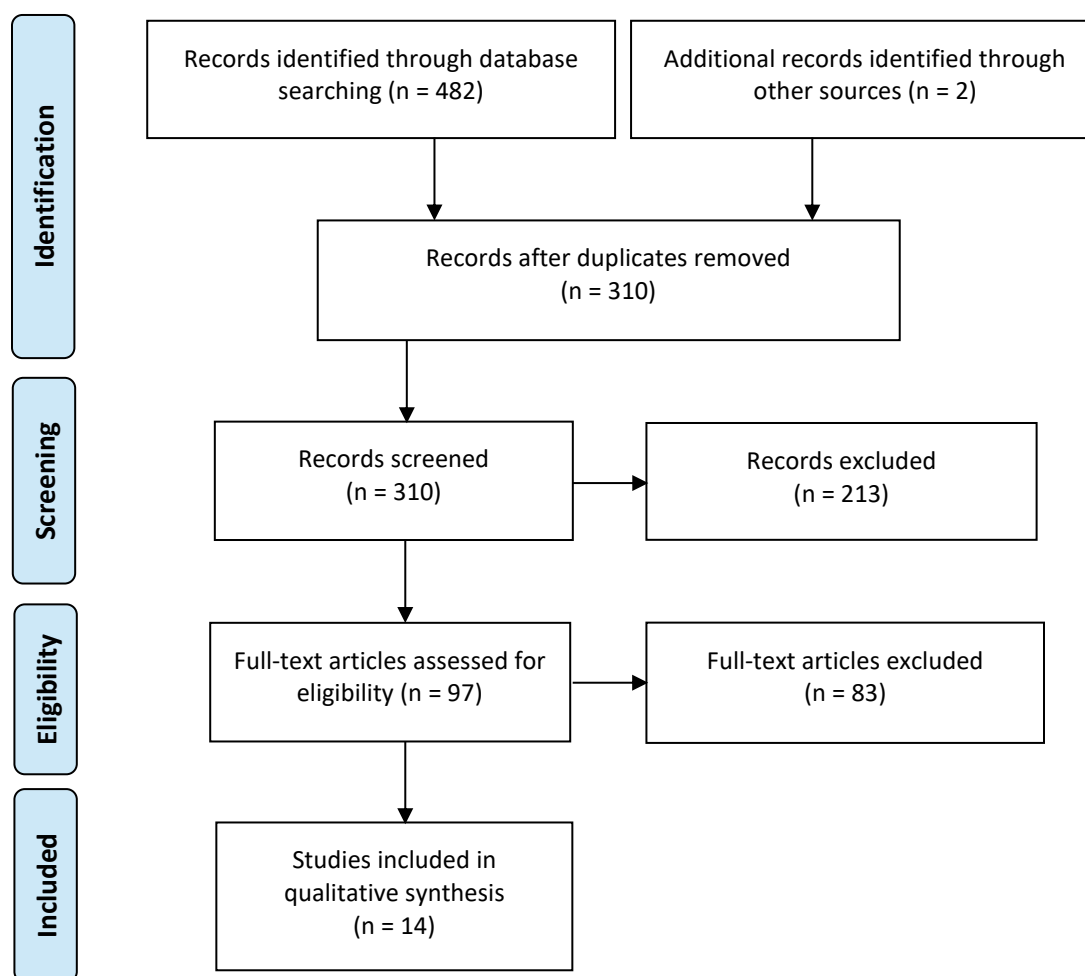


Figure 6: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Moher et al, 2009.⁴²

Overview of Included Economic Studies

We identified a total of 14 studies, including five that focused on diabetic foot ulcers⁸⁶⁻⁹⁰ and nine that focused on venous leg ulcers.⁹¹⁻¹⁰⁰ A summary of the economic literature review is presented in Appendix 6, Tables A3 (diabetic foot ulcers) and A4 (venous leg ulcers).

Most studies were cost-effectiveness analyses and reported outcome measures in cost per ulcer-free day, week, or month or in cost per additional ulcer healed. Only two studies (one on diabetic foot ulcers⁸⁶ and the other on venous leg ulcers⁹¹) conducted cost-utility analyses and reported outcomes in cost per number of quality-adjusted life-years (QALYs). Of the 14 included studies, two (on venous leg ulcers) were Canadian.^{96,97} The remaining were conducted in France,^{90,95} the Netherlands,⁸⁸ the United Kingdom,¹⁰⁰ and the United States.^{86,87,89,91-93,98-100} Markov models and decision trees were the most common study designs (used in five^{87,88,90,92,93} and four^{86,91,96,97} of the included studies, respectively). Of the remaining studies, one was a trial-based economic evaluation,⁸⁹ and the other⁹⁵ adopted a meta-

analysis approach. Across all studies, adverse events were assumed to be minimal and similar between the intervention and comparator cohorts, and a time horizon of 12 months or less was adopted.

In total, four types of skin substitute were evaluated in the included studies. Specifically, these were a simple collagen-containing dressing (two studies^{86,91}), Apligraf (Organogenesis, Inc.; eight studies^{88,89,95-100}), Dermagraft (Organogenesis, Inc.; one study⁹⁰), and Oasis (Smith and Nephew, Inc.; two studies^{87,92}). In addition, one study⁹³ compared three products (i.e., Apligraf, Dermagraft, and Oasis) with standard care in one evaluation.

Of the studies on diabetic foot ulcers, the costs and resource use included for standard care varied widely, with the mean cost ranging from £2,897⁸⁶ (over 4 months) to 47,418 French francs (FF)⁹⁰ (over 12 months). For instance, one study⁸⁶ included the costs of wound care products (e.g., dressings, bandages) and professional fees associated with at-home nurse visits and outpatient physician visits, while another study⁸⁷ also included the cost of inpatient care for the proportion of patients who developed complications requiring vascular surgery and the cost of two alternative adjunctive treatments: negative pressure wound therapy and hyperbaric oxygen therapy. Hospitalization costs make up the highest proportion of total costs and are the key drivers of costs in standard care. Of the remaining three studies⁸⁸⁻⁹⁰ that accounted for similar cost components (i.e., wound care products, offloading devices, amputation, professional fees), the one⁹⁰ that reported a significantly higher mean cost of standard care had also included the costs of 14 to 20 days of hospitalization for a proportion of the unhealed cohort that developed osteomyelitis (open deep infection).

Comparatively, there was less variation in the range of costs and resource use that accounted for standard care in the venous leg ulcer studies. Most studies accounted for the costs of wound care products, professional services associated with clinician visits (e.g., debridement, home care), and compression stockings. One study that reported a significantly higher mean cost of standard care (\$27,493 over 12 months) had also accounted for hospitalization costs for a proportion of unhealed patients.⁹⁹ The remaining studies reported standard care costs ranging from \$1,454 (over 3 months)⁹⁷ to £6,328 (over 6 months).⁹¹ These costs may be considered relatively comparable after taking into account currency exchange rates, inflation, and the period over which mean costs were reported.

Across the studies that reported skin substitute unit costs, the cost per skin substitute application and number of applications per person constituted the total additional costs associated with the adjunctive treatment with skin substitutes. Only one study included an additional professional fee associated with applying the skin substitute (\$450 per application).⁹⁹ The unit costs and number of applications per person were as follows:

- Simple collagen-containing dressing: £10.41, 3 to 13 applications^{86,91}
- Apligraf: €817⁸⁸ to \$1,578.73,⁹³ 1 to 5 applications
- Dermagraft: \$1,518.75⁹³ to 2,600 FF,⁹⁰ 4 to 7 applications
- Oasis: \$152.04⁹³ to \$527,⁸⁷ 5.73 to 8 applications

The skin substitute cost per person and the cost of skin substitute as a percentage of total cost ranged widely:

- Simple collagen-containing dressing: £31.23 (1%)⁹¹ to £135.33 (6%)⁸⁶
- Apligraf: \$950 (54%)⁹⁷ and €1,634 (35%)⁸⁸ to \$5,596 (76%)⁸⁹
- Dermagraft: 18,200 FF (33%)⁹⁰
- Oasis: \$3,019.71 (22%)⁸⁷

Most studies derived the probability of ulcer healing for the skin substitute and standard care cohorts from a single randomized controlled trial.^{87-90,92,93,96,99} Four studies derived their parameter inputs from pooled analyses of several clinical studies,^{86,91,95,100} and one⁹⁷ relied on clinical expert estimates informed by a single clinical trial.⁷⁷ The probability of ulcer healing under standard care ranged from 0.078 (over 4 months)⁸⁶ to 0.38 (over 12 weeks)^{88,89} for diabetic foot ulcers, and from 0.11 (over 6 months)⁹¹ to 0.65 (over 8 weeks)⁹² for venous leg ulcers. Comparatively, the treatment effect of skin substitutes (i.e., the difference in the probability of healing compared with the control group) ranged from 0.18 (over 12 weeks)^{88,89} to 0.453⁸⁶ (over 4 months) across diabetic foot ulcer studies, and from around 0.05⁹⁵ (over 12 weeks) to 0.38⁹¹ (over 6 months) across venous leg ulcer studies.

Six studies found skin substitutes to be the dominant strategy (i.e., less costly and more effective) compared with standard care.^{86-88,91,92,99} The savings per person ranged from \$104⁸⁷ to £654⁸⁸ for diabetic foot ulcers, and from \$13⁹² to \$7,452⁹⁹ for venous leg ulcers. Five studies found skin substitutes to be more costly but more effective than standard care.^{89,90,93,96,97} Outcomes were reported as cost per ulcer-free day (\$14 to \$21.58),^{96,97} week (\$86),⁹³ or month (\$6,683),⁸⁹ or as cost per additional ulcer healed (38,784 FF).⁹⁰ Across these studies, the main drivers of reported results included treatment effect and the additional cost of adjunctive treatment with skin substitutes. The remaining three studies^{95,98,100} found that skin substitutes were more costly and less effective than modern hydrocolloid dressings.

Applicability and Limitations of the Included Studies

Table A5 (Appendix 7), provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. All included studies were deemed partially applicable to the research question. Table A6 (Appendix 7), presents our assessment of the limitations of these studies. Of the included studies, seven^{86-88,91,95,98,100} had potentially serious limitations, and seven^{89,90,92,93,96,97,99} had potentially minor limitations. Two venous leg ulcer studies were relevant to the Ontario setting as they were conducted in Canada.^{96,97} However, these studies were published nearly two decades ago (in 2001), and the models in these studies were informed by one of the earliest clinical trials on Apligraf, published in 1998.⁷⁷ As such, neither study reflects updated clinical evidence on this skin substitute. Moreover, Apligraf is not currently licensed by Health Canada.

Discussion

Our literature review found 14 published economic evaluations on select skin substitute products for the treatment of diabetic foot ulcers and venous leg ulcers. However, it was difficult to compare results as there were significant differences across studies.

First, there was wide variation in both the reported cost of standard care and the cost of skin substitutes across diabetic foot ulcer studies, regardless of the skin substitute product under evaluation. The

variation in cost of standard care was primarily driven by the inclusion of inpatient care and hospitalization costs for a proportion of patients with unhealed ulcers that were expected to develop deep open infections or gangrene in some studies^{86,90} but not in others.⁸⁷⁻⁸⁹ The variation in cost of skin substitute was largely attributed to the differences in reported unit costs and the number of applications needed per person. In comparison, while there was greater consistency in the resources accounted for in standard care, and consequently less variation in the reported cost of standard care, a similar range of variation was observed across venous leg ulcer studies with regard to the cost of skin substitutes.

Second, the probability of ulcer healing with standard care and the treatment effect of skin substitutes differed significantly across studies. Given that treatment effect and skin substitute cost were identified as the main drivers of study outcomes, these variations across studies may have contributed to the considerable differences in reported outcomes.

Finally, four distinct skin substitute products (i.e., simple collagen-containing dressing, Apligraf, Dermagraft, Oasis) were evaluated across the included studies, and these products differed from each other in several ways, including cellularity (cellular or acellular), layering (single layer or bi-layer), replaced region (epidermis, dermis, or both), materials used (natural, synthetic, or both), permanence (temporary or permanent), and manufacturing method.¹⁰¹ As such, the unique characteristics of these various products makes it challenging to generalize treatment effect to one class of health technology.

We identified a number of limitations across studies. For instance, several studies derived treatment effect and average number of skin substitute applications from different sources. However, it may be important to obtain these parameters from the same source, as the number of applications used may impact the treatment effect of the skin substitute. In addition, most studies conducted cost-effectiveness analyses and evaluated outcomes using cost per ulcer-free day, week, or month or cost per additional ulcer healed. Only two studies conducted cost-utility analyses that evaluated cost per QALY.^{86,91} The Canadian guidelines for economic evaluations recommend the use of QALYs when possible, as this unit facilitates the broad comparison of different technologies and the allocation of resources across different conditions. Further, except for two studies,^{90,96} most studies either declared a conflict of interest or were sponsored by or received funding from a manufacturer, which may be indicative of bias. This included the three studies that found skin substitutes to be less effective and more costly than hydrocolloid dressings.^{95,98,100} All three studies were sponsored by ConvaTec, manufacturer of the hydrocolloid dressings Duoderm and Granuflex. Similar limitations in quality of evidence and study methodology were also reflected in the findings of a previous systematic review of cost-effectiveness studies on skin substitutes.¹⁰²

Conclusions

Our economic literature review identified 14 studies that evaluated the cost-effectiveness of skin substitutes as an adjunct to standard care compared with standard care alone for the treatment of diabetic foot ulcers and venous leg ulcers. These studies presented mixed results: five found skin substitutes to be cost saving; six found skin substitutes to be more costly and more effective than standard care alone; and three found skin substitutes to be more costly and less effective than standard care alone. None of the included studies was directly applicable to our research questions, and we found several important limitations across studies. Therefore, we were unable to determine the cost-effectiveness of skin substitutes from the results of the economic literature review.

Primary Economic Evaluation

Although we found several published economic evaluations that addressed interventions of interest in our target populations, these studies had limitations, and their results may not be generalizable to the Ontario setting. We found two Canadian studies, but neither evaluated health outcomes using quality-adjusted life-years (QALYs).^{96,97} Moreover, both studies were published nearly two decades ago (in 2001) and thus may not accurately reflect clinical practice today. Owing to these limitations, we conducted a primary economic evaluation.

Research Questions

1. What is the cost-effectiveness of skin substitutes as an adjunct to standard care, compared with standard care alone, for the treatment of adults with neuropathic diabetic foot ulcers from the perspective of the Ontario Ministry of Health?
2. What is the cost-effectiveness of skin substitutes as an adjunct to standard care, compared with standard care alone, for the treatment of adults with venous leg ulcers from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.¹⁰³ We developed two models, one for each of our target populations: adults with diabetic foot ulcers and adults with venous leg ulcers.

Type of Analysis

We conducted a cost–utility analysis, because this is the recommended reference case approach and adheres to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines.¹⁰⁴ We reported the results as incremental cost per quality-adjusted life-years (QALYs) gained. We also conducted a cost-effectiveness analysis, which reported results as incremental cost per ulcer-free week, because this is a clinically meaningful unit of measurement.

Target Populations

Our target population were adults presenting with uninfected, difficult-to-heal neuropathic diabetic foot ulcers or uninfected difficult-to-heal venous leg ulcers.

We defined our target populations based on several considerations. First, most clinical studies of skin substitutes included only patients with uninfected ulcers, because the majority of commercially available skin substitutes are contraindicated in clinically infected ulcers.¹⁰⁵ Second, studies have shown that the people who may benefit most from skin substitutes are those with difficult-to-heal ulcers (i.e., diabetic foot ulcers and venous leg ulcers that have not shown at least 50% or 40% healing after 4 weeks of standard care treatment, respectively).^{106,107} Difficult-to-heal wounds are also more likely to develop complications (e.g., deep infections) that require greater use of health care resources (e.g., hospitalization); therefore, it was important that we capture the additional costs associated with greater health care resource use. Third, we did not consider ischemic or neuroischemic ulcers (two ulcer subtypes), because these wounds tend to be difficult to heal owing to underlying peripheral arterial disease, and improved wound care may not be sufficient to promote healing in these types of wound.¹⁰⁸

For these ulcers, improving blood flow to the wound through vascular intervention (i.e., revascularization) is essential and the primary determinant of wound healing.¹⁰⁵

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Intervention and Comparator

Our intervention of interest was skin substitute dressings as an adjunct to standard care, and the comparator was standard care alone. Table 7 summarizes the intervention, comparators, and outcomes evaluated in our economic models.

Table 7: Disease Intervention and Comparators Evaluated in the Primary Economic Models

Populations	Intervention	Comparator	Outcomes
Adults with DFUs	Skin substitute dressings as an adjunct to standard care	Standard care alone	QALYs
Adults with VLUs		• Routine debridement • Routine dressing changes • Modern wound dressings • Medication (e.g., antibiotics, pain medications) as appropriate	Number of ulcer-free weeks Costs ICERs

Abbreviations: DFU, diabetic foot ulcer; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VLU, venous leg ulcer.

For simplicity, we focused on costs and outcomes that would differ between the intervention and comparator, and therefore excluded the following from our analysis:

- Costs related to lifestyle choices, such as nutrition, glycemic control, exercise, and smoking status
- Costs related to pressure-relieving devices for diabetic foot ulcers
- Costs related to compression therapy for venous leg ulcers

Although healthy lifestyle choices (e.g., proper nutrition, glycemic control, exercise, not smoking) are part of standard care for the routine management of diabetic foot ulcers and venous leg ulcers and do affect wound healing,^{9,109} the costs associated with lifestyle choices are highly variable and can differ significantly on an individual basis. Moreover, maintaining a healthy lifestyle is part of the routine long-term management of these wounds, and, as such, we did not expect these costs to differ between the intervention and comparator arms.

We similarly excluded costs associated with publicly funded pressure-relieving (i.e., offloading) devices¹¹⁰ in our economic model for diabetic foot ulcers because these costs are also highly variable and were unlikely to differ significantly between our two cohorts. For instance, a range of offloading devices is available, including removable cast walkers, nonremovable cast walkers, and total contact casting. Depending on the device used, the device costs, frequency of device replacements, and professional labour costs can vary widely.¹¹¹ It is also common for patients to switch from one offloading

device to another over the course of ulcer treatment.¹¹¹ Further, given the time horizon of our analysis, we did not expect a significant difference in resource use associated with offloading devices between our intervention and comparator arms.

We excluded the costs associated with compression therapy (i.e., compression stockings) in our economic model for venous leg ulcers, because we expected identical use of this resource between the intervention and comparator groups over the time horizon of our analysis.¹¹² This was because compression therapy is part of routine management in both the prevention and treatment of venous leg ulcers.⁸ Moreover, clinical practice guidelines in Ontario recommend the lifelong use of compression therapy for the management of all people presenting with or at risk of developing venous leg ulcers.¹¹³

Time Horizon and Discounting

Although diabetic foot ulcers and venous leg ulcers can be considered chronic wounds owing to their high rate of recurrence, we determined that a short time horizon would be sufficient to capture meaningful differences between the intervention and comparator arms, as well as all health effects and costs relevant to wound healing.¹¹⁴ Specifically, we considered:

- **Treatment indication:** Although skin substitutes may play a role in improving wound healing, they are not intended to resolve the underlying disease, such as peripheral neuropathy or venous insufficiency, which precipitate the development of foot and leg ulcers, respectively¹¹⁵
- **Treatment effect:** We did not expect skin substitutes to have a treatment effect on the rate of ulcer recurrence over the long term

Therefore, we used a 26-week time horizon for our reference case analyses. Because this time horizon is less than 1 year, we did not apply a discount rate to either costs or QALYs. We chose a cycle length of 1 week to reflect the typical frequency of skin substitute applications and wound debridement.¹¹⁶ We also built a half-cycle correction into both Markov models to account for the fact that health state transitions can take place at any point in the weekly cycle.¹¹⁷

Main Assumptions

The models' main assumptions were as follows:

- All people with diabetic foot ulcers or venous leg ulcers enter the model presenting with a single ulcer, because it is considered less common for a person to present with bilateral or multiple ulcers¹¹⁸⁻¹²⁰
- There are no significant adverse effects directly associated with using skin substitutes. This assumption was based on our clinical evidence review, which found that adverse effects associated with skin substitutes were rare to nonexistent. In addition, the included clinical studies were not adequately powered to evaluate this outcome, so a comparison of adverse effects between the intervention and comparator arms could not be conducted
- For simplicity, we considered amputation to be curative, and a person could undergo only one minor or major amputation within the model time horizon
- Owing to a lack of data, we assumed that people with healed ulcers had the same probability of death as those with active ulcers

- We did not consider other adjunctive treatments (e.g., negative pressure wound therapy, hyperbaric oxygen therapy), because such treatments are not recommended as part of standard care for diabetic foot ulcers or venous leg ulcers in Canadian clinical practice guidelines^{113,121}

Model Structure—Diabetic Foot Ulcers

We developed a Markov model for diabetic foot ulcers that consisted of seven health states representing changes to a person's condition over time (Figure 7). Each state was mutually exclusive and exhaustive, such that a person could be in only one state at any given time.¹²² The health states were as follows:

- **Unhealed ulcer:** All people entered the model in this health state, in which they presented with active, unhealed ulcers. In each model cycle, people in this health state could heal, remain unhealed, die, or develop a life-threatening infection that required a minor or major lower-extremity amputation
- **Healed ulcer:** This health state defined people with ulcers that healed after treatment. Ulcers were considered healed if full wound closure (i.e., 100% re-epithelialization) was achieved. People in this health state may remain healed or die during each model cycle
- **Minor lower-extremity amputation:** This was a temporary health state in which people with unhealed ulcers developed a life-threatening deep infection (e.g., osteomyelitis) that required a minor lower-extremity amputation. The definition of “minor lower-extremity amputation” varies in the literature; for this report, we defined it as partial amputation of a foot or amputation of a toe (Appendix 8, Table A7). People in this health state had an increased risk of death due to the amputation procedure. If death did not occur, people transitioned to the post-minor lower-extremity amputation health state
- **Major lower-extremity amputation:** This was a temporary health state in which people with unhealed ulcers developed a life-threatening deep infection that required a major lower-extremity amputation. We defined a major lower-extremity amputation as an amputation above the ankle (Appendix 8, Table A7). People in this health state had an increased risk of death due to the amputation procedure. If death did not occur, people transitioned to the post-major lower-extremity amputation health state
- **Post-minor lower-extremity amputation:** This health state represented people who had undergone a minor lower-extremity amputation. People in this health state were considered healed of their ulcers. They either remained in this health state or died during each model cycle
- **Post-major lower-extremity amputation:** This health state represented people who had undergone a major lower-extremity amputation. People in this health state were considered healed of their ulcers. They either remained in this health state or died during each model cycle
- **Dead:** In each health state, people had a risk of death and therefore a possibility of moving to the dead state. The dead state was an absorbing state, in which there were no possible transitions to other health states¹²²

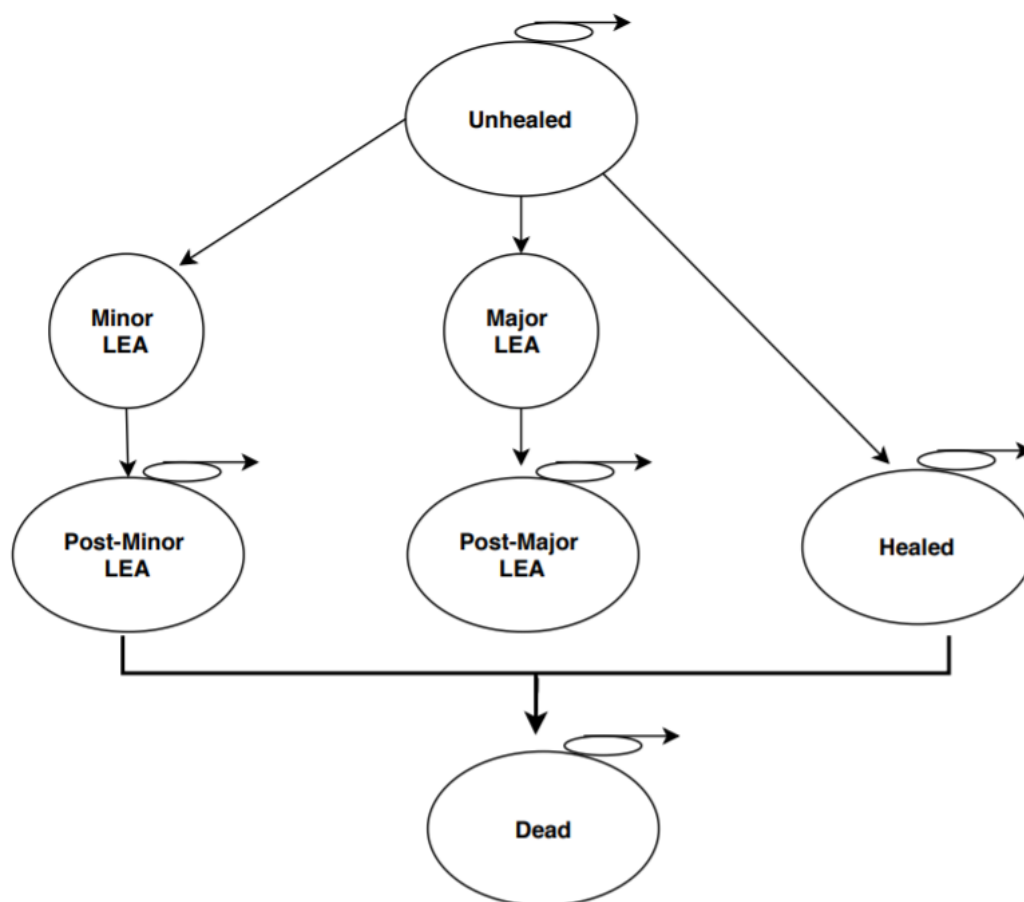


Figure 7: Model Schematic—Diabetic Foot Ulcers

Abbreviation: LEA, lower-extremity amputation.

CLINICAL OUTCOMES AND UTILITY PARAMETERS

We used several input parameters to populate the model:

- Variables to model the natural history of diabetic foot ulcers (Table 8)
- Variables to modify the natural history model to account for the treatment effect of skin substitutes as an adjunct to standard care (Table 9)
- Variables to capture health state utilities (i.e., quality of life; Table 10)

Table 8: Natural History Inputs Used in the Economic Model—Diabetic Foot Ulcers

Model Parameter	Weekly Transition Probability, % ^a	Patients, %	Length of Time	Source
Unhealed DFU → Healed DFU	5.77	51	12 weeks	Pooled analysis of Zelen et al, 2016, ⁶² and Tettelbach et al, 2019 ⁵⁷ (see Appendix 2)
Unhealed DFU → Minor LEA	0.11	5.4	1 year	Jeffcoate et al, 2006 ¹²³
Unhealed DFU → Major LEA	0.10	5.3	1 year	Jeffcoate et al, 2006 ¹²³
Unhealed DFU → Dead	0.17	16	2 years	Vadiveloo et al, 2018 ¹²⁴
Healed DFU → Dead	0.17	16	2 years	Assumed the same probability as Unhealed → Dead
Minor LEA → Dead	0.76	3	4 weeks	Gurney et al, 2018 ¹²⁵
Major LEA → Dead	2.9	11.1	4 weeks	Gurney et al, 2018 ¹²⁵
Post-minor LEA → Dead	0.21	41.4	5 years	Jones et al, 2008 ¹²⁶
Post-major LEA → Dead	0.39	63.6	5 years	Jones et al, 2008 ¹²⁶

Abbreviations: DFU, diabetic foot ulcer; LEA, lower-extremity amputation.

^aWeekly probabilities calculated, as appropriate, using probability-to-rate conversions ($p = e^{(-rt)}$) and rate-to-probability conversions ($r = \frac{-\ln(1-p)}{t}$), where p, r, t denoted probability, rate, and time.¹¹⁷

Table 9: Summary Estimates (Risk Difference) Used in the Economic Model—Diabetic Foot Ulcers

Intervention	Variable	RD (95% CI)	Length of Time	Source
Skin substitutes	Treatment effect	33% (11%–56%)	12 weeks	Pooled analysis of Zelen et al, 2016, ⁶² and Tettelbach et al, 2018 ⁵⁷ (see Appendix 2)

Abbreviation: RD, risk difference.

Table 10: Health State Utilities Used in the Economic Model—Diabetic Foot Ulcers

Health State	Utility	Source
Healed DFU	0.60	Tennvall and Apelqvist, 2000 ¹²⁷
Unhealed DFU	0.44	
Minor LEA (below the ankle)	0.61	Assumed the same utility value as for minor LEA
Major LEA (foot or leg)	0.31	
Post-minor LEA	0.61	
Post-major LEA	0.31	

Abbreviations: DFU, diabetic foot ulcer; LEA, lower-extremity amputation.

Ulcer Healing and Treatment Effect

Our clinical evidence review identified 26 randomized controlled trials that evaluated the effectiveness of skin substitutes as an adjunct to standard care compared with standard care alone for the treatment of diabetic foot ulcers. However, due to substantial heterogeneity in the types of skin substitute and the modes of standard care evaluated, we did not conduct a meta-analysis across studies of different skin substitutes.

For our economic analysis, we focused on studies that evaluated skin substitutes with an active Health Canada licence. Five studies met this criterion: three assessed the same dermal skin substitute^{57,62,75} and two assessed two different multi-layered skin substitutes.^{65,70} Of the three studies on the dermal skin substitute, Zelen et al (2015)⁷⁵ was an interim study to Zelen et al (2016)⁶² so we focused on the latter publication, which reported the final results of the clinical trial.

For the reference case analysis, we derived input parameters from Zelen et al (2016)⁶² and Tettelbach et al.⁵⁷ This was because, in contrast to one of the multi-layered skin substitutes evaluated,⁷⁰ the price of this dermal skin substitute is more representative of the majority of skin substitute products commercially available in Canada. The studies that evaluated the dermal skin substitute^{57,62} also had a longer follow-up time (i.e., 12 weeks^{57,62} vs. 6 weeks⁶⁵), a larger sample size (i.e., $n = 100$ ⁶² and $n = 110$ ⁵⁷ vs. $n = 46$ ⁶⁵), and a standard care arm that was more reflective of current best practice in Ontario than the study that evaluated the second multi-layered skin substitute.⁶⁵

We therefore considered that our reference case would be based on a skin substitute similar to the dermal skin substitute assessed by Zelen et al⁶² and Tettelbach et al⁵⁷ and conducted a pooled analysis of the results from these studies (see Appendix 2), which found that at week 12, 51% (95% confidence interval 40%–61%) of patients who received standard care alone had achieved complete wound closure. For treatment effect, the pooled analysis showed a risk difference of 33% (95% confidence interval 11%–56%) by week 12 for the skin substitute group compared with the standard care alone group (Table 9). We derived the weekly probabilities of ulcer healing for both treatment arms based on these estimates and assumed that the probabilities remained constant beyond 12 weeks.

In separate scenario analyses, we evaluated the cost-effectiveness of the two multi-layered skin substitutes based on the clinical studies by Cazzell et al⁷⁰ and Campitiello et al⁶⁵ and unit prices.

Minor and Major Lower-Extremity Amputations

We derived the probability of amputation in people with diabetic foot ulcers from a United Kingdom study, in which data were collected at a specialist multidisciplinary clinic from patients presenting with this type of ulcer between 2000 and 2003.¹²³ In this study, the percentage of patients who had a minor amputation and major amputation in the first year following diagnosis was 5.4% and 5.3%, respectively.

Mortality

We derived model inputs for mortality from three large longitudinal studies.^{124–126} Vadiveloo et al¹²⁴ followed people with diabetes between 2008 and 2011 from the Scotland-wide diabetes register. The authors found that the probability of death within 2 years for people with an active ulcer was 16%. We found no studies that reported mortality for those with healed ulcers. This may have been due to the high recurrence rate of these wounds, which has led some studies to define healed ulcers as being in remission rather than fully healed.¹¹⁵ Gurney et al¹²⁵ was a 10-year longitudinal trial conducted in New Zealand that followed a cohort of people with diabetes who had undergone a lower-limb amputation.

The authors reported a cumulative mortality of 3% and 11% for those with a minor (below the ankle) and major (above or through the ankle) amputation, respectively, within 30 days following surgery. Jones and Marshall¹²⁶ conducted a longitudinal study in the United States that followed people with diabetes who had undergone a lower-extremity amputation between 1992 and 1998. The authors found that the 5-year cumulative mortality following a minor or major amputation was 41.4% and 63.6%, respectively.

HEALTH STATE UTILITIES

A health state utility represents a person's preference for a certain health state or outcome. Utilities are often measured on a scale from 0 (death) to 1 (full health). We obtained health state utility values from a Swedish study that used the EuroQol–Five Dimensions (EQ-5D) questionnaire to survey people with type 1 and type 2 diabetes who had been treated for foot ulcers.¹²⁸ The utilities reported in this study fell within the range of those identified in a recent systematic review of utility values for the economic modelling of complications relating to type 2 diabetes.¹²⁹

COST PARAMETERS

All costs are reported in 2020 Canadian dollars. See Table 11 for details.

**Table 11: Resource Use and Cost Parameters Used in the Economic Model—
Diabetic Foot Ulcers**

Variable	Unit Cost	Number of Units	Mean Cost	Source
Standard care, weekly cost (includes surgical sharp, 100% of the time)	\$374.59	1	\$374.59	Woo et al, 2015 ¹¹⁶
Skin substitute + standard care, weekly cost (includes surgical sharp, 100% of the time)	\$374.59	1	\$374.59	Woo et al, 2015 ¹¹⁶
Skin substitute				
Unit price, 14 mm disk			\$293.20	CMS, 2020, ¹³⁰ adjusted to CAD
Unit price, 2 cm × 3 cm			\$1,149.82	CMS, 2020, ¹³⁰ adjusted to CAD
Weighted average (60.8% 14 mm disk, 39.2% 2 cm × 3 cm sheet)			\$629.00	
Application		5.97		MiMedx Group, email communication, July 20, 2020
Total cost per treatment			\$3,755.12	
Minor LEA				
Physician fee, initial consult ^a	\$90.30	1	\$90.30	Schedule of Benefits ¹³¹
Physician fee, surgery ^a	\$577.52	1	\$577.52	Schedule of Benefits ¹³¹
Physician fee, follow-up visit ^a	\$31.00	2.5	\$77.50	Schedule of Benefits ¹³¹
Hospitalization	\$1,082.71	2	\$2,165.43	Hopkins et al, 2015 ¹³² ; P. Mayer, MD, telephone communication, October 8, 2020
Total cost per event			\$2,910.75	
Major LEA				
Physician fee, initial consult ^a	\$90.30	1	\$90.30	Schedule of Benefits ¹³¹
Physician fee, surgery ^a	\$706.80	1	\$706.80	Schedule of Benefits ¹³¹
Physician fee, follow-up visit ^a	\$31.00	2.5	\$77.50	Schedule of Benefits ¹³¹
Hospitalization ^b	—	—	\$35,500.00	OCC ¹³³
Total cost per event			\$36,180.03	
Post-minor LEA, weekly cost			\$114.44	O'Reilly et al, 2007 ¹³⁴
Post-major LEA, weekly cost			\$114.44	O'Reilly et al, 2007 ¹³⁴

Abbreviations: CAD, Canadian dollars; CMS, US Centers for Medicare and Medicaid Services; LEA, lower-extremity amputation; OCC, Ontario Case Costing.

^aPhysician fees calculated include services of a surgeon, surgical assistant, and anesthesiologist (see Appendix 8, Tables A8 and A9, for cost breakdowns).

^bThe average length of stay for a major LEA was 25.5 days at a total average cost of \$34,674 in 2018 CAD (Appendix 8, Table A10).

Standard Care

We derived the cost of standard care from a recent Canadian study by Woo et al¹¹⁶ that analyzed the costs of various debridement methods for cleaning the wound beds of diabetic foot ulcers, venous leg ulcers, and pressure ulcers. The analysis included direct and indirect costs associated with wound debridement, including supplies (i.e., wound dressings, gloves, trays, other medical equipment), medications (e.g., antibiotics, anaesthetics), professional fees (e.g., physicians, nurses, personal support workers), and out-of-pocket expenses (e.g., transportation, parking).

We assumed that all debridement procedures performed would use the surgical sharp method, because this is the gold standard in clinical practice for preparing the wound beds of diabetic foot ulcers (P. Mayer, MD, telephone communication, September 15, 2020).

In Woo et al,¹¹⁶ surgical sharp debridement consisted of modern wound dressings (50% hydrogel and 50% hydrocolloid), dressing changes every 3 to 4 days, and debridement once a week. We assumed that debridement was performed by a physician 70% of the time and by a nurse 30% of the time. Transfers for additional care to a hospital operating room (for 1–2% of patients) and from a long-term care facility to a wound clinic (20% of patients) were also accounted for. Other additional expenses included were costs to address bleeds requiring suture (5% of patients), minor bleeds (50% of patients), infections requiring medication (50%–60% of patients), pain requiring medication (20% of patients), and out-of-pocket expenses for three visits to a hospital wound clinic. The overall cost of surgical sharp debridement was \$1,123.76 over 3 weeks, or \$374.39 per week (inflated to 2020 CAD).

Skin Substitutes as an Adjunct to Standard Care

Based on information provided by the manufacturer, an average of 5.97 applications of the dermal skin substitute are required to heal a diabetic foot ulcer wound (MiMedx, email communication, July 20, 2020). Dermal skin substitutes should be stored at room temperature and have a shelf life of 5 years.⁸⁴ Because cryopreservation is not required for this product, we did not consider costs associated with deep-freezer storage.

Currently, the dermal skin substitute product is available in the following formats and sizes on the international market: 14 mm and 16 mm disks; and 2 cm × 3 cm, 4 cm × 4 cm, 5 cm × 6 cm, and 7 cm × 7 cm sheets (MiMedx, email communication, August 21, 2020). In a Canadian study by Roth-Albin et al,¹² 60.8% of diabetic foot ulcers were less than 1 cm², 18.4% were between 1 cm² and 3 cm², and 20.8% were larger than 3 cm². Based on these estimates, we assumed that 14 mm disks (with a surface area of 1.53 cm²) would be used for diabetic foot ulcers less than 1 cm², and that 2 cm × 3 cm sheets would be used for diabetic foot ulcers larger than 1 cm². We then calculated a weighted average cost based on the costs of the 14 mm disk and 2 cm × 3 cm sheets and the proportions of wound size reported in Roth-Albin et al¹² for the average person with a diabetic foot ulcer who was eligible to receive skin substitutes. We derived the unit costs of the 14 mm disk and the 2 cm × 3 cm sheet from the US Centers for Medicare and Medicaid Services Average Sales Price July 2020 payment limits,¹³⁰ which we then converted to Canadian dollars. These unit costs (i.e., the costs per application) were \$293.20 for the 14 mm disk and \$1,149.82 for the 2 cm × 2 cm sheet. We then estimated the overall weighted average cost of a skin substitute dressing to be \$629 per application.

In addition to the cost of the skin substitute, we assumed that dressing changes and debridement would continue to take place as needed. Therefore, the cost of standard care would remain the same.

Minor and Major Lower-Extremity Amputations

The costs associated with amputation in our model captured both physician fees and hospitalization costs, which were derived from the costs of services listed in the Ontario Health Insurance Plan Schedule of Benefits and Fees,¹³¹ the Ontario Case Costing administrative database,¹³³ and the literature.¹³²

The physician cost for performing a minor lower-extremity amputation was \$577.52; this was based on the average physician fee for amputation of the metatarsal/phalanx, ray, ankle joint, and transmetatarsal/transarsal, and toe (Appendix 8, Table A8).¹³¹ The average hospitalization cost associated with a minor lower-extremity amputation was \$1,082.71; this was estimated using the average cost per hospital day reported in a Canadian study by Hopkins et al¹³² (inflated to 2020 Canadian dollars). Based on this study, we estimated that the total average cost per hospital stay following a minor lower-extremity amputation was \$2,165.43. This estimate accounted for an average length of stay of 2 days (P. Mayer, MD, telephone communication, October 8, 2020).

The physician cost for performing a major lower-extremity amputation was \$706.80; this was based on the average physician fee for the amputation of the femur, knee, and tibia fibula (Appendix 8, Table A8).¹³¹ Based on data derived from the Ontario Case Costing database,¹³³ the average total hospitalization cost associated with a major lower-extremity amputation was \$34,674, which corresponded to an average length of stay of approximately 4 weeks. This cost included the cost of resource use associated with rehabilitation (i.e., physiotherapy, occupational therapy).

For both minor and major amputations, we further accounted for one initial consult (at \$90.30) and 2.5 physician follow-up visits (at \$31.00 per visit) to reflect current practice for the average patient with a diabetic foot ulcer (P. Mayer, MD, telephone communication, October 8, 2020) (Appendix 8, Table A9).

Post-Lower-Extremity Amputation

Costs related to post-amputation care were derived from a Canadian cost-utility study by O'Reilly et al¹³⁴ based on the Ontario Diabetes Economic Model, a computer-simulated model that estimates the life expectancy, QALYs, and cost of complications associated with type 2 diabetes. Costs associated with each diabetes-related complication were based on individual patient histories developed to reflect the average health care resource use of each complication, including inpatient and outpatient hospital care, physician visits, prescription drugs, and home care services. All costs in the Ontario Diabetes Economic Model are derived from Canadian sources (e.g., Ontario Drug Benefit Formulary, Statistics Canada) and are reported for the year in which the complication occurs (i.e., immediate costs) and for the subsequent year in which ongoing management of the complication takes place (i.e., long-term costs).¹³⁴ O'Reilly et al found that the average annual cost in the subsequent years following a diabetes-related amputation was \$5,952 (adjusted to 2020 CAD), or \$114.44 per week. For simplicity, we assumed the same post-amputation costs for both minor and major lower-extremity amputations.

Model Structure—Venous Leg Ulcers

We developed a Markov model for venous leg ulcers that consisted of three health states representing changes to a person's condition over time (Figure 8). Each state was mutually exclusive and exhaustive, such that a person could be in only one state at any given time.¹²² The health states were as follows:

- **Unhealed ulcer:** All people entered the model in this health state, in which they presented with active, unhealed ulcers. In each model cycle, people in this health state could heal, remain unhealed, or die

- **Healed ulcer:** This health state defined people with ulcers that healed following treatment. Ulcers were considered healed if full wound closure (i.e., 100% re-epithelialization) was achieved. Individuals in this health state could remain healed or die during each model cycle
- **Dead:** In each health state, people have a risk of death and therefore a possibility of moving to the dead state. The dead state was an absorbing state, in which there were no possible transitions to other health states¹²²

According to experts and the literature, the likelihood of amputation related to venous leg ulcers is rare.¹³⁵ For this reason, we did not consider amputation health states in this model.

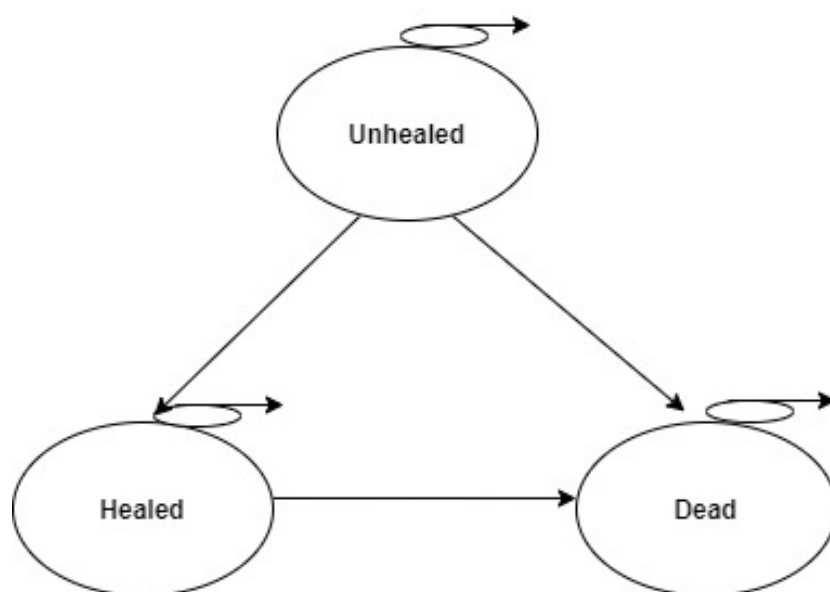


Figure 8: Model Schematic—Venous Leg Ulcers

CLINICAL OUTCOMES AND UTILITY PARAMETERS

We used several input parameters to populate the model:

- Variables to model the natural history of venous leg ulcers (Table 12)
- Variables to modify the natural history model to account for treatment effects of skin substitutes as an adjunct to standard care (Table 13)
- Variables to capture health state utilities (i.e., quality of life; Table 14)

Table 12: Natural History Inputs Used in the Economic Model—Venous Leg Ulcers

Model Parameter	Weekly Transition Probability, % ^a	Patients, %	Length of Time	Source
Unhealed VLU → Healed VLU	3.04	39	16 weeks	Bianchi, 2019 ⁶⁴
Unhealed VLU → Dead	0.27	37	5 years	Nelzen et al, 1997 ¹³⁵
Healed VLU → Dead	0.27	37	5 years	Assumed the same probability as Unhealed → Dead

Abbreviation: VLU, venous leg ulcer.

^aWeekly probabilities calculated, as appropriate, using probability-to-rate conversions ($p = e^{(-rt)}$) and rate-to-probability conversions ($r = \frac{-\ln(1-p)}{t}$), where p, r, t denoted probability, rate, and time.¹¹⁷

Table 13: Summary Estimates (Risk Difference) Used in the Economic Model—Venous Leg Ulcers

Intervention	Variable	RD (95% CI)	Length of Time	Source
Skin substitutes	Treatment effect	20% (3.4%–37.3%)	16 weeks	Bianchi et al, 2019 ⁶⁴

Abbreviation: RD, risk difference.

Table 14: Health State Utilities Used in the Economic Model—Venous Leg Ulcers

Health State	Utility	Source
Healed VLU	0.73	Clegg et al, 2007 ¹³⁶
Unhealed VLU	0.64	

Abbreviation: VLU, venous leg ulcer.

Ulcer Healing and Treatment Effect

Our clinical evidence review identified 11 randomized controlled trials that evaluated the effectiveness of skin substitutes as an adjunct to standard care compared with standard care alone for the treatment of venous leg ulcers. As with our diabetic foot ulcer model, we focused on studies that evaluated skin substitutes with an active Health Canada licence. Two studies met this criterion: one that assessed the same dermal skin substitute evaluated in the diabetic foot ulcer reference case analysis,⁶⁴ and one that assessed the same multi-layered skin substitute evaluated in one of the diabetic foot ulcer scenario analyses.⁷⁹ Similar to the diabetic foot ulcer model, we derived model input parameters from a published study on the dermal skin substitute.⁶⁴ Analysis from this study found that at week 16, 39% of the control group had achieved complete wound closure.⁶⁴ For treatment effect, the authors reported a risk difference of 20% (95% confidence interval 3.4%–37.3%) by week 16 for the skin substitute group compared with the standard care alone group. We derived the weekly probabilities of ulcer healing for

both treatment arms based on these estimates and assumed that the probabilities remained constant beyond 16 weeks.

In a separate scenario analysis, we evaluated the cost-effectiveness of the multi-layered skin substitute based on the clinical study by Mostow et al⁷⁹ and unit price.

Mortality

We derived the model input for mortality from a large observational study conducted in Sweden.¹³⁵ The authors found that the 5-year probability of survival in people with venous leg ulcers was 63%. We assumed the same for our model.

HEALTH STATE UTILITIES

We derived health utilities for all health states from a cost-effectiveness study that used the standard gamble method to survey members of the general public in the United Kingdom.¹³⁷

COST PARAMETERS

All costs are reported in 2020 Canadian dollars. See Table 15 for details.

**Table 15: Resource Use and Cost Parameters Used in the Economic Model—
Venous Leg Ulcers**

Variable	Unit Cost	Number of Units	Mean Cost	Source
Standard care, weekly cost (includes surgical sharp, 100% of the time)	\$374.59	1	\$374.59	Woo et al, 2015 ¹¹⁶
Skin substitute + standard care, weekly cost (includes surgical sharp, 100% of the time)	\$374.59	1	\$374.59	Woo et al, 2015 ¹¹⁶
Skin substitute				
Unit price, 2 cm × 3 cm			\$1,149.82	CMS, 2020, ¹³⁰ adjusted to CAD
Unit price, 4 cm × 4 cm			\$3,066.19	CMS, 2020, ¹³⁰ adjusted to CAD
Weighted average (60.8% 2 cm × 3 cm sheet, 39.2% 4 cm × 4 cm sheet)			\$1,901.04	
Applications		7.2		MiMedx Group, email communication, July 20, 2020
Total cost per treatment			\$13,687.48	

Abbreviations: CAD, Canadian dollars; CMS, US Centers for Medicare and Medicaid Services.

Standard Care

As with the diabetic foot ulcer model, we derived the cost of standard care from Woo et al,¹¹⁶ which evaluated the costs of various debridement methods used for cleaning the wound beds of diabetic foot ulcers, venous leg ulcers, and pressure ulcers. We assumed that all debridement procedures performed would use the surgical sharp method, because this is the gold standard in clinical practice for preparing

the wound beds of venous leg ulcers (P. Mayer, telephone communication, September 15, 2020). As described above, the overall cost of surgical sharp debridement was \$374.39 per week (inflated to 2020 CAD).

Skin Substitute as an Adjunct to Standard Care

Based on information provided by the manufacturer, the dermal skin substitute requires an average of 7.2 applications to heal a venous leg ulcer wound (MiMedx, email communication, July 20, 2020).

In a Canadian study by Hopman et al,¹³ which evaluated 564 patients with active venous leg ulcers, 60.8% of wounds had a surface area of 5 cm² or less, and the remaining 39.2% of wounds had a surface area greater than 5 cm². Using these data, we assumed that 2 cm × 3 cm sheets would be used for wounds less than 5 cm², and 4 cm × 4 cm sheets would be used for wounds larger than 5 cm². We then calculated a weighted average cost based on the prices of these two sizes of dermal skin substitute sheet and the proportions of wound size described in Hopman et al¹³ for the average person with a venous leg ulcer eligible to receive skin substitutes. We derived the unit costs of the sheets from the US Centers for Medicare and Medicaid Services Average Sales Price July 2020 payment limits,¹³⁰ which we then converted to Canadian dollars. These unit costs (i.e., the costs per application) were \$1,149.82 for the 2 cm × 3 cm sheet and \$3,066.19 for the 4 cm × 4 cm sheet. We then estimated the overall weighted average cost of a skin substitute dressing to be \$1,901.04 per application.

In addition to the cost of the skin substitute, we assumed that dressing changes and debridement would continue to take place as needed. As such, the cost of standard care remained the same.

Internal Validation

The secondary health economist conducted formal internal validation. This included testing the mathematical logic of both models and checking for errors and accuracy in the parameter inputs and equations.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis adhered to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines¹¹² when appropriate and represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results were affected by varying input parameters and model assumptions.

REFERENCE CASE AND PROBABILISTIC SENSITIVITY ANALYSIS

We calculated the reference case by running 5,000 simulations (i.e., a probabilistic analysis) that simultaneously captured the uncertainty in all parameters expected to vary. We set distributions for variables within the model. We calculated mean costs with credible intervals and mean QALYs with credible intervals for each intervention assessed. We also calculated the mean incremental costs with credible intervals, incremental QALYs with credible intervals, and incremental cost-effectiveness ratios (ICERs) for the interventions of skin substitutes plus standard care versus standard care alone.

The results of the probabilistic analysis are also presented on a cost-effectiveness acceptability curve. We present uncertainty quantitatively, as the probability that an intervention is cost-effective at specific willingness-to-pay values. We also present uncertainty qualitatively, in one of five categories defined by

the Ontario Decision Framework¹³⁸: highly likely to be cost-effective (80–100% probability of being cost-effective), moderately likely to be cost-effective (60–79% probability), uncertain if cost-effective (40–59% probability), moderately likely not to be cost-effective (20–39% probability), or highly likely not to be cost-effective (0–19% probability). Tables A11 and A12 (Appendix 9) list the model variables and corresponding distributions for diabetic foot ulcer and venous leg ulcer models, respectively.

SCENARIO ANALYSES

We conducted 12 probabilistic scenario analyses for the diabetic foot ulcer model and five for the venous leg ulcer model. Of these scenarios, we varied a set of common parameters for both models: (1) increasing the number of skin substitute applications to a maximum of 12 (the highest number applications reasonably needed to treat a wound); (2) increasing the time horizon (and subsequently the treatment effect) to 52 weeks; and (3) applying a treatment effect over the duration of the original studies,^{57,62,64} rather than extrapolating it over the duration of the model.

Diabetic Foot Ulcers

In the diabetic foot ulcer model, we ran scenarios for a 10% (\$566.10) and 20% (\$503.20) price reduction to the unit cost of a skin substitute (\$629.00), and we ran a scenario that assumed that 2 cm × 3 cm sheets would be required for all eligible people to assess the effect on our ICER in a scenario with price discounts or a larger mean wound surface area. In another scenario, we derived utility values from a study by Redekop et al¹³⁷ that used a direct method of utility elicitation (i.e., time trade-off) to survey the preferences of the general population. In comparison, the parameter input utility values used in our reference case were derived from a study by Tennvall and Apelqvist,¹²⁷ which used an indirect method of utility elicitation: a survey (the EQ-5D) of the preferences of people with diabetes. As such, the utility values reported in Redekop et al¹³⁷ were higher across all health states than those in the study we used in our reference case¹²⁷; the largest differences in reported utilities were in the unhealed (0.75 vs. 0.44) and major amputation (0.68 vs. 0.31) health states. In general, studies that use direct elicitation methods tend to report higher utility values than those that use indirect elicitation methods.¹³⁹ Moreover, studies that survey the preferences of the general public may underestimate the consequences of health outcomes, whereas those that survey the preferences of the population of interest may risk overestimating them.¹³⁷ As such, we ran this scenario to account for the differences in reported health state utilities relating to diabetic foot ulcers.

We also ran scenarios that increased the weekly costs associated with post–minor and post–major lower-extremity amputations, at double and triple the value used in our reference case. We also explored a scenario using higher a probability of amputations in people with diabetic foot ulcers, using parameter values derived from a Canadian study that focused on people with more severe wounds who received care through acute care admissions, emergency room visits, hospital-based ambulatory care, hospital-based clinics, home care, or long-term care in Ontario.¹³²

We then ran two scenarios using input parameters for ulcer healing, treatment effect, and number of skin substitute applications per person from the studies that evaluated the two multi-layered skin substitutes.^{65,70} We derived the unit costs of these skin substitutes from the US Centers for Medicare and Medicaid Services Average Sales Price July 2020 payment limits¹³⁰ and converted them to Canadian dollars.

Venous Leg Ulcers

In the venous leg ulcer model, we ran threshold analyses on the unit price of skin substitutes for ICERs of \$100,000 per QALY and \$50,000 per QALY, because these parameters were identified by several studies as key drivers of outcomes in our economic literature review. As in our diabetic foot ulcer model, we also explored a scenario that assumed 2 cm × 3 cm sheets would be adequate to treat all eligible people. This scenario allowed us to assess what effect a smaller mean wound surface area would have on the ICER.

We also ran a scenario using input parameters for ulcer healing, treatment effect, and number of skin substitute applications per person from the study that evaluated the multi-layered skin substitute for the treatment of venous leg ulcers.⁷⁹ We derived the unit costs for this skin substitute using the methodology described previously.

Results

Diabetic Foot Ulcers

REFERENCE CASE ANALYSIS

The mean total costs for the skin substitute strategy (skin substitute plus standard care) and the standard care strategy (standard care alone) were \$6,371 and \$5,313, respectively. Although the skin substitute strategy had a higher overall incremental cost of \$1,058 due to the additional \$3,755.12 (\$629/application × 5.97 weekly applications) versus standard care, this additional cost was offset by savings associated with minor and major lower-extremity amputations avoided and a greater number of ulcer-free weeks (6.69 weeks over 26 weeks).

The mean total effects of the skin substitute strategy were 0.279 QALYs and 18.95 ulcer-free weeks, compared with the standard care strategy at 0.257 QALYs and 12.26 ulcer-free weeks; the skin substitute strategy resulted in a small increase of 0.022 QALYs and a larger increase of 6.69 ulcer-free weeks over the duration of the model. Given the short time horizon of the model (26 weeks), the small difference in QALYs was expected.

Treatment with skin substitutes plus standard care compared with standard care alone resulted in an ICER of \$48,242 per QALY and a cost per ulcer-free week of \$158 over 26 weeks. Table 16 provides the details of the reference case analysis results for the diabetic foot ulcer model.

Table 16: Reference Case Results—Diabetic Foot Ulcers

	Strategy	
	Skin Substitute + Standard Care	Standard Care Alone
Mean cost, \$ (95% CrI)	6,371 (5,016 to 7,480)	5,313 (5,150 to 5,519)
Unhealed	6,083 (4,865 to 7,073)	4,770 (4,738 to 4,799)
Minor LEA	22 (10 to 37)	43 (28 to 61)
Post–minor LEA	12 (6 to 19)	19 (12 to 27)
Major LEA	243 (107 to 407)	464 (288 to 683)
Post–major LEA	11 (6 to 17)	17 (11 to 25)
Mean QALYs (95% CrI)	0.279 (0.211 to 0.345)	0.257 (0.204 to 0.308)
Mean of ulcer-free weeks, n (95% CrI)	18.95 (16.20 to 22.31)	12.26 (12.20 to 12.32)
Incremental cost, ^a \$ (95% CrI)	1,058 (–311 to 2,161)	
Unhealed	1,313 (100 to 2,311)	
Minor LEA	–21 (–36 to –10)	
Post–minor LEA	–7 (–13 to –3)	
Major LEA	–222 (–395 to –109)	
Post–major LEA	–6 (–\$12 to –3)	
Incremental QALYs ^d (95% CrI)	0.022 (–0.007 to 0.056)	
Incremental ulcer-free weeks, n ^b (95% CrI)	6.69 (3.97 to 10.05)	
ICER, \$/QALY	48,242	
\$/Ulcer-free week	158	

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; LEA, lower-extremity amputation; QALY, quality-adjusted life-year.

^aIncremental cost = average cost (strategy B) – average cost (strategy A).

^bIncremental effect = average effect (strategy B) – average effect (strategy A).

Note: Results may appear inexact due to rounding. Negative costs indicate savings. Reference case results were derived from probabilistic analysis by running 5,000 simulations.

PROBABILISTIC SENSITIVITY ANALYSIS

When the results of the probability sensitivity analysis were plotted in a cost-effectiveness acceptability curve (Figure 9), we found that at the commonly used willingness-to-pay of \$50,000 per QALY, the probability of the skin substitute strategy being cost-effective was approximately 47% (i.e., uncertain if cost-effective). The likelihood of being cost-effective increased for the skin substitute strategy as the willingness-to-pay increased. At the commonly used willingness-to-pay of \$100,000 per QALY, the probability of the skin substitute strategy being cost-effective was approximately 71% (i.e., moderately likely to be cost-effective).

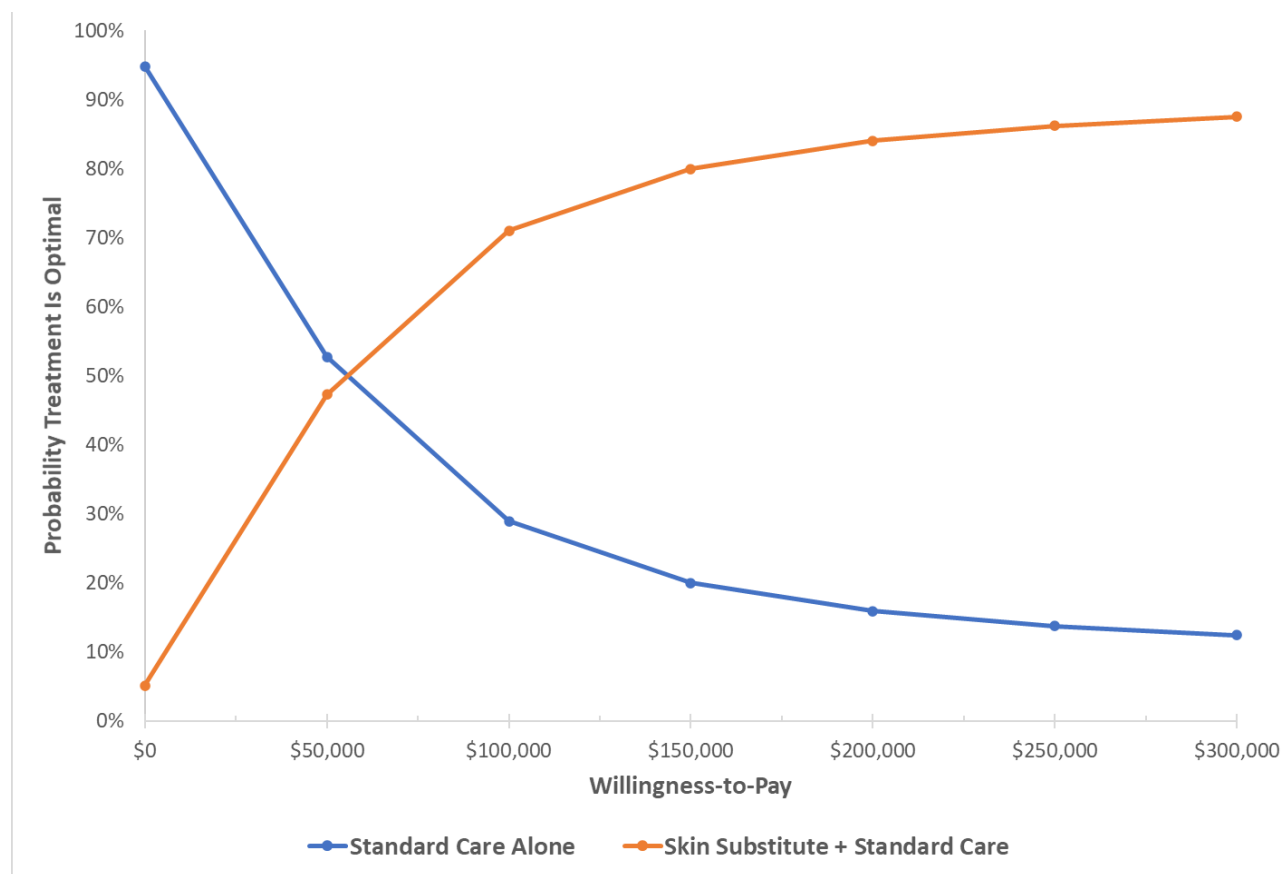


Figure 9: Cost-Effectiveness Acceptability Curve—Diabetic Foot Ulcers

SCENARIO ANALYSES

Our scenario analyses found that some parameters affected the results (i.e., ICER) of our reference case more substantially than others.

For instance, a 10% price reduction in the unit cost of the skin substitute (to \$566.10) saw the ICER drop to \$28,956 per QALY and the cost per ulcer-free week drop to \$94; a 20% price reduction (to \$503.20) saw the ICER drop to \$13,315 per QALY and the cost per ulcer-free week drop to \$43. The ICER was further affected when we increased the time horizon, which subsequently extrapolated the treatment effect of the skin substitute strategy from 26 weeks to 52 weeks. In this scenario, the ICER fell to \$2,154 per QALY, and the cost per ulcer-free week fell to \$7. This effect was predominantly attributable to the greater cost savings associated with faster healing and amputations avoided accrued over a longer time horizon. Our reference case ICER also decreased, but to a lesser degree in scenarios in which we increased the weekly post-minor and post-major lower-extremity amputation costs, and when we accounted for a higher probability of minor and major lower-extremity amputations. This suggests that variations in these parameters were less likely to substantially affect the cost-effectiveness of the skin substitute strategy.

In contrast, the remaining scenarios resulted in an increase in the ICER of our reference case. For instance, when we assumed the mean wound surface area to be larger than in our reference case (thus requiring 2 cm × 3 cm sheets for all eligible people), the skin substitute strategy became unfavourable (\$194,423/QALY, \$617/ulcer-free week) due to the increase in skin substitute unit cost from \$629 per application to \$1,149.82 per application. When we increased the number of weekly skin substitute applications to 12 per person, the ICER increased substantially to \$222,441 per QALY, and the cost per ulcer-free week increased to \$709. When we used alternative utility values (i.e., smaller differences between the healed and unhealed health states), the decrease in incremental QALYs resulted in a higher cost per QALY (\$87,112/QALY), but only a marginal impact on the cost per ulcer-free week (\$154/ulcer-free week). In another scenario in which treatment effect was not extrapolated beyond the duration of the original trial (12 weeks), the ICER also increased, but to a lesser degree (to \$61,131/QALY and \$199/ulcer-free week).

When we used unit prices and clinical input parameters from multi-layered skin substitutes,^{65,70} the ICER changed substantially, and the skin substitute strategy became dominant (i.e., less costly and more effective). This was largely attributable to the difference in unit price associated with different skin substitute products and the number of applications required. For instance, one of the multi-layered skin substitutes costs approximately \$135.25 per application and requires eight weekly applications,⁷⁰ whereas the other multi-layered skin substitute costs approximately \$5,648.81 per application and requires only one application.⁶⁵ This shows that although most skin substitute products have demonstrated effectiveness in complete wound healing, the cost-effectiveness of the skin substitute strategy may be product-specific, because there is a large variation in unit price and the average number of applications required across products.

Overall, the cost-effectiveness results were most sensitive to changes in cost parameters related to the skin substitute used (i.e., unit price and number of applications required). This finding was consistent with those of several studies included in our economic literature review.^{89,90,97} Table 17 provides a summary of the parameters varied in the diabetic foot ulcer model scenario analyses.

Table 17: Scenario Analysis Results—Diabetic Foot Ulcers

Scenario	Results		
	Mean and Incremental Costs	Mean and Incremental Effects	ICER and Cost per Ulcer-Free Week
Reference case	Skin substitute: \$6,371 SC: \$5,313 ΔC: \$1,058	Skin substitute: 0.279 QALYs, 18.95 ulcer-free wk SC: 0.257 QALYs, 12.26 ulcer-free wk ΔE: 0.022 QALYs, 6.69 ulcer-free wk	\$48,242/QALY \$158
10% reduction in unit cost of skin substitute Reference case: \$629 Scenario: \$566.10	Skin substitute: \$5,956 SC: \$5,316 ΔC: \$640	Skin substitute: 0.279 QALYs, 19.05 ulcer-free wk SC: 0.257 QALYs, 12.26 ulcer-free wk ΔE: 0.022 QALYs, 6.79 ulcer-free wk	\$28,956/QALY \$94
20% reduction in unit cost of skin substitute Reference case: \$629 Scenario: \$503.20	Skin substitute: \$5,607 SC: \$5,317 ΔC: \$290	Skin substitute: 0.279 QALYs, 18.99 ulcer-free wk SC: 0.257 QALYs, 12.26 ulcer-free wk ΔE: 0.022 QALYs, 6.73 ulcer-free wk	\$13,315/QALY \$43
2 cm × 3 cm sheets required for all patients Reference case: \$629 Scenario: \$1,149.82	Skin substitute: \$9,466 SC: \$5,312 ΔC: \$4,153	Skin substitute: 0.278 QALYs, 18.99 ulcer-free wk SC: 0.256 QALYs, 12.26 ulcer-free wk ΔE: 0.021 QALYs, 6.73 ulcer-free wk	\$194,423/QALY \$617
Increase in number of skin substitute applications Reference case: 5.97 Scenario: 12	Skin substitute: \$10,128 SC: \$5,318 ΔC: \$4,810	Skin substitute: 0.279 QALYs, 19.04 ulcer-free wk SC: 0.257 QALYs, 12.26 ulcer-free wk ΔE: 0.022 QALYs, 6.79 ulcer-free wk	\$222,441/QALY \$709
Increase in time horizon Reference case: 26 wk Scenario: 52 wk	Skin substitute: \$6,492 SC: \$6,428 ΔC: \$64	Skin substitute: 0.559 QALYs, 42.76 ulcer-free wk SC: 0.530 QALYs, 33.40 ulcer-free wk ΔE: 0.030 QALYs, 9.37 ulcer-free wk	\$2,154/QALY \$7
Reduction in treatment effect time horizon Reference case: 26 wk Scenario: 12 wk	Skin substitute: \$6,555 SC: \$5,314 ΔC: \$1,241	Skin substitute: 0.277 QALYs, 18.49 ulcer-free wk SC: 0.257 QALYs, 12.26 ulcer-free wk ΔE: 0.020 QALYs, 6.24 ulcer-free wk	\$61,131/QALY \$199
Alternative utility values Reference case: 0.6 (healed), 0.44 (unhealed), 0.61 (post-minor LEA), 0.31 (post-major LEA) Scenario: 0.84 (healed), 0.75 (unhealed), 0.74 (post-minor LEA), 0.68 (post-major LEA)	Skin substitute: \$6,352 SC: \$5,313 ΔC: \$1,039	Skin substitute: 0.399 QALYs, 19.00 ulcer-free wk SC: 0.387 QALYs, 12.26 ulcer-free wk ΔE: 0.012 QALYs, 6.74 ulcer-free wk	\$87,112/QALY \$154
Alternative probabilities of minor and major LEAs at 1 year Reference case: minor LEA, 5.4%; major LEA, 5.3% Scenario: minor LEA, 10.7%; major LEA, 10%	Skin substitute: \$6,622 SC: \$5,702 ΔC: \$920	Skin substitute: 0.278 QALYs, 18.72 ulcer-free wk SC: 0.257 QALYs, 12.09 ulcer-free wk ΔE: 0.021 QALYs, 6.63 ulcer-free wk	\$43,243/QALY \$139

Scenario	Results		
	Mean and Incremental Costs	Mean and Incremental Effects	ICER and Cost per Ulcer-Free Week
Doubled weekly costs for post-minor and post-major LEAs Reference case: post-minor LEA, \$114.44; post-major LEA, \$114.46 Scenario: post-minor LEA, \$228.88; post-major LEA, \$228.92	Skin substitute: \$6,406 SC: \$5,354 ΔC: \$1,052	Skin substitute: 0.278 QALYs, 18.93 ulcer-free wk SC: 0.256 QALYs, 12.26 ulcer-free wk ΔE: 0.022 QALYs, 6.67 ulcer-free wk	\$47,678/QALY \$158
Tripled weekly costs for post-minor and post-major LEAs Reference case: post-minor LEA, \$114.44; post-major LEA, \$114.46 Scenario: post-minor LEA, \$343.33; post-major LEA, \$343.38	Skin substitute: \$6,393 SC: \$5,388 ΔC: \$1,005	Skin substitute: 0.277 QALYs, 19.01 ulcer-free wk SC: 0.256 QALYs, 12.26 ulcer-free wk ΔE: 0.022 QALYs, 6.76 ulcer-free wk	\$46,128/QALY \$149
Input parameters derived from Cazzell et al⁷⁰ (multi-layered skin substitute) Reference case: probability of ulcer healing at 12 wk, 51%; treatment effect, RD = 0.33; cost of skin substitute, \$629; mean number of applications, 5.97 Scenario: probability of ulcer healing at 12 wk, 32%; treatment effect, RD = 0.23; cost of skin substitute, \$135.25; mean number of applications, 8	Skin substitute: \$6,061 SC: \$7,023 ΔC: -\$962	Skin substitute: 0.261 QALYs, 13.10 ulcer-free wk SC: 0.244 QALYs, 8.03 ulcer-free wk ΔE: 0.017 QALYs, 5.07 ulcer-free wk	Dominant
Input parameters derived from Campitiello et al⁶⁵ (multi-layered skin substitute) Reference case: probability of ulcer healing at 12 wk, 51%; treatment effect, RD = 0.33; cost of skin substitute, \$629; mean number of applications, 5.97 Scenario: probability of ulcer healing at 6 wk, 52%; treatment effect, RD = 0.35; cost of skin substitute, \$5,648.81; mean number of applications, 1	Skin substitute: \$6,887 SC: \$3,186 ΔC: \$3,701	Skin substitute: 0.292 QALYs, 22.37 ulcer-free wk SC: 0.275 QALYs, 17.54 ulcer-free wk ΔE: 0.016 QALYs, 4.83 ulcer-free wk	\$226,280/QALY \$766

Abbreviations: ΔC, change in cost; ΔE, change in effect; ICER, incremental cost-effectiveness ratio; LEA, lower-extremity amputation; QALY, quality-adjusted life-year; RD, risk difference; SC, standard care alone.

Note: Scenario results were derived from probabilistic analysis by running 1,000 simulations.

Venous Leg Ulcers

REFERENCE CASE ANALYSIS

The mean total costs for the skin substitute strategy (skin substitute plus standard care) and the standard care strategy (standard care alone) were \$19,415 and \$7,148, respectively. The incremental cost between the two strategies was \$12,267, which is due to the additional cost associated with skin substitutes (\$1,901.04/application × 7.2 weekly applications = \$13,687.49), which was only partially offset by cost savings associated with a faster healing time of 3.80 ulcer-free weeks over 26 weeks.

The mean total effects of the skin substitute strategy were 0.330 QALYs and 10.12 ulcer-free weeks, compared with the standard care strategy at 0.324 QALYs and 6.33 ulcer-free weeks; the skin substitute strategy resulted in a negligible increase of 0.007 QALYs but a larger increase of 3.80 ulcer-free weeks over the duration of the model.

Treatment with skin substitutes plus standard care compared with standard care alone resulted in an ICER of \$1,868,850 per QALY and a cost per ulcer-free week of \$3,235 over 26 weeks. Table 18 provides the details of the reference case analysis results for the venous leg ulcer model.

Table 18: Reference Case Analysis Results—Venous Leg Ulcers

	Strategy	
	Skin Substitute + Standard Care	Standard Care Alone
Mean cost, \$ (95% CrI)	19,415 (18,503–20,323)	7,148 (6,265–7,929)
Mean QALYs (95% CrI)	0.330 (0.326–0.334)	0.324 (0.320–0.328)
Mean number of ulcer-free weeks (95% CrI)	10.12 (7.69–12.55)	6.33 (4.24–8.68)
Incremental cost, ^a \$ (95% CrI)	12,267 (11,020–13,503)	
Incremental QALYs ^b (95% CrI)	0.007 (0.001–0.012)	
Incremental number of ulcer-free weeks ^c (95% CrI)	3.80 (0.50–7.12)	
ICER, \$/QALY)	1,868,850	
\$/Ulcer-free week	3,235	

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

^aIncremental cost = average cost (strategy B) – average cost (strategy A).

^bIncremental effect = average effect (strategy B) – average effect (strategy A).

Note: Results may appear inexact due to rounding. Reference case results were derived from probabilistic analysis by running 5,000 simulations.

PROBABILISTIC SENSITIVITY ANALYSIS

When the results of the probabilistic sensitivity analysis were plotted in a cost-effectiveness acceptability curve (Figure 10), it was shown that at the commonly used willingness-to-pay range of \$50,000 to \$100,000 per QALY, the probability of the skin substitute strategy being cost-effective was 0% (i.e., highly unlikely to be cost-effective).

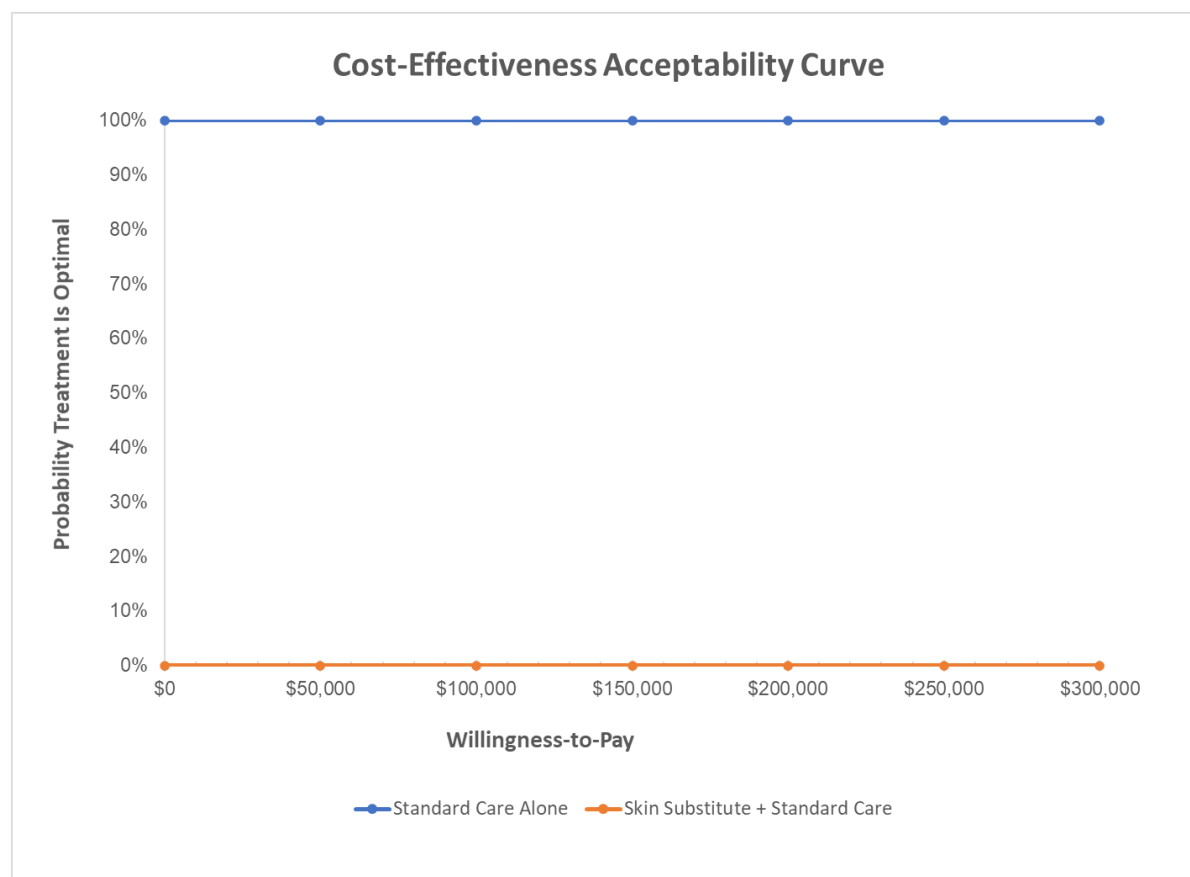


Figure 10: Cost-Effectiveness Acceptability Curve—Venous Leg Ulcers

SCENARIO ANALYSES

As with the diabetic foot ulcer model, our scenario analyses for the venous leg ulcer model found that some parameters affected the results (i.e., ICER) of our reference case more substantially than others.

For instance, when we increased the time horizon, which subsequently extrapolated the treatment effect of the skin substitute strategy from 26 weeks to 52 weeks, the ICER dropped to \$777,952 per QALY and the cost per ulcer-free week dropped to \$1,346. This effect was predominantly attributable to the greater cost savings associated with the additional number of ulcer-free weeks accrued over the longer time horizon compared with the reference case (i.e., 7.95 vs. 3.80 ulcer-free weeks). We also explored a scenario that assumed a smaller mean wound surface area than in our reference case, whereby 2 cm × 3 cm sheets were considered suitable for all eligible people. In this scenario, the ICER decreased to \$1,057,440 per QALY, and the cost per ulcer-free week decreased to \$1,830; these decreases were attributable to the decrease in skin substitute unit cost from \$1,901.04 per application to \$1,149.82 per application.

The subsequent scenarios, in contrast, resulted in an increase to the ICER of our reference case. For instance, the ICER increased substantially to \$3,190,954 per QALY, and the cost per ulcer-free week increased to \$5,523 when the number of skin substitute applications was increased to 12 weekly

applications (vs. 7.2 in the reference case), which consequently raised the overall skin substitute treatment cost from \$13,687.87 per person to \$22,812.48 per person. The ICER in our reference case also increased, but to a lesser degree (\$2,097,966/QALY, \$3,631/ulcer-free week), in a scenario in which treatment effect was not extrapolated beyond the duration of the original trial (16 weeks). This smaller effect on the ICER was due to the marginal difference that varying this parameter had on the incremental effectiveness (i.e., QALYs and number of ulcer-free weeks) of the skin substitute strategy compared with the standard care alone strategy.

As with our scenario analyses for the diabetic foot ulcer model, when we used unit prices and clinical input parameters from the multi-layered skin substitute study by Mostow et al,⁷⁹ the ICER changed substantially, and the skin substitute strategy became dominant (i.e., less costly and more effective). This was similarly attributable to the differences in unit price for different skin substitute products and the number of applications required for the various products. For instance, the multi-layered skin substitute in this scenario was estimated to cost \$135.25 per application at 8 weekly applications per person, whereas the dermal skin substitute that we modelled our reference case on was estimated to cost \$1,901.04 at 7.2 weekly applications per person.

We also ran two threshold analyses to assess the skin substitute unit cost needed to result in willingness-to-pay values of \$50,000 per QALY and \$100,000 per QALY. To reach these thresholds, we found that a substantial price reduction (around 86% and 84%, respectively) would be required.

Overall, as with the scenario analyses for the diabetic foot ulcer model, the cost-effectiveness results for the venous leg ulcer model were most sensitive to changes in cost parameters related to the skin substitute (i.e., unit price and number of applications needed). Table 19 provides a summary of the parameters varied in the venous leg ulcer model scenario analyses.

Table 19: Scenario Analysis Results—Venous Leg Ulcers

Scenario	Results		
	Mean and Incremental Costs	Mean and Incremental Effects	ICER and Cost per Ulcer-Free Week
Reference case	Skin substitute: \$19,415 SC: \$7,148 ΔC: \$12,267	Skin substitute: 0.330 QALYs, 10.12 ulcer-free wk SC: 0.324 QALYs, 6.33 ulcer-free wk ΔE: 0.007 QALYs, 3.80 ulcer-free wk	\$1,868,850/QALY, \$3,235
Increase in number of skin substitute applications	Skin substitute: \$28,503 SC: \$7,139 ΔC: \$21,363	Skin substitute: 0.330 QALYs, 10.22 ulcer-free wk SC: 0.324 QALYs, 6.35 ulcer-free wk ΔE: 0.007 QALYs, 3.87 ulcer-free wk	\$3,190,954/QALY, \$5,523
Reference case: 7.2 Scenario: 12			
Increase in time horizon	Skin substitute: \$21,626 SC: \$10,918 ΔC: \$10,708	Skin substitute: 0.661 QALYs, 28.48 ulcer-free wk SC: 0.647 QALYs, 20.52 ulcer-free wk ΔE: 0.014 QALYs, 7.95 ulcer-free wk	\$777,952/QALY, \$1,346
Reference case: 26 wk Scenario: 52 wk			
Treatment effect not extrapolated beyond 16 wk	Skin substitute: \$19,563 SC: \$7,156 ΔC: \$12,408	Skin substitute: 0.330 QALYs, 9.72 ulcer-free wk SC: 0.324 QALYs, 6.30 ulcer-free wk ΔE: 0.006 QALYs, 3.42 ulcer-free wk	\$2,097,966/QALY, \$3,631
Reference case: 26 wk Scenario: 16 wk			
Input parameters derived from Mostow et al¹⁴⁰ (multi-layered skin substitute)	Skin substitute: \$5,712.36 SC: \$6,250.55 ΔC: -\$538.20	Skin substitute: 0.335 QALYs, 13.05 ulcer-free wk SC: 0.328 QALYs, 8.72 ulcer-free wk ΔE: 0.0075 QALYs, 4.33 ulcer-free wk	Dominant
Reference case: probability of ulcer healing at 12 wk, 39%; treatment effect, RD = 0.20; cost of skin substitute, \$1,901.04; mean number of applications, 7.2 Scenario: probability of ulcer healing at 12 wk, 34%; treatment effect, RD = 0.20; cost of skin substitute, \$135.25; mean number of applications, 8			
2 cm × 3 cm sheets required for all patients	Skin substitute: \$14,015 SC: \$7,143 ΔC: \$6,872	Skin substitute: 0.330 QALYs, 10.10 ulcer-free wk SC: 0.324 QALYs, 6.34 ulcer-free wk ΔE: 0.006 QALYs, 3.76 ulcer-free wk	\$1,057,440/QALY, \$1,830
Reference case: \$1,901.04 Scenario: \$1,149.82			

Abbreviations: ΔC, change in cost; ΔE, change in effect; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RD, risk difference; SC, standard care alone.

Note: Scenario results were derived from probabilistic analysis by running 1,000 simulations.

Discussion

Our reference case results showed that at the commonly used willingness-to-pay of \$50,000 per QALY, the likelihood of skin substitutes being cost-effective was uncertain for the treatment of difficult-to-heal diabetic foot ulcers and highly unlikely for the treatment of difficult-to-heal venous leg ulcers. At the commonly used willingness-to-pay of \$100,000 per QALY, the likelihood of skin substitutes being cost-effective became moderately likely for the treatment of difficult-to-heal diabetic foot ulcers and remained highly unlikely for the treatment of difficult-to-heal venous leg ulcers.

The difference in our diabetic foot ulcer and venous leg ulcer reference case results can be predominantly explained by the higher overall cost of skin substitutes for the treatment of venous leg ulcers and the lower cost savings attributed to skin substitutes for treating this type of wound. There were lower cost savings here because, compared with diabetic foot ulcers, the unit cost of skin substitutes for venous leg ulcers is higher (due to the larger average wound surface area) and more applications are required to treat these wounds. Additionally, although the use of skin substitutes may lead to substantial cost savings associated with amputations avoided for people with diabetic foot ulcers, the likelihood of amputations for people with venous leg ulcers is low.

Overall, the use of skin substitutes plus standard care led to a marginal benefit in QALYs compared with standard care alone, with an incremental effectiveness of 0.022 QALYs and 0.007 QALYs gained for diabetic foot ulcers and venous leg ulcers, respectively. The QALY benefit was very small partly because we used a short time horizon in our models, which we chose because skin substitutes are not intended to resolve the underlying disease that precipitates foot and leg ulcerations in the long term.

In comparison, the use of skin substitutes plus standard care led to a larger increase in the number of ulcer-free weeks compared with standard care alone in a 26-week period, at 6.69 and 3.80 ulcer-free weeks for diabetic foot ulcers and venous leg ulcers, respectively. For diabetic foot ulcers, the use of skin substitutes also resulted in 1.35% of lower-extremity amputations avoided (i.e., 0.68% of minor amputations and 0.67% of major amputations) over the model time horizon, which represented a reduction of nearly 50% in the probability (2.8%) of having a lower-extremity amputation under the standard care alone strategy. Despite having a 26-week time horizon, the treatment effect in both models was extrapolated beyond the duration used in the original trial studies (12 weeks and 16 weeks, respectively, for the diabetic foot ulcer and venous leg ulcer models). As such, future studies with longer treatment periods may provide further insight into the effect of skin substitutes on the healing rate of chronic wounds over a longer period of time and support economic modelling over the longer term.

Of the parameters varied in our scenario analyses, the skin substitute unit price and the average number of applications required per person had the largest effect on the ICERs for both models. The skin substitute cost (unit cost $\times$ number of applications) represented a large proportion of the total mean cost in the skin substitute strategy (approximately 60% and 70% for diabetic foot ulcers and venous leg ulcers, respectively). Compared with the included studies in our economic literature review, our skin substitute costs were most comparable to those reported for Apligraf^{88,89,97} (35–76% of total mean cost) and least comparable to those reported for simple collagen-containing dressings (1–6% of total mean cost)^{86,91} and Oasis (22% of total mean cost).⁸⁷

Strengths and Limitations

Our primary economic evaluation provides comprehensive, updated cost–utility and cost-effectiveness analyses of skin substitutes as an adjunct to standard care versus standard care alone from the perspective of the Ontario public payer. Key model parameters were derived from studies that focused on a Health Canada–approved product and included a comparator reflective of current best practice (i.e., use of modern wound dressings vs. basic dressings) in Ontario. The unit cost of skin substitutes was determined based on the cost of the size of sheets closest to the estimated wound surface area for both diabetic foot ulcers and venous leg ulcers. Given the high cost associated with skin substitutes, this approach allowed us to identify costs that would account for minimal product waste. The number of weekly applications required was provided by the vendor and validated by clinical experts as reasonable in the Ontario setting.

A number of skin substitute products with a Health Canada licence are currently available, and a wider range available internationally. However, there are multiple differences in characteristics across available skin substitutes, such as cellularity (acellular or cellular), layering (single-layer or bi-layer), replaced region (epidermis, dermis, or both), materials used (natural, synthetic, or both), and permanence (temporary or permanent).¹⁰¹ For the purposes of our report, we aimed to evaluate skin substitutes as a class of medical device. Due to the wide variations in skin substitute products (in terms of effectiveness and unit price), we focused on those with a Health Canada licence. We evaluated these products either in our reference case analysis or in scenario analyses. Our reference case analysis focused on a single dermal skin substitute, because this product was associated with the best available published evidence (i.e., longest treatment period, larger sample size, and with a comparator most reflective of the Ontario setting), and its unit price was considered to be within a reasonable range of other commercially available skin substitutes.

We derived the costs associated with routine wound management under the standard care alone strategy from an Ontario costing study¹¹⁶ for both our diabetic foot ulcer and venous leg ulcer models, and this allowed us to include a resource use for wound management that closely reflected clinical practice in Ontario. We also validated all model parameters and assumptions with clinical experts who have expertise in wound care or skin substitutes in Ontario.

There were some limitations to our analysis that should be noted. First, standard care for diabetic foot ulcers and venous leg ulcers is not consistent across the province. Specifically, there may be wide variation in the frequency and/or availability of dressing changes, debridement, and other resource use (i.e., antibiotics, pain medication) due to varying health care resource levels across regions (P. Mayer, MD, July 17, 2020; L. Teague, PhD, September 2019). However, both models assumed that all people received the level of standard care considered best practice, which may not reflect current practice across Ontario. Furthermore, the frequency of the provision of these services is also specific to the individual patient and the unique characteristics of the individual wound. As such, although we aimed to derive the parameter values in our models based on the average case of difficult-to-heal diabetic foot ulcers and venous leg ulcers, this approach did not reflect the nuances and diversity of needs in care for these chronic wounds.

The unit costs of skin substitutes in our reference case and scenario analyses were all derived from United States pricing (i.e., from the US Centers for Medicare and Medicaid Services payment limits for drugs), which may differ from Canadian pricing. To account for this uncertainty, we explored the effect

on our results of scenarios in which the unit price was discounted at 10% to 20% in the diabetic foot ulcer model and 25% to 50% in the venous leg ulcer model.

Overall, our analyses showed that the high cost of skin substitutes may be partially offset by cost savings associated with less time needed for complete wound closure, because active, open ulcers continue to accrue resource use and costs for wound management. The higher the cost of standard care, the more likely the cost of skin substitutes is to be offset. People with active, open diabetic foot ulcers have the added risk of lower-extremity amputations, which are associated with a high level of resource use and cost. As such, the cost savings associated with avoided amputations are likely the predominant cause of the cost offset of skin substitutes in the short term for this type of wound.

Conclusions

For the treatment of difficult-to-heal neuropathic diabetic foot ulcers, we estimated the ICER of skin substitutes as an adjunct to standard care compared with standard care alone to be \$48,242 per QALY, and the cost per ulcer-free week to be \$158. At the commonly used willingness-to-pay of \$50,000 per QALY, the likelihood of skin substitutes plus standard care being cost-effective for the treatment of diabetic foot ulcers was uncertain, with a probability of approximately 47%. At the commonly used willingness-to-pay of \$100,000 per QALY, the probability of this strategy being cost-effective was approximately 71%, and therefore moderately likely to be cost-effective.

For the treatment of difficult-to-heal venous leg ulcers, we estimated the ICER of skin substitutes as an adjunct to standard care compared with standard care alone to be \$1,868,850 per QALY, and the cost per ulcer-free week to be \$3,235. For venous leg ulcers, the skin substitute strategy was highly unlikely to be cost-effective (0% probability) at both commonly used willingness-to-pay values of \$50,000 and \$100,000 per QALY.

For both diabetic foot ulcers and venous leg ulcers, the cost-effectiveness results were most sensitive to variations in the cost parameters associated with the skin substitute strategy—specifically the unit cost of skin substitutes and the number of applications needed to treat the wounds.

Budget Impact Analysis

Research Questions

1. What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding skin substitutes for adults with neuropathic diabetic foot ulcers?
2. What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding skin substitutes for adults with venous leg ulcers?

Methods

Analytic Framework

We estimated the budget impact of publicly funding skin substitutes using the cost difference between two scenarios: (1) current clinical practice without public funding for skin substitutes (the current scenario), and (2) anticipated clinical practice with public funding for skin substitutes (the new scenario). Figure 11 presents the budget impact model schematic.

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represented the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results were affected by varying input parameters and model assumptions.

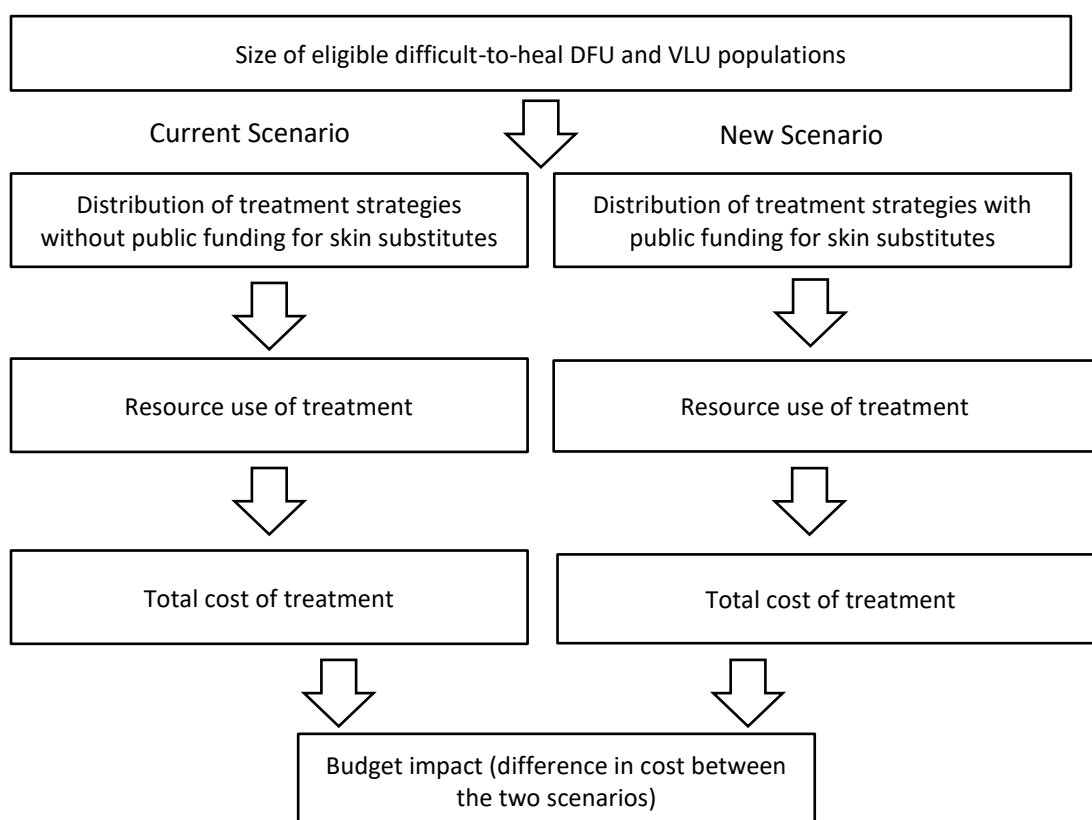


Figure 11: Budget Impact Model Schematic

Key Assumptions

The model's main assumptions were as follows:

- 50% and 60% of difficult-to-heal diabetic foot ulcers and venous leg ulcers, respectively, are eligible for treatment with skin substitutes (MiMedx, email communication, August 21, 2020)
- Eligible people with diabetic foot ulcers and venous leg ulcers will be treated with 5.97 and 7.2 weekly applications of skin substitute dressings, respectively
- For simplicity, we assumed that the annual prevalence rate of diabetic foot ulcers and venous leg ulcers would remain constant over the next 5 years
- We assumed that the uptake rate of skin substitutes in eligible populations would be gradual in the first 2 years and will then increase more quickly in years 3 through 5: 3% in year 1, 5% in year 2, 10% in year 3, 15% in year 4, and 20% in year 5 (P. Mayer, telephone communication, July 17, 2020; MiMedx, telephone communication, July 17, 2020)
- For simplicity, we assumed that publicly funded skin substitute products could be stored at room temperature and did not require cryopreservation
- For simplicity, we assumed that all people with diabetic foot ulcers or venous leg ulcers would present with a single ulcer, because bilateral or multiple ulcers on a single person are considered less common¹¹⁸⁻¹²⁰

Target Population

We estimated our target populations using published epidemiology data. Tables 20 and 21 present the input parameters used to estimate these populations.

For diabetic foot ulcers, we estimated the target population from Ontario's total population in 2019. To project the population over the next 5 years, we applied an annual growth rate of 1.53%, calculated as the average of growth rates in Ontario every year from 2015 to 2019. This rate fell within the range of the low-growth and high-growth rate scenarios of 0.6% and 1.6%, respectively, projected by the Ontario Ministry of Finance.¹⁴¹ For venous leg ulcers, we estimated the target population from Ontario's population in 2019 who were aged 25 years and older. To project this population, we applied an annual growth rate of 1.74%, calculated as the average of growth rate of this population in Ontario every year from 2015 to 2019.

We then estimated the target populations expected each year based on the proportions of difficult-to-heal diabetic foot ulcers and venous leg ulcers eligible for treatment with skin substitutes using the following parameters derived from the literature:

- Annual prevalence of diabetes in the general population in Ontario (8.8%)¹⁴²
- Annual prevalence rates of diabetic foot ulcers (2.5% in people with diabetes)¹⁴³ and venous leg ulcers (1.8 cases per 1,000 people¹⁴⁴ in people aged 25 years and older)
- Proportion of these wounds reported to be difficult to heal (33% of diabetic foot ulcers¹⁴⁵ and 26% of venous leg ulcers¹⁴⁶)
- Proportion of difficult-to-heal wounds eligible for treatment with skin substitutes (50% of diabetic foot ulcers and 60% of venous leg ulcers; MiMedx, email communication, August 21, 2020)

Table 20: Input Parameters for Estimating Target Populations—Diabetic Foot Ulcers

Input Parameter	Value	Source
Ontario population (year 1), n	14,566,547	Statistics Canada, 2019 ¹⁴⁷
Annual growth rate ^a	1.53%	Calculated
Annual prevalence of diabetes in Ontario	8.8%	Lipscombe, 2007 ¹⁴²
Annual prevalence of DFU	2.5%	Woo et al, 2007 ¹⁴³
Proportion of difficult-to-heal DFUs	33%	Nube et al, 2016 ¹⁴⁸
Proportion of difficult-to-heal DFUs eligible for skin substitutes	50%	MiMedx Group, email communication, July 20, 2020

Abbreviation: DFU, diabetic foot ulcer.

^aCalculated as the average of growth rate of Ontario's population for every year from 2015 to 2019.

Table 21: Input Parameters for Estimating Target Populations—Venous Leg Ulcers

Input Parameter	Value	Source
Ontario population ≥ 25 years (year 1), n	10,389,567	Statistics Canada, 2019 ¹⁴⁷
Annual growth rate ^a	1.74%	Calculated
Prevalence of VLU, rate per 1,000 people ≥ 25 years and older	1.8	Lorimer et al, 2003 ¹⁴⁴
Proportion of difficult-to-heal VLUs	26%	Guest et al, 1999 ¹⁴⁶
Proportion of difficult-to-heal VLUs eligible for skin substitutes	60%	MiMedx Group, email communication, July 20, 2020

Abbreviation: VLU, venous leg ulcer.

^aCalculated as the average of growth rate of Ontario's population of people aged 25 years and older for every year from 2015 to 2019.

Uptake of the New Intervention

We expected that the uptake of skin substitutes would take place at wound clinics that employ specialists with expertise in and previous experience with these products to ensure appropriateness of use and limit waste given the high cost of these products. We estimated the uptake of skin substitutes based on feedback from a clinical expert (P. Mayer, telephone communication, July 17, 2020) and the manufacturer (MiMedx, telephone communication, July 17, 2020). We expected the uptake rate to be low in year 1, starting at 3%, and then rise gradually to 20% in year 5.

We estimated the annual numbers of people with diabetic foot ulcers (Table 22) and venous leg ulcers (Table 23) expected to receive skin substitutes to be 159 in year 1 to 1,124 in year 5, and 88 in year 1 to 625 in year 5, respectively.

Table 22: Target Population or Volume of Intervention—Diabetic Foot Ulcers

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5
Ontario population, all ages, n	14,566,547	14,789,730	15,016,332	15,246,406	15,480,005
People with diabetes, all ages, n	1,281,856	1,301,496	1,321,437	1,341,684	1,362,240
People with DFUs, all ages, n	32,046	32,537	33,036	33,542	34,056
People with difficult-to-heal DFUs, n	10,575	10,737	10,902	11,069	11,238
People with difficult-to-heal DFUs eligible for skin substitutes, n	5,288	5,369	5,451	5,534	5,619
Uptake rate	3%	5%	10%	15%	20%
People with difficult-to-heal DFUs who receive skin substitutes, n	159	268	545	830	1,124

Abbreviation: DFU, diabetic foot ulcer.

Table 23: Target Population or Volume of Intervention—Venous Leg Ulcers

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5
Ontario population, ≥ 25 years, n	10,389,567	10,569,831	10,753,223	10,939,797	11,129,609
People with VLU, ≥ 25 years, n	18,701	19,026	19,356	19,692	20,033
People with difficult-to-heal VLUs, n	4,862	4,947	5,033	5,120	5,209
People with difficult-to-heal VLUs eligible for skin substitutes, n	2,917	2,968	3,020	3,072	3,125
Uptake rate	3%	5%	10%	15%	20%
People with difficult-to-heal VLUs who receive skin substitutes, n	88	148	302	461	625

Abbreviation: VLU, venous leg ulcer.

Current Intervention Mix

Skin substitutes are not publicly funded in Ontario at present. Therefore, we assumed that all people with difficult-to-heal diabetic foot ulcers or venous leg ulcers were receiving standard care alone.

Standard care costs for diabetic foot ulcers accounted for professional fees (e.g., physician, nurse, personal support worker) and costs associated with:

- Routine dressing changes, medications (e.g., antibiotics, anaesthetics), and out-of-pocket expenses (e.g., transportation, parking), as appropriate
- Routine wound debridement (100% surgical sharp debridement)
- Minor or major lower-extremity amputation, if required
- Hospital stay post-amputation, as appropriate

As stated previously, although publicly funded pressure-relieving (i.e., offloading) devices are considered part of standard care for the treatment of diabetic foot ulcers, our analysis did not account for these costs because they were unlikely to differ substantially between the current and new scenarios.

Standard care costs for venous leg ulcers accounted for professional fees (e.g., physician, nurse, personal support worker) and costs associated with:

- Routine dressing changes, medications (e.g., antibiotics, anaesthetics), and out-of-pocket expenses (e.g., transportation, parking), as appropriate
- Routine wound debridement (100% surgical sharp debridement)

As stated previously, although compression therapy (i.e., compression stockings) is considered part of standard care for the treatment of venous leg ulcers, our analysis did not account for these costs because we expected identical use of this item in the current and new scenarios over the long term.

New Intervention Mix

In the new intervention mix for diabetic foot ulcers, skin substitutes were used as an adjunct treatment to standard care at a cost of \$629 per application for 5.97 weekly applications. In the new intervention mix for venous leg ulcers, skin substitutes were used as an adjunct treatment to standard care at a cost of \$1,901.04 per application for 7.2 weekly applications.

Resources and Costs

Our analyses accounted for disease-associated resources and costs, which we obtained by running cost-effectiveness analyses (see Primary Economic Evaluation) over the time horizon of the budget impact analysis (without discounting) to obtain the relevant costs. See Tables 11 and 15 for a breakdown of the resources and costs used in our analyses for diabetic foot ulcers and venous leg ulcers, respectively.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We calculated the budget impact as the cost difference between the current scenario (skin substitutes not publicly funded) and the new scenario (skin substitutes publicly funded) for people with difficult-to-heal diabetic foot ulcers or venous leg ulcers who were eligible for treatment with skin substitutes. We calculated the total cost of each scenario using the average cost per person multiplied by the target population in each year. We calculated the annual budget impact for the next 5 years and estimated the total 5-year net budget impact.

In addition to the reference case, we also calculated the budget impact in 13 scenarios for diabetic foot ulcers and in nine scenarios for venous leg ulcers to evaluate the impact of uncertainty relating to cost, size of target population, and rate of uptake in our reference case analysis.

For diabetic foot ulcers, we ran scenarios for 10% (\$566.10) and 20% (\$503.20) price reductions to the unit cost of skin substitutes (\$629.00), and for a scenario that assumed that 2 cm × 3 cm sheets would

be required to treat all eligible people to assess the impact on our ICER when price discounts or a larger mean wound surface area were accounted for. We explored scenarios that assumed higher weekly costs associated with post-minor and post-major lower-extremity amputations, as well as a scenario that assumed a higher probability of amputations. We also ran two scenarios for two multi-layered skin substitutes that met the inclusion criteria for our clinical evidence review and have a Health Canada licence for the treatment of diabetic foot ulcers.^{65,70} Last, we ran a scenario that accounted for multiple ulcers per person, using the demographic characteristics of diabetic foot ulcers described in a cross-sectional study.¹⁴⁹ This study found that the proportion of people with one, two, three, and four diabetic foot ulcers at one time was 40%, 28.3%, 21.7%, and 10%, respectively. Based on these proportions, we applied a weighted average of 2.017 ulcers to the number of diabetic foot ulcers in Ontario each year to estimate the annual volume of these wounds for this scenario.

For venous leg ulcers, we ran scenarios for 25% (\$1,425.78) and 50% (\$950.52) price reductions to the unit cost of skin substitutes (\$1,901.04) and a scenario that assumed that 2 cm × 3 cm sheets would be required to treat all eligible people. We also conducted a scenario analysis for a multi-layered skin substitute that met the inclusion criteria of our clinical evidence review and has a Health Canada licence for the treatment of venous leg ulcers.⁷⁹ Last, we ran a scenario that accounted for multiple ulcers per person, using the demographic characteristics of venous leg ulcers described in a retrospective cohort study.¹⁵⁰ This study found that the proportion of people with one, two, and more than two venous leg ulcers at the same time was 61.7%, 30.9%, and 7.4%, respectively. For simplicity, we assumed that the average number of ulcers for people with more than two venous leg ulcers at the same time was three. Based on these proportions, we applied a weighted average of 1.457 ulcers to the number of venous leg ulcers in Ontario each year to estimate the annual volume of these wounds for this scenario.

For both budget impact analyses, we ran scenarios for an increase in the number of skin substitute applications to a maximum of 12 weekly applications, an increased time horizon of 52 weeks, and a treatment effect over the duration of that of the original studies^{57,62,64} rather than extrapolating it over the duration of the model. Last, we ran scenarios for double the annual uptake rate used in both reference cases.

Results

Budget Impact Analysis—Diabetic Foot Ulcers

REFERENCE CASE

Table 24 presents the projected total costs associated with skin substitutes for the treatment of diabetic foot ulcers over the next 5 years. The annual budget impact was \$167,764 in year 1, increasing to \$1,188,559 in year 5. The total 5-year budget impact was approximately \$3 million. When we took the projected cost of skin substitutes alone into account, the annual budget impact was \$595,674 in year 1, increasing to \$4,220,188 in year 5, for a total 5-year budget impact of approximately \$11 million.

Table 24: Budget Impact Results—Diabetic Foot Ulcers

Parameter	Budget Impact ^{a,b}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Current scenario, \$	28,095,563	28,526,031	28,963,096	29,406,857	29,857,417	144,848,963
Uptake rate	3%	5%	10%	15%	20%	—
New scenario						
Patients receiving skin substitutes, n	159	268	545	830	1,124	2,926
Skin substitutes, \$	1,010,630	1,710,191	3,472,789	5,288,996	7,160,042	18,642,649
Patients receiving standard care, n	5,129	5,100	4,906	4,704	4,495	24,335
Standard care, \$	27,252,696	27,099,730	26,066,786	24,995,828	23,885,933	129,300,973
Total budget impact, \$	28,263,326	28,809,921	29,539,575	30,284,824	31,045,976	147,943,622
Budget impact, \$ ^{b,c}						
All health care costs	167,764	283,890	576,479	877,967	1,188,559	3,094,659
Cost of skin substitutes alone	595,674	1,008,001	2,046,890	3,117,378	4,220,188	10,988,130

^aIn 2020 Canadian dollars.

^bResults may appear inexact due to rounding.

Note: The budget impact was calculated using probabilistic model results from the Primary Economic Evaluation.

SENSITIVITY ANALYSIS

Table 25 presents the results of the 13 scenario analyses conducted for the budget impact analysis of publicly funding skin substitutes for the treatment of difficult-to-heal diabetic foot ulcers. Compared with the reference case, scenarios showed a lower budget impact when the overall cost associated with skin substitutes (i.e., unit cost of skin substitutes × number of weekly applications) decreased or when the cost of standard care increased. We found the greatest decrease from the reference case results in the scenario for the first multi-layered skin substitute.⁷⁰ This scenario resulted in annual cost savings of \$152,676 in year 1 to approximately \$1 million in year 5, for a total cost savings of approximately \$2.8 million over the next 5 years—predominantly due to the lower cost of skin substitutes (at \$135.25/application × 8 applications) compared with the reference case. Notably, when the treatment effect of skin substitutes was extrapolated to a longer time horizon of 52 weeks, the budget impact also decreased substantially, resulting in an annual budget impact of \$10,094 in year 1 to \$71,516 in year 5, for a total of \$186,206 over the next 5 years. This reduction resulted largely from the greater cost savings associated with faster healing time accrued over the longer period of time.

In contrast, scenarios showed a higher budget impact when the overall cost associated with skin substitutes increased or when the cost of standard care decreased. For instance, when we accounted for multiple ulcers, the budget impact approximately doubled each year compared with the reference case results: \$328,917 in year 1 to approximately \$2.3 million in year 5, for a total of approximately \$6 million over the next 5 years. The scenario assuming higher annual uptake rates of 6%, 10%, 20%, 30%, and 40% in years 1 to 5, respectively, also saw a similar increase from the reference case results. We found the greatest increase in the scenario for the second multi-layered skin substitute.⁶⁵ This scenario resulted in a budget impact of \$587,138 in year 1 to approximately \$4.2 million in year 5, for a total of approximately

\$10.8 million over the next 5 years, predominantly due to the higher cost of this skin substitute (\$5,648.81/application × 1 application) compared with the reference case.

Table 25: Scenario Analysis Results—Diabetic Foot Ulcers

Scenario	Budget Impact, \$ ^{a,b}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Reference case	167,764	283,890	576,479	877,967	1,188,559	3,094,659
10% reduction in unit cost of skin substitute Reference case: \$629 Scenario: \$566.10	101,555	171,852	348,970	531,476	719,492	1,873,346
20% reduction in unit cost of skin substitute Reference case: \$629 Scenario: \$531.20	46,000	77,841	158,067	240,733	325,895	848,534
2 cm × 3 cm sheets required for all patients Reference case: \$629 Scenario: \$1,149.82	658,862	1,114,928	2,264,022	3,448,065	4,667,860	12,153,738
Increase in number of skin substitute applications Reference case: 5.97 Scenario: 12	762,961	1,291,084	2,621,731	3,992,851	5,405,370	14,073,998
Increase in time horizon Reference case: 26 wk Scenario: 52 wk	10,094	17,082	34,687	52,827	71,516	186,206
Reduction in treatment effect time horizon Reference case: 26 wk Scenario: 12 wk	196,861	333,128	676,464	1,030,243	1,394,704	3,631,400
Alternative probabilities of minor and major LEAs at 1 year Reference case: minor LEA, 5.4%; major LEA, 5.3% Scenario: minor LEA, 10.7%; major LEA, 10%	145,930	246,944	501,454	763,706	1,033,877	2,691,911
Doubled weekly costs for post–minor and post–major LEAs Reference case: post–minor LEA, \$114.44; post–major LEA, \$114.46 Scenario: post–minor LEA, \$228.88; post–major LEA, \$228.92	166,815	282,285	573,220	873,003	1,181,839	3,077,161

Scenario	Budget Impact, \$ ^{a,b}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Tripled weekly costs for post-minor and post-major LEAs Reference case: post-minor LEA, \$114.44; post-major LEA: \$114.46 Scenario: post-minor LEA, \$343.33; post-major LEA, \$343.38	159,410	269,753	547,773	834,249	1,129,374	2,940,559
Input parameters derived from Cazzell et al⁷⁰ (multi-layered skin substitute) Reference case: probability of ulcer healing at 12 wk, 51%; treatment effect, RD = 0.33; cost of skin substitute, \$629; mean number of applications, 5.97 Scenario: probability of ulcer healing at 12 wk, 32%; treatment effect, RD = 0.23; cost of skin substitute, \$135.25; mean number of applications, 8	-152,676	-258,358	-524,634	-799,008	-1,081,666	-2,816,342
Input parameters derived from Campitiello et al⁶⁵ (multi-layered skin substitute) Reference case: probability of ulcer healing at 12 wk, 51%; treatment effect, RD = 0.33; cost of skin substitute, \$629; mean number of applications, 5.97 Scenario: probability of ulcer healing at 6 wk, 52%; treatment effect, RD = 0.35; cost of skin substitute, \$5,648.81; mean number of applications: 1	587,138	993,557	2,017,559	3,072,707	4,159,714	10,830,675
Multiple DFUs per person Reference case: 1 ulcer per person Scenario: 2.017 ulcers per person	328,917	556,595	1,130,246	1,721,344	2,330,291	6,067,393
Increased uptake rate Reference case: 3% in year 1, 5% in year 2, 10% in year 3, 15% in year 4, 20% in year 5 Scenario: 6% in year 1, 10% in year 2, 20% in year 3, 30% in year 4, 40% in year 5	330,581	559,411	1,135,964	1,730,053	2,342,080	6,098,088

Abbreviations: DFU, diabetic foot ulcer; LEA, lower-extremity amputation.

^aIn 2020 Canadian dollars.

^bResults may appear inexact due to rounding.

Note: The budget impact was calculated using probabilistic model results from the Primary Economic Evaluation.

Budget Impact Analysis—Venous Leg Ulcers

REFERENCE CASE

Table 26 presents the projected total costs of the resource use associated with skin substitutes for the treatment of venous leg ulcers over the next 5 years. The annual budget impact was approximately \$1 million in year 1, increasing to approximately \$7.7 million in year 5. The total 5-year budget impact was approximately \$20 million. When the projected cost of skin substitutes alone was taken into account, the annual budget impact was approximately \$1.2 million in year 1, increasing to approximately \$8.6 million in year 5, for a total 5-year budget impact of approximately \$22 million.

Table 26: Budget Impact Results—Venous Leg Ulcers

Scenario	Budget Impact ^{a,b}					Total ^{b,c}
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current scenario, \$	20,844,133	21,205,790	21,573,721	21,948,036	22,328,846	107,900,526
Uptake rate	3%	5%	10%	15%	20%	
New scenario						
Patients receiving skin substitutes, n	88	148	302	461	625	1,624
Skin substitutes, \$	1,699,679	2,881,949	5,863,904	8,948,469	12,138,306	31,532,306
Patients receiving standard care, n	2,830	2,820	2,718	2,611	2,500	13,478
Standard care, \$	20,218,809	20,145,500	19,416,349	18,655,831	17,863,077	96,299,566
Total budget impact, \$	21,918,488	23,027,449	25,280,253	27,604,300	30,001,383	127,831,872
Budget impact, \$ ^{b,c}						
All health care costs	1,074,355	1,821,659	3,706,532	5,656,263	7,672,537	19,931,346
Cost of skin substitutes alone	1,197,952	2,031,228	4,132,942	6,306,976	8,555,207	22,224,305

^aIn 2020 Canadian dollars.

^bResults may appear inexact due to rounding.

Note: The budget impact was calculated using probabilistic model results from the Primary Economic Evaluation.

SENSITIVITY ANALYSIS

Table 27 presents the results of the nine scenario analyses conducted for the budget impact analysis of publicly funding skin substitutes for the treatment of difficult-to-heal venous leg ulcers. Compared with the reference case, scenarios showed a lower budget impact when the overall costs associated with skin substitutes (i.e., unit cost of skin substitutes × number of weekly applications) decreased or when the cost of standard care increased. We found the greatest decrease from the reference case results in the scenario for the first multi-layered skin substitute.⁷⁹ This scenario resulted in annual cost savings of \$47,104 in year 1 to \$336,395 in year 5, for a total cost savings of \$873,871 over the next 5 years, predominantly due to the lower cost of skin substitutes (at \$135.25/application × 8 applications) compared with the reference case. Compared with the budget impact analysis for diabetic foot ulcers, we found a much smaller effect on the reference case when the treatment effect of skin substitutes was extrapolated to a longer time horizon of 52 weeks (resulting in a budget impact of \$937,504 in year 1 to

around \$6.7 million in year 5, for a total of around \$17 million over the next 5 years). This finding indicated that the cost associated with skin substitutes for the treatment of venous leg ulcers was substantially greater than the cost savings associated with faster healing accrued over a longer period. In contrast, scenarios showed a greater budget impact when the overall cost associated with skin substitutes increased or when the cost of standard care decreased. When we accounted for multiple ulcers, the budget impact increased to approximately \$1.6 million in year 1 to approximately \$11 million in year 5, for a total of approximately \$29 million over the next 5 years. The scenario that assumed higher annual uptake rates of 6%, 10%, 20%, 30%, and 40% in years 1 to 5, respectively, saw the greatest increase from the reference case results, at approximately \$2.1 million in year 1 to approximately \$15.3 million in year 5, for a total of approximately \$40 million over the next 5 years.

Table 27: Scenario Analysis Results—Venous Leg Ulcers

Scenario	Budget Impact, \$ ^{a,b}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Reference case	1,074,355	1,821,659	3,706,532	5,656,263	7,672,537	19,931,346
25% reduction in unit cost of skin substitute Reference case: \$1,901.04 Scenario: \$1,425.78	775,560	1,315,027	2,675,687	4,083,167	5,538,683	14,388,125
50% reduction in unit cost of skin substitute Reference case: \$1,901.04 Scenario: \$950.52	476,881	808,591	1,645,242	2,510,681	3,405,657	8,847,052
2 cm × 3 cm sheets required for all patients Reference case: \$1,901.04 Scenario: \$1,149.82	598,399	1,014,636	2,064,480	3,150,450	4,273,483	11,101,447
Increase in number of skin substitute applications Reference case: 5.97 Scenario: 12	1,874,343	3,178,106	6,466,496	9,868,040	13,385,674	34,772,661
Increase in time horizon Reference case: 26 wk Scenario: 52 wk	937,504	1,589,617	3,234,395	4,935,770	6,695,211	17,392,496
Reduction in treatment effect time horizon Reference case: 26 wk Scenario: 16 wk	1,086,700	1,842,591	3,749,122	5,721,257	7,760,699	20,160,369

Scenario	Budget Impact, \$ ^{a,b}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Input parameters derived from Cazzell et al⁷⁰ (multi-layered skin substitute)	-47,104	-79,869	-162,509	-247,994	-336,395	-873,871
Reference case: probability of ulcer healing at 12 wk, 34%; treatment effect, RD = 0.20; cost of skin substitute: \$1901.04; mean number of applications, 7.2						
Scenario: probability of ulcer healing at 12 wk, 32%; treatment effect, RD = 0.23; cost of skin substitute, \$135.25; mean number of applications: 8						
Multiple VLU's per person	1,565,697	2,654,771	5,401,665	8,243,080	11,181,469	29,046,683
Reference case: 1 ulcer per person						
Scenario: 1.457 ulcers per person						
Increased uptake rate	2,144,562	3,636,285	7,398,753	11,290,687	15,315,449	39,785,735
Reference case: 3% in year 1, 5% in year 2, 10% in year 3, 15% in year 4, 20% in year 5						
Scenario: 6% in year 1, 10% in year 2, 20% in year 3, 30% in year 4, 40% in year 5						

Abbreviations: VLU, venous leg ulcer.

^aIn 2020 Canadian dollars.

^bResults may appear inexact due to rounding.

Note: The budget impact was calculated using probabilistic model results from the Primary Economic Evaluation.

Discussion

Skin substitutes for the treatment of difficult-to-heal diabetic foot ulcers and venous leg ulcers are associated with high costs. It is therefore important to ensure minimal product waste through measures such as limiting the eligibility for skin substitutes to those whom the product would most benefit and restricting the prescription and administration of skin substitutes to specialist physicians trained in wound care who have experience with these products. The total 5-year budget impact to publicly fund skin substitutes for the treatment of difficult-to-heal diabetic foot ulcers and difficult-to-heal venous leg ulcers would be approximately \$3 million and \$20 million, respectively (which corresponds to an estimated 2,926 and 1,624 people eligible to receive this treatment for diabetic foot ulcers and venous leg ulcers, respectively).

Overall, the budget impact for both diabetic foot ulcers and venous leg ulcers could be expected to decrease if the overall cost associated with skin substitutes (i.e., unit cost of skin substitutes × number of weekly applications) decreased or the cost of standard care increased. On the other hand, the budget impact for both could be expected to increase if the overall cost associated with skin substitutes increased or the cost of standard care decreased. Notably, when the treatment effect of skin substitutes was extrapolated to a longer time period of 52 weeks, the budget impact for diabetic foot ulcers dropped substantially, whereas the budget impact for venous leg ulcers was only marginally affected. However, given that existing clinical studies on skin substitutes typically have treatment periods

between 6 and 16 weeks, extrapolating these outcomes too far beyond the original trial period introduces greater uncertainty. As such, future studies with longer treatment periods may provide further insight into the effect of skin substitutes on the healing rate of chronic wounds over the long term.

Strengths and Limitations

A strength of our budget impact analysis was that we derived the estimates for our analyses from administrative data (i.e., from Statistics Canada) where available, and from the published literature. Further, we validated our assumptions and estimates with clinical experts who had expertise in wound care and the use of skin substitutes in Ontario.

With regard to limitations, as with our primary economic evaluation, our budget impact analyses assumed that standard care was consistent across the province and did not consider differences in wound care based on the individual needs of the patient. Our budget impact analysis was also highly dependent on the type of skin substitute under evaluation, because there are large variations in unit price and average number of applications required across products.

Conclusions

We estimate that publicly funding skin substitutes as an adjunct to standard care for the treatment of difficult-to-heal neuropathic diabetic foot ulcers in Ontario would lead to an annual budget impact ranging from an additional \$0.17 million in year 1 to an additional \$1.2 million in year 5, for a total of approximately \$3 million over the next 5 years. We estimate that publicly funding skin substitutes as an adjunct to standard care for the treatment of difficult-to-heal venous leg ulcers would lead to an annual budget impact ranging from an additional \$1 million in year 1 to an additional \$7.7 million in year 5, for a total of approximately \$20 million over the next 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of diabetic foot ulcers or venous leg ulcers and with treatments for these wounds.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).¹⁵¹⁻¹⁵³ Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with diabetic foot ulcers or venous leg ulcers in two ways:

- A review by Ontario Health of previous health technology assessments on diabetic foot ulcers and venous leg ulcers
- Direct engagement by Ontario Health with people with these conditions through interviews

Direct Patient Engagement

Outreach for this health technology assessment yielded three participants. This low recruitment number was due to restrictions on outreach to clinicians during the novel coronavirus disease (COVID-19) pandemic and the limited use of skin substitutes in Ontario. As a result, we used information from previous health technology assessments focusing on diabetic foot ulcers and venous leg ulcers and integrated it with the qualitative preferences evidence to present a complete overview of patient preferences and values.

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with diabetic foot ulcers and venous leg ulcers, as well as those of their families and other caregivers. We engaged people via phone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with diabetic foot ulcers and venous leg ulcers, as well as those of their families and caregivers.¹⁵⁴ The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,¹⁵⁵⁻¹⁵⁸ which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including Wounds Canada, the Meyer Institute, Sunnybrook Health Sciences Centre, and various support groups, to spread the word about this engagement activity and to contact people with diabetic foot ulcers and venous leg ulcers, family members, and caregivers, including those with experience using skin substitutes.

Inclusion Criteria

We sought to speak with patients and their caregivers who have been actively managing diabetic foot ulcers or venous leg ulcers. Participants were not required to have had direct experience with skin substitutes. We sought broad geographic, cultural, and socioeconomic representation to elicit possible equity issues in accessing treatment for diabetic foot ulcers and venous leg ulcers.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

For this project, we spoke with three people living in Ontario: two with diabetic foot ulcers and one with venous leg ulcers. Because of the low recruitment number, we used information from previous health technology assessments that focused on diabetic foot ulcers and venous leg ulcers and integrated it with the qualitative preferences evidence we collected for this health technology assessment. This additional information included the experiences of 39 people with diabetic foot ulcers and 15 people with venous leg ulcers. We spoke with people who had experience with current standard care for diabetic foot ulcers and venous leg ulcers. No participants had experience using skin substitutes.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 10). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 45 to 60 minutes. Interviews were loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.¹⁵⁹ Questions focused on the impact diabetic foot ulcers and venous leg ulcers on people's quality of life, people's experiences with treatments to manage or treat their condition, and people's perceptions of the benefits or limitations of skin substitutes. For family members and caregivers, questions focused on their perceptions of the impact of diabetic foot ulcers and venous leg ulcers and

treatments on the quality of life of patients, as well as on their family members and caregivers. See Appendix 11 for our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.^{160,161} We used the qualitative data analysis software program NVivo¹⁶² to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of diabetic foot ulcers and venous leg ulcers and treatments on patients, as well as on their family members and caregivers.

Results

EFFECTS OF ULCERS ON DAILY LIFE

People we interviewed reported a variety of experiences living with diabetic foot ulcers or venous leg ulcers. Participants noted the tremendous effect these ulcers had on their daily lives. They reported painful and deep sores that were difficult to heal despite the variety of treatment options used. Living with these ulcers had an effect on their mobility, employment, social activities, and emotional and mental health.

My foot was just a little bit swollen, [a] little bit red. It looked fine, and then two days later, just looked like volcanoes that had exploded, and it was like eight different wounds that were really deep.

The symptom was a small open sore, a quarter of a centimetre [in] depth.

Mobility

A majority talked about the reduced functionality of their leg because of diabetic foot ulcers or venous leg ulcers; the ulcers had a significant effect on their mobility. Issues with mobility meant that most reported a negative impact on their quality of life and restrictions in their daily activities. Limited mobility led to difficulty walking, exercising, and driving. Several people noted that they had to change the way they did certain everyday tasks, or they had to get support from friends and family.

The only major impediment was showering. I had to rig a system so that my legs were outside the shower.

I had the commode for the bed because I didn't want to go to the washroom ... I couldn't walk to the washroom. So it had to be beside the bed.

I didn't bring on this sickness. I didn't do this to myself. I would appreciate some help ... [Being able to] stand in the shower and take a shower like a normal human being would do it. That is what I would like for myself.

Employment

For some, diabetic foot ulcers or venous leg ulcers affected their employment, leading to leaves of absence, modified work duties, or scheduling their treatments around work.

I arranged to have early-morning appointments. I would go in the morning, they would wrap my legs, and I would go to work.

Others had to quit their job altogether. This led to people worrying about their financial situation and how they would take care of their families and themselves.

I did work at one time, but I haven't worked because my legs have been really bad. I have fibromyalgia, restless legs, diabetic neuropathy ... Right now, I can't work because my legs are really bad, and my hips are bad, and my back is bad. But I still go out and walk. I try to walk every day. I try to do my stuff. I go into the grocery store. But it hurts all the time.

Until it really got bad, I wasn't doing much differently because I didn't know. After that, I was being told to stay off my feet as much as possible, and at that time I was working, so I had to take time off to just stay off the feet.

Especially now you can't walk, you're off work, you've got a family to raise and children, and now you can't work, and you're spiralling down into the abyss pretty quick.

Social Activities

People also reported the effect of diabetic foot ulcers and venous leg ulcers on their social and leisure activities. They felt they were confined to their house or room because of limited mobility or lack of mobility, and this led to decreased visiting with friends and cancelled vacations or social outings.

There is no social life—no going out to watch a movie or going to a baseball or hockey game. We used to do all that stuff before.

I don't think I had a life. I was stuck on the bed watching TV.

Those with less severe ulcers reported being able to take part in social activities, but they found it more tiresome than usual.

I would still do all my activities, but they just took more energy and were more tiring. Everything took more effort to do in the same capacity.

Emotional and Mental Health

People described how living with diabetic foot ulcers or venous leg ulcers took a toll on their emotional and mental health. Some reported being depressed because of their inability to leave their home and the impact on their independence. Participants also expressed pain and frustration, complaining about slow healing times.

It was just killing me physically and emotionally. My whole body ached from head to toe. And I hardly saw any of my friends because I just I didn't want to go out. I had no life.

After the collapse one night, I really found myself in a depressive mood. I couldn't walk for four years. I was bedridden.

People also emphasized fear and stress about the ulcer coming back, not healing, or leading to amputation. This led to increased vigilance: they reported constantly monitoring their feet for cuts and bruises.

I live in constant fear that the “other shoe will drop” and either the ulcer will return or occur elsewhere.

Caregivers also expressed the emotional burden of seeing their loved ones in pain.

Her life shrank to her house, essentially, and to her bed. She was spending a lot of time in bed sleeping, and she was overwhelmed with trying to deal with all of this and deal with the inevitable fear of this potential amputation looming over her head.

It breaks my heart to see them when they are full-blown because they are so painful. It is heartbreaking to see him in the amount of pain he is in.

People spoke about their support system of family and friends, who helped by driving them to appointments and running household errands. They also acknowledged the hardship for their caregivers because of increased responsibilities.

Without my family, without my close friends, I don’t know where I would have been. I don’t think I would have been in my home; I wouldn’t have been able to manage on my own those early months.

I think it was hard on him [husband] because he was doing all the cleaning, my laundry, putting me in the shower, emptying my commode bowl, cooking, and doing the dishes.

STANDARD TREATMENT FOR ULCERS

Options

People reported familiarity with a wide variety of treatment options for diabetic foot ulcers, including dressings, bandages, silver nitrate, packing, and offloading devices (e.g., total contact casts, air casts, removable cast walkers, orthopedic shoes, ankle foot orthoses, Charcot restraint orthotic walker boots, felt padding, wheelchairs, crutches, canes, and walkers). Participants reported encountering these treatment options in the community at hospitals, wound care clinics, and chiropody clinics, and at home through nursing visits arranged through community care access centres. Participants reported being unfamiliar with skin substitutes.

The first type of treatment they tried to put was manuka honey patches on the wound. And then putting a sterile pad and wrapping it. I had an allergic reaction to the honey, and that got worse. Then they tried silver dressing with sterile contrast ... wrapped with gauze. That was changed every two days. The wounds were stable, but they were not getting better.

It started seven years ago ... before I had an amputation. They had tried all kinds of different dressings. They tried everything ... Oh, I even had a skin graft.

The possibility of amputation was a huge concern. A number of people had experience with amputations, including single-toe, multiple-toe, foot, and below-the-knee. Participants made clear the physical and emotional effects of amputation.

You've had a member of your body attached to you for 66 years, and all of sudden, it's gone. It was a pretty traumatic experience to go through.

It's not easy losing a limb. It was the hard part, and when I woke up, I was not a happy person. I wasn't sure how this prosthetic thing worked, or who paid for it, or anything.

People stressed the importance of getting their ulcers to fully heal. They highlighted the long treatment journey and treatment options they had tried. They noted the burdens of treatment, such as pain when changing dressings, maintenance, and management.

Well, it was a little bit cumbersome and heavy and hot, but I knew the downside if it didn't get healed up: I [would] probably face a further amputation.

The vinegar soak stings, so it's painful every time you remove the bandage, especially if it's been a couple of days. The removal of the bandage was painful.

One person mentioned the struggle and the amount of paperwork involved in getting set up at a wound clinic for bandage changes.

[The physician] filled out a form ... I waited and didn't get a response. There's no contact information. I called a central line. They didn't process the form, and then I was sent another form. And then it got to the point where I had to get a friend who was a GP [general practitioner] to call ... That was another set of paperwork. It was just the bureaucracy.

Cost

Most people mentioned cost as a barrier to accessing treatment for diabetic foot ulcers and venous leg ulcers. This was especially true for those who did not have access to private health insurance or government disability insurance. Because of the extreme consequences of leaving ulcers untreated, including amputation, people felt desperate and paid out of pocket for treatment. Cost also depended on the severity of the ulcer and the time it took to heal; longer healing times increased costs.

I don't care about the cost anymore. He has to have what he needs. If that means that I'm paying for it, I don't care ... We are not rich, but as his power of attorney, I make the decisions as to what is important, and I have decided that I don't care what it costs: he needs this.

We've been on pension for 20 years, but if the doctor says you need it or they're going to amputate your leg, what are you going to do?

Others were given treatment options that were fully publicly funded.

I had absolutely no cost myself at all. All the bandages and supplies they give you at the clinic to do this at home were excellent.

Some participants noted that other out-of-pocket costs increased because of their diabetic foot ulcers or venous leg ulcers, including transportation, parking, and food.

The major cost was that I had to take a lot of Ubers and stuff to work ... maybe also eating out more or ordering in because you're tired.

Others expressed gratitude for health insurance that covered most or all of the treatment options.

I think we are very fortunate for the health benefits my husband has through his employer. We are probably in a better place than most people. But there are so many people who don't have this advantage.

SKIN SUBSTITUTES

No participants had direct experience with skin substitutes or had been offered skin substitutes as a form of treatment. When the interviewer described biologic, synthetic, and biosynthetic skin substitutes, interviewees said they would be open to trying skin substitutes if they were recommended by their physician.

If there are good reports on it. Whatever [my physician] says, I will do. So if he was aware of it and wanted to try it, yes, I'd jump in a minute.

Another person said they would need to confirm whether skin substitutes would increase the chances of their wound healing and reduce infection and scarring before they would consider trying them.

I guess it would depend on the effectiveness of the skin substitute, like whether it actually significantly accelerated the healing. I guess the factors I would weigh would be, does it significantly cut down the healing, like 50% or more? The second thing would be, does it reduce the risk of infection? And then the third would be, does it improve the scarring outcome significantly?

Access

Only one of the three interviewees was aware of skin substitutes from their own, but they were not aware that skin substitutes were a treatment option available to the public. The others had never heard of skin substitutes or had not been offered them as a treatment option.

I didn't know [skin substitutes were] an available option. I knew that there had been research ... I didn't think [they were] publicly accessible.

Cost

When cost was mentioned, one person who reported being from a lower income bracket stated that even if skin substitutes were offered, they would not be able to afford them if they were not publicly funded.

I went to a few clinics here and there. They didn't even give me the option, not that I could have paid for it anyway.

Participants were also asked if they had any issues with the source of skin substitutes, given that some contain materials from humans or animals. Most had no objections about the source of the skin substitutes, but some raised concerns about how the material was derived.

It's all part of it. They have to develop it somewhere.

I wouldn't have an ethical issue unless people are selling their own biological matter ... where sometimes someone is forced into that.

Discussion

People with diabetic foot ulcers or venous leg ulcers discussed the effects of living with these wounds and their treatment journey. Participants spoke about the pain and discomfort they experienced because of their ulcers. They shared the burden of their condition and its disruption of their daily lives, including mobility, employment, social activities, and mental health. Participants also spoke about the variety of treatment options available and the financial barriers to accessing these treatments.

Interviewees reported cost as a barrier to accessing treatment for their ulcers. Those with ulcers that were difficult to heal described the many treatment options they had tried in an attempt to accelerate healing and avoid amputation.

We spoke to people who had experienced various forms of treatment to heal their ulcers, but none had experience using skin substitutes. Participants reported that they had not been given skin substitutes as a treatment option but said they would be open to using them if they were recommended by a physician or were likely to heal their ulcer. People also reported that the cost of skin substitutes would be a barrier if they had to pay out of pocket.

Our low recruitment number can be attributed to the fact that very few clinics currently use skin substitutes to treat diabetic foot ulcers or venous leg ulcers. Another limitation was the restrictions placed on recruitment because of the ongoing COVID-19 pandemic. No participants had experience with skin substitutes. Participants' reflections on skin substitutes are based on what we described to them, not from their actual use of them.

Conclusions

People with diabetic foot ulcers or venous leg ulcers reported the substantial effects of their condition on their quality of life, especially relating to mobility. They spoke of their long and difficult care journey: they had tried many treatment options to heal their ulcers and avoid amputation.

None of our interviewees had experience with skin substitutes. When we described the technology to them, they reported being open to this form of treatment if it meant their ulcers would heal. Barriers to skin substitutes included cost, if this treatment were not publicly funded, and access, because a limited number of clinics currently offer them.

Conclusions of the Health Technology Assessment

Dermal skin substitutes, when used as an adjunct to standard care, are more effective than standard care alone in promoting complete wound healing for adults with difficult-to-heal neuropathic diabetic foot ulcers (GRADE: High) or venous leg ulcers (GRADE: Moderate). Multi-layered skin substitutes, when used as an adjunct to standard care, are more effective than standard care alone in promoting complete wound healing for adults with difficult-to-heal neuropathic diabetic foot ulcers (GRADE: Moderate) or venous leg ulcers (GRADE: High). The effectiveness of epidermal skin substitutes for complete wound healing could not be determined for diabetic foot ulcers because we found no studies on this topic, and evidence was uncertain for venous leg ulcers (GRADE: Very low). We could not evaluate our certainty in the evidence for volume of wound healed, because the authors of the included studies reported their findings for this outcome in graph form only (which lacked curves for risk difference with confidence bounds). Finally, we were unable to form conclusions about the safety of skin substitutes versus standard care because of an insufficient number of events.

Skin substitutes as an adjunct to standard care were more costly and more effective compared with standard care alone for treatment of difficult-to-heal neuropathic diabetic foot ulcers and venous leg ulcers. For adults with diabetic foot ulcers, the likelihood of skin substitutes being cost-effective compared with standard care depends on the willingness to pay. The likelihood of skin substitutes being cost-effective compared with standard care is uncertain at \$50,000 per QALY and moderately likely at \$100,000 per QALY. For adults with venous leg ulcers, skin substitutes were highly unlikely to be cost-effective compared with standard care. We estimate that publicly funding skin substitutes for adults with diabetic foot ulcers or venous leg ulcers in Ontario would result in additional costs of \$3 million and \$20 million, respectively.

Patient preferences and values, obtained through interviews, indicated support for the use of skin substitutes as a treatment option. Participants spoke about the burden of their condition, which negatively affected their quality of life, presenting issues with mobility, employment, social activities, and emotional and mental health. Participants also spoke of slow healing time and the fear that unhealed ulcers could lead to amputation. They mentioned the need to be vigilant with their treatment despite the burdens it created. Barriers to accessing skin substitutes included the limited use of skin substitutes across Ontario, lack of knowledge about skin substitutes, and cost.

Abbreviations

GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
NICE	National Institute for Health and Care Excellence
QALY	Quality-adjusted life-year
SD	Standard deviation

Glossary

Adverse event	An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.
Ankle-brachial pressure index	The ankle-brachial index is a ratio of the blood pressure at the ankle to the blood pressure in the upper arm.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Compression therapy	Compression therapy is a treatment that uses stockings to increase blood flow activity in the lower limbs through strengthening vein support.
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness acceptability curve	In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.
Cost-effectiveness analysis	Used broadly, “cost-effectiveness analysis” may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, “cost-effectiveness analysis” may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.
Debridement	Debridement involves the removal of damaged tissue or foreign objects from a wound.

Decision tree	A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.
Dermal skin	Dermal skin is the layer of skin between the epidermis (the topmost layer of the skin) and subcutaneous tissue.
Deterministic sensitivity analysis	Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.
Diabetic neuropathy	Diabetic neuropathy is a type of nerve damage caused by long-term high blood sugar levels.
Discounting	Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.
Disutility	A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).
Dominant	A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).
Epidermal skin	Epidermal skin is the topmost layer of the skin.
EuroQol–Five Dimensions (EQ-5D)	The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Health state	A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.
Incremental cost	The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.
Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.
Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Natural history of a disease	The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.
Peripheral arterial disease	An abnormal narrowing of arteries other than those that supply the heart or brain

Probabilistic analysis	A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Risk difference	Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Societal perspective	The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Standard gamble	In economic evaluations, standard gamble is a direct method of measuring people's preferences for various health states. In a standard gamble, respondents are asked about their preference for either (a) remaining in a certain health state for the rest of their life, or (b) a gamble scenario in which there is a chance of having optimal health for the rest of one's life but also a chance of dying immediately. Respondents are surveyed repeatedly, with the risk of immediate death varying each time (e.g., 75% chance of optimal health, 25% chance of immediate death) until they are indifferent about their choice. The standard gamble is considered the gold standard for eliciting preferences as it incorporates individual risk attitudes, unlike other methods of eliciting preferences.
Time horizon	In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.
Time trade-off	In economic evaluations, time trade-off is a direct method of measuring people's preferences for various health states. In a time trade-off, respondents are asked about their preference for either (a) living with a chronic health condition for a certain amount of time, followed by death, or (b) living in optimal health but for less time than in scenario (a). That is, respondents decide how much time in good health they would be willing to "trade off" for more time spent in poorer health. Respondents are surveyed repeatedly, with the amount of time spent in optimal health varying each time until they are indifferent about their choice.
Toe-brachial pressure index	The toe-brachial pressure index is a way of determining arterial perfusion in feet and toes using a Doppler device and a sphygmomanometer.
Uptake rate	In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.
Utility	A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost-utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search Date: November 26, 2019

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 20, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 47>, Ovid MEDLINE(R) ALL <1946 to November 22, 2019>

Search Strategy:

-
- 1 Diabetic Foot/ (24210)
 - 2 Foot Ulcer/ (7289)
 - 3 Diabetic Neuropathies/ (31116)
 - 4 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath*))).ti,ab,kf. (70735)
 - 5 or/1-4 (91176)
 - 6 Foot Diseases/ (17376)
 - 7 Foot Dermatoses/ (43973)
 - 8 Foot Injuries/ (7383)
 - 9 Wound Healing/ (203436)
 - 10 (skin ulcer* or ((foot or feet) adj2 (disease* or injur* or wound*)) or (wound* adj2 heal*)).ti,ab,kf. (172231)
 - 11 or/6-10 (352013)
 - 12 exp Diabetes Mellitus/ (1336850)
 - 13 exp Diabetes Complications/ (266484)
 - 14 (diabet* or MODY or IDDM or NIDDM).ti,ab,kf. (1571111)
 - 15 or/12-14 (1809556)
 - 16 11 and 15 (27327)
 - 17 5 or 16 (101382)
 - 18 Varicose Ulcer/ (13478)
 - 19 (((venous or varicose or varicosis or stasis) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).ti,ab,kf. (19380)
 - 20 Venous Insufficiency/ (10805)
 - 21 (((venous or vein) adj2 insufficienc*) or CVI).ti,ab,kf. (17599)
 - 22 Leg Ulcer/ (20974)
 - 23 ((leg* or lower extremity*) adj2 ulcer*).ti,ab,kf. (17971)
 - 24 Saphenous Vein/ (28617)
 - 25 (saphenous adj vein*).ti,ab,kf. (33766)
 - 26 or/18-25 (102353)
 - 27 17 or 26 (199557)
 - 28 Biological Dressings/ (1860)

- 29 ((allograft* or autograft* or biologic* or xenograft* or heterograft* or homograft* or biosynthetic* or bio-synthetic* or bioimplant* or bio-implant*) adj3 (dressing* or therap* or treatment*)).ti,ab,kf. (76534)
- 30 ((cellular* or "liv* cell*" or "liv* skin*") adj3 (dressing* or product\$1 or construct\$1)).ti,ab,kf. (6049)
- 31 Skin, Artificial/ (4699)
- 32 ((tissue* or dermal* or dermis* or epiderm* or skin*) adj3 (matrix or matrices or substitute* or artificial* or synthetic* or biosynthetic* or bio-synthetic* or replacement*)).ti,ab,kf. (46194)
- 33 Tissue Engineering/ (81703)
- 34 (((tissue-engineer* or bioengineer* or bio-engineer*) and (skin* or dermal* or dermis* or epiderm* or dressing* or product\$1 or dermal* or dermis* or epiderm*)) or ((bioengineer* or bio-engineer*) adj3 tissue*)).ti,ab,kf. (14733)
- 35 exp Extracellular Matrix/tr [Transplantation] (369)
- 36 (("extracellular matri*" or "cellular matri*" or ECM or ECMs) adj4 (dressing* or therap* or product\$1 or treatment*)).ti,ab,kf. (2601)
- 37 ((wound* adj3 (matrix or matrices)) or AWCM or AWCMs or hVWM or hVWMs).ti,ab,kf. (1893)
- 38 Tissue Scaffolds/ (31057)
- 39 (((tissue* or skin* or dermal* or dermis* or epiderm*) adj3 scaffold*) or bioscaffold* or bio-scaffold*).ti,ab,kf. (21855)
- 40 Biocompatible Materials/ (100309)
- 41 (((biocompatible or bio-compatible) adj material*) or biomaterial* or bio-material* or biomembrane* or bio-membrane*).ti,ab,kf. (80302)
- 42 Acellular Dermis/ (2828)
- 43 ((acellular* or decellular* or noncellular* or non-cellular*) adj3 (skin* or graft* or matrix or matrices or tissue* or dermis* or dermal* or scaffold* or membrane* or substitute*)).ti,ab,kf. (14732)
- 44 Amnion/ (17035)
- 45 exp Chorion/ (11643)
- 46 Placenta/tu, th, tr [Therapeutic Use, Therapy, Transplantation] (165)
- 47 ((amnio* or chorio* or placenta* or cadaver*) adj4 (membrane* or matrix or matrices or allograft*)).ti,ab,kf. (32862)
- 48 (ADM or ADMs or HACM or HACMs or dHACM or dHACMs or HADM or HADMs or dACM or dACMs or HADWM or HADWMs or DAMA or DAMAs or dHACA or dHACAs).ti,ab,kf. (14543)
- 49 ((porcine* or bovine* or equine* or ovine* or fish* or cow\$1 or pig\$1 or horse* or sheep) adj4 (membrane* or matrix or matrices or xenograft* or xenogenic* or collagen*)).ti,ab,kf. (34800)
- 50 exp Cryopreservation/ (76347)
- 51 ((cryopreserv* adj4 (tissue* or membrane* or placenta* or skin*)) or vCPM or vCPMs).ti,ab,kf. (6711)
- 52 Allogeneic Cells/ (157)
- 53 (((allogen* or homolog*) adj3 (skin* or cell* or membrane*)) or allocell*).ti,ab,kf. (96823)
- 54 Collagen/ad, tu [Administration & Dosage, Therapeutic Use] (4636)
- 55 (collagen* adj4 (dressing* or product\$1)).ti,ab,kf. (3262)
- 56 Fibroblasts/tr [Transplantation] (1125)
- 57 Keratinocytes/tr [Transplantation] (686)
- 58 (((fibroblast* or keratinocyte*) adj2 (dressing* or product\$1 or allograft* or autolog* or autograft*)) or "fibroblast-derived" or (cultured adj2 keratinocyte*)).ti,ab,kf. (11857)
- 59 ((Affinity* adj3 allograft*) or Alloderm* or AlloPatch* or AlloSkin* or AlloWrap* or AltiPlast* or AltiPly* or AmnioBand* or AmnioExcel* or AmnioFill* or AmnioFix* or Amniomatrix* or Apligraf* or (Architect* adj3 matrix) or Artacent* or Avagen* or Biobrane* or Bio-ConneKt* or BioDFactor* or

- Biodfence* or BioFix* or Biovance* or Cellasta* or Colla-pad* or Collapad* or CollaSorb* or CollaWound* or Collexa* or Cygnus* or Cytal* or Dermacell* or Dermagraft* or Dermavest* or Dermapure* or DermaSpan* or Endoform* or Epicord* or Epifix* or Excellagen* or EZ Derm* or E-Z Derm* or FloGraft* or Floweramnio* or FlowerDerm* or FortaDerm* or GammaGraft* or Grafix* or GraftJacket* or Graftskin* or Helicoll* or hMatrix* or HYAFF* or Hyalograft* or Hyalomatrix* or Integra or (integra* adj3 matrix) or InteguPly* or Interfyl* or Kaloderm* or Kerecis* or Matriderm* or MatriStem* or Matrix HD* or Matrix H-D* or Merigen* or MicroMatrix* or Miroderm* or Nanoderm* or Neox* or NuShield* or OASIS* or ologen* or OrCel* or PalinGen* or Permacol* or Plurivest* or PriMatrix* or Puracol* or PuraPly* or Restrata* or Revita* or Smart Matrix* or Suprathel* or Talymed* or TheraForm* or TheraSkin* or WoundEx* or Xwrap*).ti,ab,kf. (23899)
- 60 or/28-59 (656664)
- 61 27 and 60 (4925)
- 62 (Systematic Reviews or Meta Analysis).pt. (108136)
- 63 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (580789)
- 64 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (403905)
- 65 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (412350)
- 66 (evidence adj (review* or overview* or synthes#s)).ti,ab,kf. (15321)
- 67 (review of reviews or overview of reviews).ti,ab,kf. (1387)
- 68 umbrella review*.ti,ab,kf. (665)
- 69 GRADE Approach/ (276)
- 70 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (440314)
- 71 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebSCO* or scopus).ab. (453538)
- 72 cochrane.ti,ab,kf. (197096)
- 73 (meta regress* or metaregress*).ti,ab,kf. (18879)
- 74 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (25081)
- 75 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (64309)
- 76 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (51387)
- 77 Clinical Trials as Topic/ (304172)
- 78 controlled clinical trials as topic/ (14688)
- 79 exp Randomized Controlled Trials as Topic/ (310981)
- 80 controlled clinical trial.pt. (197223)
- 81 randomized controlled trial.pt. (1020446)
- 82 Pragmatic Clinical Trial.pt. (2444)
- 83 Random Allocation/ (206793)
- 84 Single-Blind Method/ (84328)
- 85 Double-Blind Method/ (444227)
- 86 Placebos/ (334685)
- 87 trial.ti. (795418)
- 88 (random* or sham or placebo* or RCT*1).ti,ab,kf. (3919700)

- 89 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (664647)
- 90 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (3730)
- 91 or/62-90 (5747644)
- 92 61 and 91 (1141)
- 93 92 use medall (372)
- 94 61 use coch,cctr,clhta,cleed (417)
- 95 93 or 94 (789)
- 96 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5378157)
- 97 95 not 96 (782)
- 98 limit 97 to english language [Limit not valid in CDSR; records were retained] (577)
- 99 diabetic foot/ (24210)
- 100 foot ulcer/ (7289)
- 101 diabetic neuropathy/ (38114)
- 102 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath*))).tw,kw. (72244)
- 103 or/99-102 (94934)
- 104 foot disease/ (20326)
- 105 foot injury/ (8366)
- 106 wound healing/ (203436)
- 107 (skin ulcer* or ((foot or feet) adj2 (disease* or injur* or wound*)) or (wound* adj2 heal*)).tw,kw. (174480)
- 108 or/104-107 (315117)
- 109 exp diabetes mellitus/ (1336850)
- 110 (diabet* or MODY or IDDM or NIDDM).tw,kw. (1587385)
- 111 or/109-110 (1821003)
- 112 108 and 111 (26409)
- 113 103 or 112 (103782)
- 114 leg varicosis/ (1535)
- 115 (((venous or varicose or varicosis or stasis) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).tw,kw. (19390)
- 116 exp vein insufficiency/ (9743)
- 117 (((venous or vein) adj2 insufficienc*) or CVI).tw,kw. (18158)
- 118 leg ulcer/ (20974)
- 119 ((leg* or lower extremity*) adj2 ulcer*).tw,kw. (17910)
- 120 saphenous vein/ (28617)
- 121 (saphenous adj vein*).tw,kw. (33952)
- 122 or/114-121 (96721)
- 123 113 or 122 (196287)
- 124 exp biological dressing/ (1880)
- 125 ((allograft* or autograft* or biologic* or xenograft* or heterograft* or homograft* or biosynthetic* or bio-synthetic* or bioimplant* or bio-implant*) adj3 (dressing* or therap* or treatment*)).tw,kw,dv. (78610)
- 126 ((cellular* or "liv* cell*" or "liv* skin*") adj3 (dressing* or product\$1 or construct\$1)).tw,kw,dv. (6069)
- 127 artificial skin/ (4777)

- 128 ((tissue* or dermal* or dermis* or epiderm* or skin*) adj3 (matrix or matrices or substitute* or artificial* or synthetic* or biosynthetic* or bio-synthetic* or replacement*)).tw,kw,dv. (46942)
- 129 exp engineered skin graft/ (1990)
- 130 (((tissue-engineer* or bioengineer* or bio-engineer*) and (skin* or dermal* or dermis* or epiderm* or dressing* or product\$1 or dermal* or dermis* or epiderm*)) or ((bioengineer* or bio-engineer*) adj3 tissue*)).tw,kw,dv. (15773)
- 131 extracellular matrix/ and exp tissue transplantation/ (4085)
- 132 (("extracellular matri*" or "cellular matri*" or ECM or ECMs) adj4 (dressing* or therap* or product\$1 or treatment* or transplant*)).tw,kw,dv. (3009)
- 133 ((wound* adj3 (matrix or matrices)) or AWCM or AWCMs or hVWM or hVWMs).tw,kw,dv. (1940)
- 134 tissue scaffold/ (36166)
- 135 (((tissue* or skin* or dermal* or dermis* or epiderm*) adj3 scaffold*) or bioscaffold* or bio-scaffold*).tw,kw,dv. (22601)
- 136 biomaterial/ (108632)
- 137 (((biocompatible or bio-compatible) adj material*) or biomaterial* or bio-material* or biomembrane* or bio-membrane*).tw,kw,dv. (85362)
- 138 acellular dermal matrix/ (2887)
- 139 ((acellular* or decellular* or noncellular* or non-cellular*) adj3 (skin* or graft* or matrix or matrices or tissue* or dermis* or dermal* or scaffold* or membrane* or substitute*)).tw,kw,dv. (14912)
- 140 amnion/ (17035)
- 141 exp chorion/ (11643)
- 142 *placenta/ (52161)
- 143 placenta tissue/ (1797)
- 144 ((amnio* or chorio* or placenta* or cadaver*) adj4 (membrane* or matrix or matrices or allograft*)).tw,kw,dv. (33099)
- 145 (ADM or ADMs or HACM or HACMs or dHACM or dHACMs or HADM or HADMs or dACM or dACMs or HADWM or HADWMs or DAMA or DAMAs or dHACA or dHACAs).tw,kw,dv. (14614)
- 146 ((porcine* or bovine* or equine* or ovine* or fish* or cow\$1 or pig\$1 or horse* or sheep) adj4 (membrane* or matrix or matrices or xenograft* or xenogenic* or collagen*)).tw,kw,dv. (35096)
- 147 exp *cryopreservation/ (33367)
- 148 ((cryopreserv* adj4 (tissue* or membrane* or placenta* or skin*)) or vCPM or vCPMs).tw,kw,dv. (6803)
- 149 allogenic cell/ (130)
- 150 (((allogen* or homolog*) adj3 (skin* or cell* or membrane*)) or allocell*).tw,kw,dv. (97661)
- 151 collagen/ and exp tissue transplantation/ (7352)
- 152 collagen derivative/ (497)
- 153 (collagen* adj4 (dressing* or product\$1)).tw,kw,dv. (3292)
- 154 fibroblast/ and exp tissue transplantation/ (4625)
- 155 keratinocyte/ and exp tissue transplantation/ (2888)
- 156 (((fibroblast* or keratinocyte*) adj2 (dressing* or product\$1 or allograft* or autolog* or autograft*)) or "fibroblast-derived" or (cultured adj2 keratinocyte*)).tw,kw,dv. (11900)
- 157 ((Affinity* adj3 allograft*) or Alloderm* or AlloPatch* or AlloSkin* or AlloWrap* or AltiPlast* or AltiPly* or AmnioBand* or AmnioExcel* or AmnioFill* or AmnioFix* or Amniomatrix* or Apligraf* or (Architect* adj3 matrix) or Artacent* or Avagen* or Biobrane* or Bio-ConneKt* or BioDFactor* or Biodfence* or BioFix* or Biovance* or Cellasta* or Colla-pad* or Collapad* or CollaSorb* or CollaWound* or Collexa* or Cygnus* or Cytal* or Dermacell* or Dermagraft* or Dermavest* or Dermapure* or DermaSpan* or Endoform* or Epicord* or Epifix* or Excellagen* or EZ Derm* or E-Z Derm* or FloGraft* or Floweramnio* or FlowerDerm* or FortaDerm* or GammaGraft* or Grafix* or

GraftJacket* or Graftskin* or Helicoll* or hMatrix* or HYAFF* or Hyalograft* or Hyalomatrix* or Integra or (integra* adj3 matrix) or InteguPly* or Interfyl* or Kaloderm* or Kerecis* or Matriderm* or MatriStem* or Matrix HD* or Matrix H-D* or Merigen* or MicroMatrix* or Miroderm* or Nanoderm* or Neox* or NuShield* or OASIS* or ologen* or OrCel* or PalinGen* or Permacol* or Plurivest* or PriMatrix* or Puracol* or PuraPly* or Restrata* or Revita* or Smart Matrix* or Suprathel* or Talymed* or TheraForm* or TheraSkin* or WoundEx* or Xwrap*).tw,kw,dv. (26701)

158 or/124-157 (653634)

159 123 and 158 (5014)

160 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (562155)

Annotation: Added Systematic review/ or "systematic review (topic)"/ for thoroughness, but these may add many results. Will monitor

161 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (577285)

162 ((systematic* or methodologic*) adj3 (review* or overview*)).tw,kw. (419252)

163 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw. (444822)

164 (evidence adj (review* or overview* or synthes#s)).tw,kw. (15710)

165 (review of reviews or overview of reviews).tw,kw. (1584)

166 umbrella review*.tw,kw. (705)

167 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).tw,kw. (465863)

168 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebSCO* or scopus).ab. (453538)

169 cochrane.tw,kw. (200866)

170 (meta regress* or metaregress*).tw,kw. (19799)

171 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes#s)) or (research adj3 overview*)).tw,kw. (26008)

172 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (64309)

173 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw. (71340)

174 "clinical trial (topic)"/ (106077)

175 "controlled clinical trial (topic)"/ (10433)

176 "randomized controlled trial (topic)"/ (170977)

177 randomization/ (186029)

178 Single Blind Procedure/ (37269)

179 Double Blind Procedure/ (164828)

180 placebo/ (330141)

181 trial.ti. (795418)

182 (random* or sham or placebo* or RCT*1).tw,kw. (3982332)

183 ((singl* or doubl*) adj (blind* or dumm* or mask*)).tw,kw. (695246)

184 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).tw,kw. (4273)

185 or/160-184 (5373889)

186 159 and 185 (1167)

187 186 use emez (517)

- 188 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. (10877296)
- 189 187 not 188 (441)
- 190 limit 189 to english language [Limit not valid in CDSR; records were retained] (414)
- 191 98 or 190 (991)
- 192 191 use medall (348)
- 193 191 use emez (414)
- 194 191 use coch (3)
- 195 191 use cctr (212)
- 196 191 use clhta (7)
- 197 191 use cleed (7)
- 198 remove duplicates from 191 (570)

CINAHL

#	Query	Results
S1	(MH "Diabetic Foot")	8,034
S2	(MH "Foot Ulcer")	1,288
S3	(MH "Diabetic Neuropathies")	4,932
S4	((diabet* N4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neural* or wound*)) or DFU or DFUs or (ulcer* N2 (foot or feet)) or (plantar N2 (ulcer* or neuropath*)))	16,251
S5	S1 OR S2 OR S3 OR S4	16,251
S6	(MH "Foot Diseases")	2,189
S7	(MH "Foot Injuries")	1,521
S8	(MH "Wound Healing")	20,389
S9	(skin ulcer* or ((foot or feet) N2 (disease* or injur* or wound*)) or (wound* N2 heal*))	43,984
S10	S6 OR S7 OR S8 OR S9	43,984
S11	(MH "Diabetes Mellitus+")	146,899
S12	(diabet* or MODY or IDDM or NIDDM)	208,422
S13	S11 OR S12	209,316
S14	S10 AND S13	7,429
S15	S5 OR S14	17,514
S16	(MH "Venous Ulcer")	2,422
S17	((((venous or varicose or varicosis or stasis) N3 ulcer*) or (venous N1 disease*) or VLU or VLU's or CVLU or CVLU's or CVU or CVU's or CVDL)	4,185
S18	(MH "Venous Insufficiency")	1,354
S19	((((venous or vein) N2 insufficienc*) or CVI)	2,401
S20	(MH "Leg Ulcer")	3,432

S21 ((leg* or lower extremity*) N2 ulcer*)	6,471
S22 (MH "Saphenous Vein")	1,388
S23 (saphenous N1 vein*)	1,958
S24 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	11,847
S25 S15 OR S24	27,787
S26 (MH "Biological Dressings")	453
((allograft* or autograft* or biologic* or xenograft* or heterograft* or homograft* or biosynthetic* or bio-synthetic* or bioimplant* or bio-implant*) N3 (dressing* or therapy* or treatment*))	101,412
S27 ((cellular* or "liv* cell*" or "liv* skin*") N3 (dressing* or product or products or construct or constructs))	212
S28 (MH "Skin, Artificial")	827
S29 ((tissue* or dermal* or dermis* or epiderm* or skin*) N3 (matrix or matrices or substitute* or artificial* or synthetic* or biosynthetic* or bio-synthetic* or replacement*))	18,812
S30 (MH "Tissue Engineering")	1,778
((tissue-engineer* or bioengineer* or bio-engineer*) and (skin* or dermal* or dermis* or epiderm* or dressing* or product or products or dermal* or dermis* or epiderm*)) or ((bioengineer* or bio-engineer*) N3 tissue*)	608
S31 (MH "Extracellular Space+/TR")	202
S32 ("extracellular matri*" or "cellular matri*" or ECM or ECMs) N4 (dressing* or therapy* or product or products or treatment*))	146
S33 ((wound* N3 (matrix or matrices)) or AWCN or AWCNs or hVWM or hVWMs)	264
S34 (MH "Tissue Scaffolds")	189
S35 (((tissue* or skin* or dermal* or dermis* or epiderm*) N3 scaffold*) or bioscaffold* or bio-scaffold*)	1,956
S36 (MH "Biocompatible Materials")	4,738
S37 (((biocompatible or bio-compatible) N1 material*) or biomaterial* or bio-material* or biomembrane* or bio-membrane*)	5,758
S38 ((acellular* or decellular* or noncellular* or non-cellular*) N3 (skin* or graft* or matrix or matrices or tissue* or dermis* or dermal* or scaffold* or membrane* or substitute*))	841
S39 (MH "Fetal Membranes+")	1,553
S40 (MH "Placenta+/TR")	7
S41 ((amnio* or chorio* or placenta* or cadaver*) N4 (membrane* or matrix or matrices or allograft*))	4,030
S42 (ADM or ADMs or HACN or HACNs or dHACN or dHACNs or HADN or HADNs or dACN or dACNs or HADWN or HADWNs or DAMA or DAMAs or dHACA or dHACAs)	704
S43 ((porcine* or bovine* or equine* or ovine* or fish* or cow\$1 or pig\$1 or horse* or sheep) N4 (membrane* or matrix or matrices or xenograft* or xenogenic* or collagen*))	4,188
S44 (MH "Cryopreservation+")	2,452

S47	((cryopreserv* N4 (tissue* or membrane* or placenta* or skin*)) or vCPM or vCPMs)	428
S48	(MH "Allogeneic Cells")	20
S49	((allogen* or homolog*) N3 (skin* or cell* or membrane*)) or allocell*)	3,543
S50	(MH "Collagen/TU")	793
S51	(collagen* N4 (dressing* or product or products))	269
S52	(MH "Fibroblasts+/TR")	79
S53	(MH "Keratinocytes/TR")	87
S54	((fibroblast* or keratinocyte*) N2 (dressing* or product or products or allograft* or autolog* or autograft*)) or "fibroblast-derived" or (cultured N2 keratinocyte*))	1,224
S55	((Affinity* N3 allograft*) or Alloderm* or AlloPatch* or AlloSkin* or AlloWrap* or AltiPlast* or AltiPly* or AmnioBand* or AmnioExcel* or AmnioFill* or AmnioFix* or Amniomatrix* or Apligraf* or (Architect* N3 matrix) or Artacent* or Avagen* or Biobrane* or Bio-ConneKt* or BioDFactor* or Biodfence* or BioFix* or Biovance* or Cellasta* or Colla-pad* or Collapad* or CollaSorb* or CollaWound* or Collexa* or Cygnus* or Cytal* or Dermacell* or Dermagraft* or Dermavest* or Dermapure* or DermaSpan* or Endoform* or Epicord* or Epifix* or Excellagen* or EZ Derm* or E-Z Derm* or FloGraft* or Floweramnio* or FlowerDerm* or FortaDerm* or GammaGraft* or Grafix* or GraftJacket* or Graftskin* or Helicoll* or hMatrix* or HYAFF* or Hyalograft* or Hyalomatrix* or Integra or (integra* N3 matrix) or InteguPly* or Interfyl* or Kaloderm* or Kerecis* or Matriderm* or MatriStem* or Matrix HD* or Matrix H-D* or Merigen* or MicroMatrix* or Miroderm* or Nanoderm* or Neox* or NuShield* or OASIS* or ologen* or OrCel* or PalinGen* or Permacol* or Plurivest* or PriMatrix* or Puracol* or PuraPly* or Restrata* or Revita* or Smart Matrix* or Suprathel* or TalyMed* or TheraForm* or TheraSkin* or WoundEx* or Xwrap*)	3,093
S56	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55	138,727
S57	S25 AND S56	1,633
S58	(PT "Meta Analysis") or (PT "Systematic Review")	86,808
S59	(MH "Systematic Review") OR (MH "Meta Analysis")	95,733
S60	((systematic* or methodologic*) N3 (review* or overview*))	121,637
S61	(meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* N1 (assessment* or overview* or appraisal*)))	76,910
S62	(evidence N2 (review* or overview* or synthes#s)))	19,268
S63	((review or overview) N2 reviews)	6,344
S64	umbrella review*	183
S65	((pool* N3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) N2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*)	80,323
S66	AB(medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco*	73,430

	or scopus)	
S67	cochrane	44,130
S68	(meta regress* or metaregress*)	2,890
S69	((integrative or collaborative or quantitative) N3 (review* or overview* or syntheses*) or (research N3 overview*))	8,105
S70	SO(cochrane or (health N2 technology assessment) or evidence report or systematic review*)	10,745
S71	((comparative N3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) N1 comparison*))	7,012
S72	(MH "Randomized Controlled Trials+")	88,011
S73	(PT "randomized controlled trial")	86,206
S74	(MH "Random Assignment")	56,291
S75	(MH "Single-Blind Studies")	12,891
S76	(MH "Double-Blind Studies")	42,882
S77	(MH "Placebos")	11,489
S78	TI trial	96,909
S79	(random* or sham or placebo* or RCT or RCTs)	387,637
S80	((singl* or doubl*) N1 (blind* or dumm* or mask*))	68,040
S81	((tripl* or trebl*) N1 (blind* or dumm* or mask*))	427
	S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81	602,364
S83	S57 AND S82	325
S84	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	983,161
S85	S83 NOT S84	312
S86	S85 Narrow by Language: - english	303

Economic Evidence Search

Search Date: November 28, 2019

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2019>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 20, 2019>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2019 Week 47>, Ovid MEDLINE(R) ALL <1946 to November 26, 2019>

Search Strategy:

-
- 1 Diabetic Foot/ (24214)
 - 2 Foot Ulcer/ (7289)
 - 3 Diabetic Neuropathies/ (31120)
 - 4 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath*))).ti,ab,kf. (70765)
 - 5 or/1-4 (91206)
 - 6 Foot Diseases/ (17378)
 - 7 Foot Dermatoses/ (43974)
 - 8 Foot Injuries/ (7384)
 - 9 Wound Healing/ (203470)
 - 10 (skin ulcer* or ((foot or feet) adj2 (disease* or injur* or wound*)) or (wound* adj2 heal*)).ti,ab,kf. (172351)
 - 11 or/6-10 (352153)
 - 12 exp Diabetes Mellitus/ (1337047)
 - 13 exp Diabetes Complications/ (266539)
 - 14 (diabet* or MODY or IDDM or NIDDM).ti,ab,kf. (1571837)
 - 15 or/12-14 (1810296)
 - 16 11 and 15 (27345)
 - 17 5 or 16 (101415)
 - 18 Varicose Ulcer/ (13478)
 - 19 (((venous or varicose or varicosis or stasis) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).ti,ab,kf. (19380)
 - 20 Venous Insufficiency/ (10805)
 - 21 (((venous or vein) adj2 insufficienc*) or CVI).ti,ab,kf. (17604)
 - 22 Leg Ulcer/ (20976)
 - 23 ((leg* or lower extremity*) adj2 ulcer*).ti,ab,kf. (17972)
 - 24 Saphenous Vein/ (28619)
 - 25 (saphenous adj vein*).ti,ab,kf. (33776)
 - 26 or/18-25 (102371)
 - 27 17 or 26 (199608)
 - 28 Biological Dressings/ (1860)
 - 29 ((allograft* or autograft* or biologic* or xenograft* or heterograft* or homograft* or biosynthetic* or bio-synthetic* or bioimplant* or bio-implant*) adj3 (dressing* or therap* or treatment*)).ti,ab,kf. (76588)

- 30 ((cellular* or "liv* cell*" or "liv* skin*") adj3 (dressing* or product\$1 or construct\$1)).ti,ab,kf. (6054)
- 31 Skin, Artificial/ (4701)
- 32 ((tissue* or dermal* or dermis* or epiderm* or skin*) adj3 (matrix or matrices or substitute* or artificial* or synthetic* or biosynthetic* or bio-synthetic* or replacement*)).ti,ab,kf. (46224)
- 33 Tissue Engineering/ (81735)
- 34 (((tissue-engineer* or bioengineer* or bio-engineer*) and (skin* or dermal* or dermis* or epiderm* or dressing* or product\$1 or dermal* or dermis* or epiderm*)) or ((bioengineer* or bio-engineer*) adj3 tissue*)).ti,ab,kf. (14752)
- 35 exp Extracellular Matrix/tr [Transplantation] (370)
- 36 (("extracellular matri*" or "cellular matri*" or ECM or ECMs) adj4 (dressing* or therap* or product\$1 or treatment*)).ti,ab,kf. (2602)
- 37 ((wound* adj3 (matrix or matrices)) or AWCm or AWCms or hVWM or hVWms).ti,ab,kf. (1894)
- 38 Tissue Scaffolds/ (31082)
- 39 (((tissue* or skin* or dermal* or dermis* or epiderm*) adj3 scaffold*) or bioscaffold* or bio-scaffold*).ti,ab,kf. (21880)
- 40 Biocompatible Materials/ (100338)
- 41 (((biocompatible or bio-compatible) adj material*) or biomaterial* or bio-material* or biomembrane* or bio-membrane*).ti,ab,kf. (80389)
- 42 Acellular Dermis/ (2828)
- 43 ((acellular* or decellular* or noncellular* or non-cellular*) adj3 (skin* or graft* or matrix or matrices or tissue* or dermis* or dermal* or scaffold* or membrane* or substitute*)).ti,ab,kf. (14744)
- 44 Amnion/ (17036)
- 45 exp Chorion/ (11645)
- 46 Placenta/tu, th, tr [Therapeutic Use, Therapy, Transplantation] (165)
- 47 ((amnio* or chorio* or placenta* or cadaver*) adj4 (membrane* or matrix or matrices or allograft*)).ti,ab,kf. (32874)
- 48 (ADM or ADMs or HACM or HACMs or dHACM or dHACMs or HADM or HADMs or dACM or dACMs or HADWM or HADWms or DAMA or DAMAs or dHACA or dHACAs).ti,ab,kf. (14547)
- 49 ((porcine* or bovine* or equine* or ovine* or fish* or cow\$1 or pig\$1 or horse* or sheep) adj4 (membrane* or matrix or matrices or xenograft* or xenogenic* or collagen*)).ti,ab,kf. (34810)
- 50 exp Cryopreservation/ (76363)
- 51 ((cryopreserv* adj4 (tissue* or membrane* or placenta* or skin*)) or vCPM or vCPMs).ti,ab,kf. (6712)
- 52 Allogeneic Cells/ (158)
- 53 (((allogen* or homolog*) adj3 (skin* or cell* or membrane*)) or allocell*).ti,ab,kf. (96862)
- 54 Collagen/ad, tu [Administration & Dosage, Therapeutic Use] (4642)
- 55 (collagen* adj4 (dressing* or product\$1)).ti,ab,kf. (3263)
- 56 Fibroblasts/tr [Transplantation] (1125)
- 57 Keratinocytes/tr [Transplantation] (686)
- 58 (((fibroblast* or keratinocyte*) adj2 (dressing* or product\$1 or allograft* or autolog* or autograft*)) or "fibroblast-derived" or (cultured adj2 keratinocyte*)).ti,ab,kf. (11860)
- 59 ((Affinity* adj3 allograft*) or Alloderm* or AlloPatch* or AlloSkin* or AlloWrap* or AltiPlast* or AltiPly* or AmnioBand* or AmnioExcel* or AmnioFill* or AmnioFix* or Amniomatrix* or Apligraf* or (Architect* adj3 matrix) or Artacent* or Avagen* or Biobrane* or Bio-ConneKt* or BioDFactor* or Biodfence* or BioFix* or Biovance* or Cellasta* or Colla-pad* or Collapad* or CollaSorb* or CollaWound* or Collexa* or Cygnus* or Cytal* or Dermacell* or Dermagraft* or Dermavest* or Dermapure* or DermaSpan* or Endoform* or Epicord* or Epifix* or Excellagen* or EZ Derm* or E-Z

Derm* or FloGraft* or Floweramnio* or FlowerDerm* or FortaDerm* or GammaGraft* or Grafix* or GraftJacket* or Graftskin* or Helicoll* or hMatrix* or HYAFF* or Hyalograft* or Hyalomatrix* or Integra or (integra* adj3 matrix) or InteguPly* or Interfyl* or Kaloderm* or Kerecis* or Matriderm* or MatriStem* or Matrix HD* or Matrix H-D* or Merigen* or MicroMatrix* or Miroderm* or Nanoderm* or Neox* or NuShield* or OASIS* or ologen* or OrCel* or PalinGen* or Permacol* or Plurivest* or PriMatrix* or Puracol* or PuraPly* or Restrata* or Revita* or Smart Matrix* or Suprathel* or Tallymed* or TheraForm* or TheraSkin* or WoundEx* or Xwrap*).ti,ab,kf. (23918)

60 or/28-59 (657002)

61 27 and 60 (4927)

62 economics/ (255166)

63 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (844714)

64 economics.fs. (427040)

65 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (912861)

66 exp "costs and cost analysis"/ (588459)

67 (cost or costs or costing or costly).ti. (270363)

68 cost effective*.ti,ab,kf. (336002)

69 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*).ab,kf. (220976)

70 models, economic/ (13059)

71 markov chains/ or monte carlo method/ (82823)

72 (decision adj1 (tree* or analy* or model*).ti,ab,kf. (43781)

73 (markov or markow or monte carlo).ti,ab,kf. (132593)

74 quality-adjusted life years/ (41099)

75 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (76820)

76 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (125374)

77 or/62-76 (2605846)

78 61 and 77 (415)

79 78 use medall,cctr (174)

80 61 use coch,clhta,cleed (21)

81 79 or 80 (195)

82 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5380989)

83 81 not 82 (186)

84 limit 83 to english language [Limit not valid in CDSR; records were retained] (159)

85 diabetic foot/ (24214)

86 foot ulcer/ (7289)

87 diabetic neuropathy/ (38118)

88 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath*))).tw,kw. (72272)

89 or/85-88 (94962)

90 foot disease/ (20328)

91 foot injury/ (8367)

92 wound healing/ (203470)

93 (skin ulcer* or ((foot or feet) adj2 (disease* or injur* or wound*)) or (wound* adj2 heal*).tw,kw. (174597)

- 94 or/90-93 (315253)
- 95 exp diabetes mellitus/ (1337047)
- 96 (diabet* or MODY or IDDM or NIDDM).tw,kw. (1588104)
- 97 or/95-96 (1821736)
- 98 94 and 97 (26427)
- 99 89 or 98 (103813)
- 100 leg varicosis/ (1535)
- 101 (((venous or varicose or varicosis or stasis) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).tw,kw. (19390)
- 102 exp vein insufficiency/ (9743)
- 103 (((venous or vein) adj2 insufficienc*) or CVI).tw,kw. (18163)
- 104 leg ulcer/ (20976)
- 105 ((leg* or lower extremit*) adj2 ulcer*).tw,kw. (17911)
- 106 saphenous vein/ (28619)
- 107 (saphenous adj vein*).tw,kw. (33962)
- 108 or/100-107 (96739)
- 109 99 or 108 (196336)
- 110 exp biological dressing/ (1880)
- 111 ((allograft* or autograft* or biologic* or xenograft* or heterograft* or homograft* or biosynthetic* or bio-synthetic* or bioimplant* or bio-implant*) adj3 (dressing* or therap* or treatment*)).tw,kw,dv. (78664)
- 112 ((cellular* or "liv* cell*" or "liv* skin*") adj3 (dressing* or product\$1 or construct\$1)).tw,kw,dv. (6074)
- 113 artificial skin/ (4779)
- 114 ((tissue* or dermal* or dermis* or epiderm* or skin*) adj3 (matrix or matrices or substitute* or artificial* or synthetic* or biosynthetic* or bio-synthetic* or replacement*)).tw,kw,dv. (46974)
- 115 exp engineered skin graft/ (1990)
- 116 (((tissue-engineer* or bioengineer* or bio-engineer*) and (skin* or dermal* or dermis* or epiderm* or dressing* or product\$1 or dermal* or dermis* or epiderm*)) or ((bioengineer* or bio-engineer*) adj3 tissue*)).tw,kw,dv. (15792)
- 117 extracellular matrix/ and exp tissue transplantation/ (4085)
- 118 (("extracellular matri*" or "cellular matri*" or ECM or ECMs) adj4 (dressing* or therap* or product\$1 or treatment* or transplant*)).tw,kw,dv. (3011)
- 119 ((wound* adj3 (matrix or matrices)) or AWCm or AWCmS or hVWM or hVWMs).tw,kw,dv. (1941)
- 120 tissue scaffold/ (36191)
- 121 (((tissue* or skin* or dermal* or dermis* or epiderm*) adj3 scaffold*) or bioscaffold* or bio-scaffold*).tw,kw,dv. (22628)
- 122 biomaterial/ (108661)
- 123 (((biocompatible or bio-compatible) adj material*) or biomaterial* or bio-material* or biomembrane* or bio-membrane*).tw,kw,dv. (85448)
- 124 acellular dermal matrix/ (2887)
- 125 ((acellular* or decellular* or noncellular* or non-cellular*) adj3 (skin* or graft* or matrix or matrices or tissue* or dermis* or dermal* or scaffold* or membrane* or substitute*)).tw,kw,dv. (14925)
- 126 amnion/ (17036)
- 127 exp chorion/ (11645)
- 128 *placenta/ (52176)
- 129 placenta tissue/ (1797)

- 130 ((amnio* or chorio* or placenta* or cadaver*) adj4 (membrane* or matrix or matrices or allograft*)).tw,kw,dv. (33112)
- 131 (ADM or ADMs or HACM or HACMs or dHACM or dHACMs or HADM or HADMs or dACM or dACMs or HADWM or HADWMs or DAMA or DAMAs or dHACA or dHACAs).tw,kw,dv. (14618)
- 132 ((porcine* or bovine* or equine* or ovine* or fish* or cow\$1 or pig\$1 or horse* or sheep) adj4 (membrane* or matrix or matrices or xenograft* or xenogenic* or collagen*)).tw,kw,dv. (35106)
- 133 exp *cryopreservation/ (33373)
- 134 ((cryopreserv* adj4 (tissue* or membrane* or placenta* or skin*)) or vCPM or vCPMs).tw,kw,dv. (6804)
- 135 allogenic cell/ (130)
- 136 (((allogen* or homolog*) adj3 (skin* or cell* or membrane*)) or allocell*).tw,kw,dv. (97700)
- 137 collagen/ and exp tissue transplantation/ (7353)
- 138 collagen derivative/ (497)
- 139 (collagen* adj4 (dressing* or product\$1)).tw,kw,dv. (3293)
- 140 fibroblast/ and exp tissue transplantation/ (4625)
- 141 keratinocyte/ and exp tissue transplantation/ (2888)
- 142 (((fibroblast* or keratinocyte*) adj2 (dressing* or product\$1 or allograft* or autolog* or autograft*)) or "fibroblast-derived" or (cultured adj2 keratinocyte*)).tw,kw,dv. (11903)
- 143 ((Affinity* adj3 allograft*) or Alloderm* or AlloPatch* or AlloSkin* or AlloWrap* or AltiPlast* or AltiPly* or AmnioBand* or AmnioExcel* or AmnioFill* or AmnioFix* or Amniomatrix* or Apligraf* or (Architect* adj3 matrix) or Artacent* or Avagen* or Biobrane* or Bio-ConneKt* or BioDFactor* or Biodfence* or BioFix* or Biovance* or Cellasta* or Colla-pad* or Collapad* or CollaSorb* or CollaWound* or Collexa* or Cygnus* or Cytal* or Dermacell* or Dermagraft* or Dermavest* or Dermapure* or DermaSpan* or Endoform* or Epicord* or Epifix* or Excellagen* or EZ Derm* or E-Z Derm* or FloGraft* or Floweramnio* or FlowerDerm* or FortaDerm* or GammaGraft* or Grafix* or GraftJacket* or Graftskin* or Helicoll* or hMatrix* or HYAFF* or Hyalograft* or Hyalomatrix* or Integra or (integra* adj3 matrix) or InteguPly* or Interfyl* or Kaloderm* or Kerecis* or Matriderm* or MatriStem* or Matrix HD* or Matrix H-D* or Merigen* or MicroMatrix* or Miroderm* or Nanoderm* or Neox* or NuShield* or OASIS* or ologen* or OrCel* or PalinGen* or Permacol* or Plurivest* or PriMatrix* or Puracol* or PuraPly* or Restrata* or Revita* or Smart Matrix* or Suprathel* or Tallymed* or TheraForm* or TheraSkin* or WoundEx* or Xwrap*).tw,kw,dv. (26720)
- 144 or/110-143 (653972)
- 145 109 and 144 (5016)
- 146 Economics/ (255166)
- 147 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (130198)
- 148 Economic Aspect/ or exp Economic Evaluation/ (460631)
- 149 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (938891)
- 150 exp "Cost"/ (588459)
- 151 (cost or costs or costing or costly).ti. (270363)
- 152 cost effective*.tw,kw. (348493)
- 153 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (232482)
- 154 Monte Carlo Method/ (65781)
- 155 (decision adj1 (tree* or analy* or model*)).tw,kw. (47613)
- 156 (markov or markow or monte carlo).tw,kw. (137651)
- 157 Quality-Adjusted Life Years/ (41099)
- 158 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (80695)

159 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (146259)
 160 or/146-159 (2235404)
 161 145 and 160 (448)
 162 161 use emez (234)
 163 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. (10880124)
 164 162 not 163 (197)
 165 limit 164 to english language [Limit not valid in CDSR; records were retained] (191)
 166 84 or 165 (350)
 167 166 use medall (117)
 168 166 use emez (191)
 169 166 use coch (3)
 170 166 use cctr (25)
 171 166 use clhta (7)
 172 166 use cleed (7)
 173 remove duplicates from 166 (231)

CINAHL

#	Query	Results
S1	(MH "Diabetic Foot")	8,034
S2	(MH "Foot Ulcer")	1,288
S3	(MH "Diabetic Neuropathies")	4,932
S4	((diabet* N4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neural* or wound*)) or DFU or DFUs or (ulcer* N2 (foot or feet)) or (plantar N2 (ulcer* or neuropath*)))	16,251
S5	S1 OR S2 OR S3 OR S4	16,251
S6	(MH "Foot Diseases")	2,189
S7	(MH "Foot Injuries")	1,521
S8	(MH "Wound Healing")	20,389
S9	(skin ulcer* or ((foot or feet) N2 (disease* or injur* or wound*)) or (wound* N2 heal*))	43,984
S10	S6 OR S7 OR S8 OR S9	43,984
S11	(MH "Diabetes Mellitus+")	146,899
S12	(diabet* or MODY or IDDM or NIDDM)	208,422
S13	S11 OR S12	209,316
S14	S10 AND S13	7,429
S15	S5 OR S14	17,514
S16	(MH "Venous Ulcer")	2,422
S17	((((venous or varicose or varicosis or stasis) N3 ulcer*) or (venous N1 disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs or CVDL)	4,185

S18	(MH "Venous Insufficiency")	1,354
S19	((venous or vein) N2 insufficienc*) or CVI)	2,401
S20	(MH "Leg Ulcer")	3,432
S21	((leg* or lower extremit*) N2 ulcer*)	6,471
S22	(MH "Saphenous Vein")	1,388
S23	(saphenous N1 vein*)	1,958
S24	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	11,847
S25	S15 OR S24	27,787
S26	(MH "Biological Dressings")	453
S27	((allograft* or autograft* or biologic* or xenograft* or heterograft* or homograft* or biosynthetic* or bio-synthetic* or bioimplant* or bio-implant*) N3 (dressing* or therap* or treatment*))	101,412
S28	((cellular* or "liv* cell*" or "liv* skin*") N3 (dressing* or product or products or construct or constructs))	212
S29	(MH "Skin, Artificial")	827
S30	((tissue* or dermal* or dermis* or epiderm* or skin*) N3 (matrix or matrices or substitute* or artificial* or synthetic* or biosynthetic* or bio-synthetic* or replacement*))	18,812
S31	(MH "Tissue Engineering")	1,778
S32	((tissue-engineer* or bioengineer* or bio-engineer*) and (skin* or dermal* or dermis* or epiderm* or dressing* or product or products or dermal* or dermis* or epiderm*)) or ((bioengineer* or bio-engineer*) N3 tissue*))	608
S33	(MH "Extracellular Space+/TR")	202
S34	((extracellular matri*" or "cellular matri*" or ECM or ECMs) N4 (dressing* or therap* or product or products or treatment*))	146
S35	((wound* N3 (matrix or matrices)) or AWCM or AWCMs or hVWM or hVWMs)	264
S36	(MH "Tissue Scaffolds")	189
S37	((tissue* or skin* or dermal* or dermis* or epiderm*) N3 scaffold*) or bioscaffold* or bio-scaffold*)	1,956
S38	(MH "Biocompatible Materials")	4,738
S39	((biocompatible or bio-compatible) N1 material*) or biomaterial* or bio-material* or biomembrane* or bio-membrane*)	5,758
S40	((acellular* or decellular* or noncellular* or non-cellular*) N3 (skin* or graft* or matrix or matrices or tissue* or dermis* or dermal* or scaffold* or membrane* or substitute*))	841
S41	(MH "Fetal Membranes+")	1,553
S42	(MH "Placenta+/TR")	7
S43	((amnio* or chorio* or placenta* or cadaver*) N4 (membrane* or matrix or matrices or allograft*))	4,030
S44	(ADM or ADMs or HACM or HACMs or dHACM or dHACMs or HADM or HADMs or dACM or dACMs or HADWM or HADWMs or DAMA or DAMAs or dHACA or dHACAs)	704

S45	((porcine* or bovine* or equine* or ovine* or fish* or cow\$1 or pig\$1 or horse* or sheep) N4 (membrane* or matrix or matrices or xenograft* or xenogenic* or collagen*))	4,188
S46	(MH "Cryopreservation+")	2,452
S47	((cryopreserv* N4 (tissue* or membrane* or placenta* or skin*)) or vCPM or vCPMs)	428
S48	(MH "Allogeneic Cells")	20
S49	((allogen* or homolog*) N3 (skin* or cell* or membrane*)) or allocell*)	3,543
S50	(MH "Collagen/TU")	793
S51	(collagen* N4 (dressing* or product or products))	269
S52	(MH "Fibroblasts+/TR")	79
S53	(MH "Keratinocytes/TR")	87
S54	((fibroblast* or keratinocyte*) N2 (dressing* or product or products or allograft* or autolog* or autograft*)) or "fibroblast-derived" or (cultured N2 keratinocyte*))	1,224
S55	((Affinity* N3 allograft*) or Alloderm* or AlloPatch* or AlloSkin* or AlloWrap* or AltiPlast* or AltiPly* or AmnioBand* or AmnioExcel* or AmnioFill* or AmnioFix* or Amniomatrix* or Apligraf* or (Architect* N3 matrix) or Artacent* or Avagen* or Biobrane* or Bio-ConneKt* or BioDFactor* or Biodfence* or BioFix* or Biovance* or Cellasta* or Colla-pad* or Collapad* or CollaSorb* or CollaWound* or Collexa* or Cygnus* or Cytal* or Dermacell* or Dermagraft* or Dermavest* or Dermapure* or DermaSpan* or Endoform* or Epicord* or Epifix* or Excellagen* or EZ Derm* or E-Z Derm* or FloGraft* or Floweramnio* or FlowerDerm* or FortaDerm* or GammaGraft* or Grafix* or GraftJacket* or Graftskin* or Helicoll* or hMatrix* or HYAFF* or Hyalograft* or Hyalomatrix* or Integra or (integra* N3 matrix) or InteguPly* or Interfyl* or Kaloderm* or Kerecis* or Matriderm* or MatriStem* or Matrix HD* or Matrix H-D* or Merigen* or MicroMatrix* or Miroderm* or Nanoderm* or Neox* or NuShield* or OASIS* or ologen* or OrCel* or PalinGen* or Permacol* or Plurivest* or PriMatrix* or Puracol* or PuraPly* or Restrata* or Revita* or Smart Matrix* or Suprathel* or TalyMed* or TheraForm* or TheraSkin* or WoundEx* or Xwrap*)	3,093
S56	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55	138,727
S57	S25 AND S56	1,633
S58	(MH "Economics")	12,865
S59	(MH "Economic Aspects of Illness")	8,815
S60	(MH "Economic Value of Life")	596
S61	MH "Economics, Dental"	122
S62	MH "Economics, Pharmaceutical"	2,083
S63	MW "ec"	168,108
S64	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*)	269,113
S65	(MH "Costs and Cost Analysis+")	107,554
S66	TI cost*	49,534

S67 (cost effective*)	37,618
S68 AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	29,084
S69 (decision N1 (tree* or analy* or model*))	7,586
S70 (markov or markow or monte carlo)	5,340
S71 (MH "Quality-Adjusted Life Years")	4,204
S72 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	10,258
S73 ((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analys?s)	16,595
S74 S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73	364,831
S75 S57 AND S74	150
S76 PT (Case Study or Commentary or Editorial or Letter or Proceedings)	983,161
S77 S75 not s76	136
S78 S77 Narrow by Language: - english	132

Grey Literature Search

Search performed: December 3–6, 2019

Websites searched: Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Université de Québec-Université Laval, Health Technology Assessment Database, Epistemonikos, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, Health Technology Wales, Oregon Health Authority Health Evidence Review Commission, Veterans Affairs Health Services Research and Development, Italian National Agency for Regional Health Services (AGENAS), Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Ministry of Health Malaysia Health Technology Assessment Section, Swedish Agency for Health Technology Assessment and Assessment of Social Services, PROSPERO, EUnetHTA, Tuft's Cost-Effectiveness Analysis Registry, clincialtrials.gov.

Keywords: diabetic ulcers, foot ulcers, venous leg ulcers, leg ulcers, skin substitutes, acellular, cellular, dermal matrix, dermal matrices, epidermal matrix, epidermal matrices, extracellular matrix, extracellular matrices, allograft, autograft, xenograft, heterograft, homograft, wound dressings, artificial skin, tissue scaffolds, amnion, chorion, cryopreserved, allogeneic, collagen, fibroblasts, keratinocytes

Clinical Results (included in PRISMA): 16
Economic Results (included in PRISMA): 2
Ongoing HTAs (PROSPERO/EUnetHTA): 1
Ongoing clinical trials: 26

Appendix 2: Forest Plots for EpiFix Studies in the Clinical Review That Were Used in the Economic Analysis

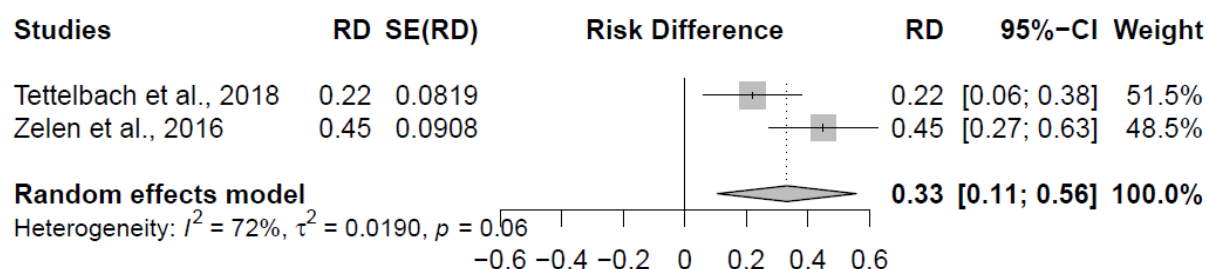


Figure A1: Complete Wound Healing—Studies Comparing EpiFix With Standard Care That Included Alginate Dressings

Abbreviations: CI, confidence interval; RD, risk difference; SE standard error.

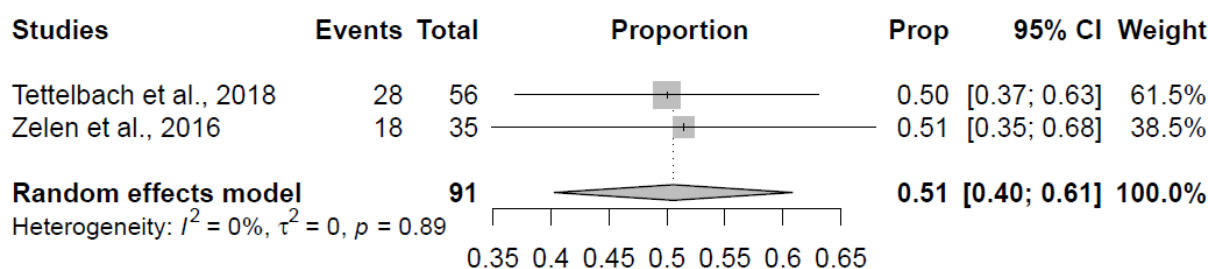


Figure A2: Proportion of Controls With Complete Wound Healing for Studies in Figure A1

Abbreviation: CI, confidence interval.

Appendix 3: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias^a Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool Version 2)

Studies	Bias Due to Randomization Process	Bias Due to Deviation From Intended Intervention (Effect of Adhering to Intervention)	Bias Due to Deviation From Intended Intervention (Effect of Assignment to Intervention)	Bias Due to Missing Outcome Data	Bias Due to Measurement of Outcome	Bias Due to Selection of Reported Results
Diabetic Foot Ulcers						
Alvarez et al, 2017 ⁶⁹	Some concerns ^b	Low	Low	Low	Low	Low
Brigido et al, 2004 ⁴³	Some concerns ^c	Low	Low	Low	Low	Low
Brigido, 2006 ⁴⁴	Some concerns ^c	Low	Low	Low	Low	Low
Campitiello et al, 2017 ⁶⁵	Low	Low	Low	Low	Low	Low
Caravaggi et al, 2003 ⁴⁵	Some concerns ^b	Low	Low	Low	Low	Low
Cazzell et al, 2015 ⁷⁰	Low	Low	Low	Low	Low	Low
Cazzell et al, 2017 ⁴⁶	Low	Low	Low	Low	Low	Low
DiDomenico et al, 2016 ⁴⁷	Low	Low	Low	Low	Low	Low
Di Mauro et al, 1991 ⁸³	Some concerns ^c	Some concerns ^d	Some concerns ^e	Some concerns ^f	Some concerns ^f	Low
Edmonds et al, 2009 ⁷¹	Some concerns ^c	Some concerns ^d	Some concerns ^e	Some concerns ^g	Low	Low
Gentzkow et al, 1996 ⁴⁸	Some concerns ^b	Low	Low	Low	Low	Low
Hanft and Surprenant, 2002 ⁴⁹	Some concerns ^b	Low	Low	Low	Low	Low
Lavery et al, 2014 ⁵⁰	Low	Low	Low	Low	Low	Low
Lipkin et al, 2003 ⁷²	Low	Low	Low	Low	Low	Low
Marston et al, 2003 ⁵¹	Low	Low	Low	Low	Low	Low
Mohajeri-Tehrani et al, 2016 ⁵²	Low	Low	Low	Low	Low	Low

Studies	Bias Due to Randomization Process	Bias Due to Deviation From Intended Intervention (Effect of Adhering to Intervention)	Bias Due to Deviation From Intended Intervention (Effect of Assignment to Intervention)	Bias Due to Missing Outcome Data	Bias Due to Measurement of Outcome	Bias Due to Selection of Reported Results
Pollak et al, 1997 ⁵³	Low	Low	Low	Low	Low	Low
Serena et al, 2020 ⁵⁴	Low	Low	Low	Low	Low	Low
Snyder et al, 2016 ⁵⁵	Low	Low	Low	Low	Low	Low
Tettelbach et al, 2019 ⁵⁶	Low	Low	Low	Low	Low	Low
Tettelbach et al, 2019 ⁵⁷	Low	Low	Low	Low	Low	Low
Uccioli et al, 2011 ⁵⁸	Low	Low	Low	Low	Low	Low
Veves et al, 2001 ⁷³	Low	Low	Low	Low	Low	Low
Veves et al, 2002 ⁷⁴	Low	Low	Low	Low	Low	Low
Zelen et al, 2013 ⁸⁴	Low	Low	Low	Low	Low	Low
Zelen et al, 2014 ⁶⁰	Low	Low	Low	Low	Low	Low
Zelen et al, 2016 ⁶²	Low	Low	Low	Low	Low	Low
Zelen et al, 2017 ⁶¹	Low	Low	Low	Low	Low	Low
Zelen et al, 2018 ⁶³	Low	Low	Low	Low	Low	Low
Venous Leg Ulcers						
Bianchi et al, 2019 ⁶⁴	Low	Low	Low	Low	Low	Low
Cazzell, 2019 ⁶⁶	Low	Low	Low	Low	Low	Low
Demling et al, 2004 ⁷⁶	Low	High ^h	Low	Low	Low	Some concerns ^h
Falanga and Sabolinski, 1999 ⁷⁸	Some concerns ^b	Some concerns ^c	Some concerns ^d	Some concerns ^g	Low	Low
Falanga et al, 1998 ⁷⁷	Low	Low	Low	Low	Low	Low
Harding et al, 2005 ⁸⁰	Low	Low	Low	Low	Low	Low
Harding et al, 2013 ⁶⁷	Low	Low	Low	Low	Low	Low

Studies	Bias Due to Randomization Process	Bias Due to Deviation From Intended Intervention (Effect of Adhering to Intervention)	Bias Due to Deviation From Intended Intervention (Effect of Assignment to Intervention)	Bias Due to Missing Outcome Data	Bias Due to Measurement of Outcome	Bias Due to Selection of Reported Results
Krishnamoorthy et al, 2003 ⁶⁸	Low	Low	Low	Low	Low	Low
Mostow et al, 2005 ⁷⁹	Low	Low	Low	Low	Low	Low
Teepe et al, 1993 ⁸¹	Low	Some concerns ^c	Low	Low	Low	Low
Wille et al, 2011 ⁸²	Low	Low	Low	Low	Low	Low

^aPossible risk-of-bias levels: low, some concerns, high.

^bUnclear if allocation sequence was done using a random mechanism; also, baseline differences suggested a problem with randomization. Direction of bias was unpredictable.

^cUnclear if allocation sequence was done using a random mechanism; also, no information to evaluate baseline differences. Direction of bias was unpredictable.

^dUnclear which method was used to estimate the effect of the assigned intervention. Direction of bias was unpredictable.

^eUnclear if participants adhered to the intervention. Direction of bias was unpredictable.

^fThe extent of wound healing was not elaborated. Direction of bias was unpredictable.

^gUnclear if outcome data were available for all or most of the patients.

^hNotable dropout rate, and intent-to-treat analysis not done. Direction of bias was unpredictable.

Table A2: GRADE Evidence Profile for the Comparison of Skin Substitutes and Standard Care

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Diabetic Foot Ulcers, Dermal Substitutes, Complete Wound Healing							
21 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕⊕ High
Diabetic Foot Ulcers, Multi-layered Substitutes, Complete Wound Healing							
8 (RCTs)	No serious limitations	Undetermined	No serious limitations	Serious limitations (−1) ^a	Undetected	None	⊕⊕⊕ Moderate
Venous Leg Ulcers, Dermal Substitutes, Complete Wound Healing							
5 (RCTs)	No serious limitations	Undetermined	No serious limitations	Serious limitations (−1) ^b	Undetected	None	⊕⊕⊕ Moderate
Venous Leg Ulcers, Multi-layered Substitutes, Complete Wound Healing							
4 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕⊕ High
Venous Leg Ulcers, Epidermal Substitutes, Complete Wound Healing							
3 (RCTs)	No serious limitations	Undetermined	No serious limitations	Serious limitations (−3) ^c	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

^aSix of eight studies had imprecise results.

^bThree of five studies had imprecise results.

^cAll studies had imprecise results.

Appendix 4: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary Reason for Exclusion
Alvarez OM, Patel M, Booker J, Markowitz L. Effectiveness of a biocellulose wound dressing for the treatment of chronic venous leg ulcers: results of a single center randomized study involving 24 patients. <i>Wounds</i> 2004;16(7):224-233.	Outcome of interest not reported
Ananian CE, Dhillon YS, Van Gils CC, Lindsey DC, Otto RJ, Dove CR, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. <i>Wound Rep Regen</i> 2018;26(3):274-83.	Wrong outcomes
Atillasoy E. The safety and efficacy of Graftskin (APLIGRAF) in the treatment of venous leg ulcers: a multicenter, randomized, controlled clinical trial. <i>Wounds</i> 2000;12(5):20A-26A.	Wrong outcomes
Baldursson BT, Kjartansson H, Konradsdottir F, Gudnason P, Sigurjonsson GF, Lund SH. Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa: a noninferiority study. <i>Int J Low Extrem Wounds</i> 2015;14(1):37-43.	Wrong outcomes
Bates D, Parsons N, King WN, Giovino KB. A bilayered living cellular construct accelerates wound healing in diabetic foot ulcers. <i>Wound Rep Regen</i> 20(5):A70.	Wrong patient population
Bayram Y, Deveci M, Imirzalioglu N, Soysal Y, Sengezer M. The cell based dressing with living allogenic keratinocytes in the treatment of foot ulcers: a case study. <i>Br J Plastic Surg</i> 2005;58(7):988-96.	Wrong patient population
Bianchi C, Cazzell S, Vayser D, Reyzelman AM, Dosluoglu H, Tovmassian G, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix) allograft for the treatment of venous leg ulcers. <i>Int Wound J</i> 2018;15(1):114-22.	Wrong patient population
Binienko MA, Kotslova AA, Davydenko VV, Vlasov TD. Application of Graftskin to accelerate healing of ulcers in diabetic foot syndrome. <i>Vestn Khir Im I I Grek</i> 2016;175(5):63-8.	Wrong study design
Blair HA. Capsaicin 8% dermal patch: a review in peripheral neuropathic pain. <i>Drugs</i> 2018;78(14):1489-500.	Wrong patient population
Blight A, Fatah MF, Datubo-Brown DD, Mountford EM, Cheshire IM. The treatment of donor sites with cultured epithelial grafts. <i>Br J Plastic Surg</i> 1991;44(1):12-4.	Full text could not be found
Bowering CK. Dermagraft in the treatment of diabetic foot ulcers. <i>J Cutan Med Surg</i> 1998;3(Suppl 1):S1-29.	Wrong patient population
Brem H, Kirsner RS. Use of Graftskin (APLIGRAF) in the treatment of pressure ulcers and acute wounds. <i>Wounds</i> 2000;12(5):72A-77A.	Wrong patient population
Brown-Etris M, Milne CT, Hodde JP. An extracellular matrix graft (Oasis wound matrix) for treating full-thickness pressure ulcers: a randomized clinical trial. <i>J Tissue Viability</i> 2019;28(1):21-6.	Wrong study design
Chalimidi KR, Kumar Y, Kini UA. Efficacy of collagen particles in chronic non healing ulcers. <i>J Clin Diagn Res</i> 2015;9(6):PC01-3.	Wrong comparator

Citation	Primary Reason for Exclusion
Chang DW, Sanchez LA, Veith FJ, Wain RA, Okhi T, Suggs WD. Can a tissue-engineered skin graft improve healing of lower extremity foot wounds after revascularization? <i>Ann Vasc Surg</i> 2000;14(1):44-9.	Non-English article
Choucair M, Faria D, Fivenson D. Use of human skin equivalent in the successful treatment of chronic venous leg ulcers. <i>Wounds</i> 1998;10(3):97-104.	Wrong study design
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. <i>Bull Emerg Trauma</i> . 2017;5(4):249-58.	Wrong study design
DiDomenico LA, Orgill DP, Galiano RD, Serena TE, Carter MJ, Kaufman JP, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. <i>Plastic Reconstr Surg</i> 2016;4(10):e1095.	Conference paper
Driver RV, Lavery LA, Reyzelman AM, Dutra TG, Dove CR, Kotsis SV, Kim HM, Chung KC. A clinical trial of Integra Template for diabetic foot ulcer treatment. <i>Wound Rep Reg</i> 2015;23:891–900	Wrong treatment (did not include standard care)
ElHeneidy H, Omran E, Halwagy A, Al-Inany H, Al-Ansary M, Gad A. Amniotic membrane can be a valid source for wound healing. <i>Int J Womens Health</i> 2016;8:225-31.	Wrong study design
Frade MA, Assis RV, Coutinho Netto J, Andrade TA, Foss NT. The vegetal biomembrane in the healing of chronic venous ulcers. <i>An Bras Dermatol</i> 2012;87(1):45-51.	Wrong comparator
Frykberg RG, Cazzell SM, Arroyo-Rivera J, Tallis A, Reyzelman AM, Saba F, et al. Evaluation of tissue engineering products for the management of neuropathic diabetic foot ulcers: an interim analysis. <i>J Wound Care</i> 2016;25(Suppl 7):S18-S25.	Duplicate
Glat P, Orgill DP, Galiano R, Armstrong D, Serena T, DiDomenico LA, et al. Placental membrane provides improved healing efficacy and lower cost versus a tissue-engineered human skin in the treatment of diabetic foot ulcerations. <i>Plastic Reconstr Surg</i> 2019;7(8):e2371.	Wrong comparator
Hanumanthappa MB, Gopinathan S, Suvarna R, Guruprasad RD, Shetty G, Shetty K, et al. Amniotic membrane dressing versus normal saline dressing in non-healing lower limb ulcers: a prospective comparative study at a teaching hospital. <i>J Clin Diagn Res</i> 2012;6(3):423-7.	Already included another paper (full study) from the same study
Letendre S, LaPorta G, O'Donnell E, Dempsey J, Leonard K. Pilot trial of biovance collagen-based wound covering for diabetic ulcers. <i>Adv Skin Wound Care</i> 2009;22(4):161-6.	Wrong comparator; did not include dressings
Pham HT, Rosenblum BI, Lyons TE, Giurini JM, Chrzan JS, Habershaw GM, et al. Evaluation of a human skin equivalent for the treatment of diabetic foot ulcers in a prospective, randomized, clinical trial. <i>Wounds</i> 1999;11(4):79-86.	Wrong study design; not an RCT
Phillips TJ, Provan A, Colbert D, Easley KW. A randomized single-blind controlled study of cultured epidermal allografts in the treatment of split-thickness skin graft donor sites. <i>Arch Dermatol</i> 1993;129(7):879-82.	Wrong study design

Citation	Primary Reason for Exclusion
Serena TE, Carter MJ, Le LT, Sabo MJ, DiMarco DT, EpiFix VLUSG. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. <i>Wound Repair Regen</i> 2014;22(6):688-93.	Wrong study design
Shen J, Falanga V. Bioengineered skin and treatment of wounds: use of an epidermal-dermal construct (Apligraf). <i>Today's Ther Trends</i> 1999;17(3):197-205.	Wrong study design; not an RCT
Shin D. The use of acellular dermal matrix paste for treatment of diabetic foot ulcer. <i>Wound Repair Regen</i> 2019;27(3):A17.	Wrong study design
Teepe RG, Koch R, Haeseker B. Randomized trial comparing cryopreserved cultured epidermal allografts with tulle-gras in the treatment of split-thickness skin graft donor sites. <i>J Trauma Inj Infect Crit Care</i> . 1993;35(6):850-4.	Already included another paper from the same study
Tettelbach W, Cazzell S, Sigal F, Caporusso JM, Agnew PS, Hanft J, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. <i>Int Wound J</i> 2019;16(1):122-30.	Wrong study design
Thompson P, Hanson DS, Langemo D, Anderson J. Comparing human amniotic allograft and standard wound care when using total contact casting in the treatment of patients with diabetic foot ulcers. <i>Adv Skin Wound Care</i> . 2019;32(6):272-7.	Conference paper
Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: a long-term follow-up study. <i>Wound Med</i> 2014;4:1-4.	Wrong comparator
Zelen CM, Serena TE, Snyder RJ. A prospective, randomised comparative study of weekly versus biweekly application of dehydrated human amnion/chorion membrane allograft in the management of diabetic foot ulcers. <i>Int Wound J</i> 2014;11(2):122-8.	Wrong comparator

Abbreviation: RCT, randomized controlled trial.

Appendix 5: R Code for Figures 2 to 5

```

library(gplots)
#####Risk difference by the run-in period#####
par(mar=c(4, 5, 2, 2),mfrow=c(1,2))

means<-
c(0.15,0.48,0.26,0.23,0.10,0.12,0.07,0.26,0.33,0.22,0.15,0.60,0.60,0.45,0.55)
ul<-
c(0.379,0.666,0.478,0.489,0.446,0.235,0.183,0.480,0.619,0.382,0.364,0.796,0.7
96,0.623,0.710)
ll<-c(-0.076,0.284,0.040,-0.072,-0.253,0.001,-0.040,0.046,0.070,0.061,-
0.061,0.330,0.330,0.267,0.343)
names(means)<-rep(" ",15)
plotCI(y=means,x=1:15, ui=ul,li=ll,ylim = c(-
0.5,1),gap=0,xlab="Studies",xlim=c(1,17),main="DFU",
      ylab ="Risk Difference",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
      cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:17, cex = 2,lwd=2,font=2,las=2,labels = c(names(means),
" ", " "),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)
abline(h=0,col="gray",lty=2,lwd=2)
means2<-c(0.41,0.19)
ul2<-c(0.586,0.321)
ll2<-c(0.229,0.054)
plotCI(y=means2,x=16:17, ui=ul2,li=ll2,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)
legend(locator(1),legend=c("2 weeks","1
week"),lty=c(1,1),lwd=c(2,2),col=c("black","blue"), pch=c(19,19),bty="n")

means3<-c(0.20,0.25,0.12,0.23,0.20,0.03)
ul3<-c(0.373,0.455,0.246,0.575,0.378,0.311)
ll3<-c(0.034,0.045,-0.009,-0.131,0.030,-0.237)
names(means3)<-rep(" ",6)
plotCI(y=means3,x=1:6, ui=ul3,li=ll3,ylim = c(-0.5,1),gap=0,xlab="Studies
",xlim=c(1,7),main="VLU",
      ylab ="",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
      cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:7, cex = 2,lwd=2,font=2,las=2,labels =
c(names(means3)," "),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)
abline(h=0,col="gray",lty=2,lwd=2)
means4<-c(0.11)
ul4<-0.245
ll4<--0.017
plotCI(y=means4,x=7, ui=ul4,li=ll4,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)
legend(locator(1),legend=c("2 weeks","4
weeks"),lty=c(1,1),lwd=c(2,2),col=c("black","blue"), pch=c(19,19),bty="n")

#####Risk difference by study duration#####

means5<-

```

```

c(0.17,0.71,0.57,0.15,0.23,0.21,0.48,0.26,0.42,0.23,0.41,0.10,0.12,0.07,0.26,
0.22,0.2,0.15,0.19,0.09,
0.84,0.45,0.26,0.60,0.55)
ul5<-
c(0.641,0.919,0.834,0.379,0.446,0.392,0.666,0.478,0.712,0.489,0.586,0.446,0.2
35,0.183,0.480,0.382,0.383,0.364,0.321,
0.197,0.973,0.623,0.478,0.796,0.710)
l15<-c(-0.148,0.406,0.180,-0.076,-0.008,-0.048,0.284,0.040,0.063,-0.072,-
0.229,-0.253,0.001,-0.040,0.046,0.061,0.025,0.025,0.054,
-0.023,0.478,0.267,0.040,0.330,0.343)

names(means5)<-rep(" ",25)
plotCI(y=means5,x=1:25, ui=ul5,li=l15,ylim = c(-0.5,1),gap=0,xlab="Studies
",xlim=c(1,31),main="DFU",
ylab ="Risk Difference ",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:31, cex = 2,lwd=2,font=2,las=2,labels =
c(names(means5),rep(" ",6)),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)
abline(h=0,col="gray",lty=2,lwd=2)
means6<-c(0.35,0.24,0.33,0.60)
ul6<-c(0.577,0.482,0.619,0.796)
l16<-c(0.081,-0.028,0.070,0.330)
plotCI(y=means6,x=26:29, ui=ul6,li=l16,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)
means7<-c(0.71,0.57)
ul7<-c(0.919,0.8342)
l17<-c(0.406,0.180)
plotCI(y=means7,x=30:31, ui=ul7,li=l17,gap=0,err="y",lwd =
2,pch=19,col="red",add=T)
legend(locator(1),legend=c(">6 weeks","6 weeks","4
weeks"),lty=c(1,1,1),lwd=c(2,2,2),col=c("black","blue","red"),
pch=c(19,19,19),bty="n")

means8<-c(0.20,-0.04,0.25,0.12,0.14,0.11,0.12,0.23,0.20,0.60)
ul8<-c(0.373,0.323,0.455,0.246,0.258,0.245,0.257,0.575,0.378,0.905)
l18<-c(0.034,-0.425,0.045,-0.009,0.025,-0.017,-0.021,-0.131,0.030,0.019)
names(means8)<-rep(" ",10)
plotCI(y=means8,x=1:10, ui=ul8,li=l18,ylim = c(-0.5,1),gap=0,xlab="Studies
",xlim=c(1,11),main="VLU",
ylab =" ",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:11, cex = 2,lwd=2,font=2,las=2,labels =
c(names(means8)," "),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)
abline(h=0,col="gray",lty=2,lwd=2)
means9<-c(0.03)
ul9<-0.311
l19<--0.237
plotCI(y=means9,x=11, ui=ul9,li=l19,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)
legend(locator(1),legend=c(">6 weeks","6
weeks"),lty=c(1,1),lwd=c(2,2),col=c("black","blue"), pch=c(19,19),bty="n")

```

#####Risk difference by the type of substitute#####


```

means10<-
c(0.71,0.57,0.15,0.21,0.48,0.42,0.23,0.41,0.12,0.24,0.07,0.26,0.33,0.22,0.20,
0.15,
    0.84,0.60,0.60,0.45,0.55)
ul10<-
c(0.919,0.834,0.379,0.392,0.666,0.712,0.489,0.586,0.235,0.482,0.183,0.480,0.6
19,0.382,0.383,0.364,
    0.973,0.796,0.796,0.62,0.710)
ll10<-c(0.406,0.180,-0.076,0.048,0.284,0.063,-0.07,0.229,0.001,-0.028,-
0.040,0.046,0.070,0.061,0.025,-0.060,
    0.478,0.330,0.330,0.267,0.343)

names(means10)<-rep(" ",21)
plotCI(y=means10,x=1:21, ui=ul10,li=ll10,ylim = c(-0.5,1),gap=0,xlab="Studies
",xlim=c(1,29),main="DFU",
    ylab ="Risk Difference ",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
    cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:29, cex = 2,lwd=2,font=2,las=2,labels =
c(names(means10),rep(" ",8)),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)
abline(h=0,col="gray",lty=2,lwd=2)
means11<-c(0.17,0.23,0.26,0.10,0.19,0.09,0.05,0.21)
ul11<-c(0.641,0.446,0.478,0.44,0.321,0.197,0.332,0.438)
ll11<-c(-0.148,-0.008,0.040,-0.253,-0.054,-0.023,-0.277,-0.012)

plotCI(y=means11,x=22:29, ui=ul11,li=ll11,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)
legend(locator(1),legend=c("Dermal","Multiyared"),lty=c(1,1),lwd=c(2,2),col=c
("black","blue"), pch=c(19,19),bty="n")

means12<-c(0.20,0.35,-0.04,0.12,0.23)
ul12<-c(0.373,0.577,0.323,0.246,0.575)
ll12<-c(0.034,0.081,-0.425,-0.009,-0.131)
names(means12)<-rep(" ",5)
plotCI(y=means12,x=1:5, ui=ul12,li=ll12,ylim = c(-0.5,1),gap=0,xlab="Studies
",xlim=c(1,12),main="VLU",
    ylab ="",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
    cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:12, cex = 2,lwd=2,font=2,las=2,labels =
c(names(means12),rep(" ",7)),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)

abline(h=0,col="gray",lty=2,lwd=2)
means13<-c(0.25,0.12,0.14,0.20)
ul13<-c(0.455,0.257,0.258,0.378)
ll13<-c(0.045,-0.021,0.025,0.030)
plotCI(y=means13,x=6:9, ui=ul13,li=ll13,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)
means14<-c(0.11,0.03,0.60)
int14<-c((0.245+0.017)/3.92,(0.311+0.237)/3.92,(0.905-0.019)/3.92)
ul14<-c(0.245,0.311,0.905)
ll14<-c(-0.017,-0.237,0.019)
plotCI(y=means14,x=10:12, ui=ul14,li=ll14,gap=0,err="y",lwd =
2,pch=19,col="red",add=T)
legend(locator(1),legend=c("Dermal","Multiyared","Epidermal"),lty=c(1,1,1),lw
d=c(2,2,2),col=c("black","blue","red"), pch=c(19,19,19),bty="n")

```

```
#####Risk difference by the type of standard of care#####
means10<-c(0.71,0.57,0.15,0.42,0.23,0.41,0.12,0.24,0.07,0.26,0.33,0.15,0.84)
ul10<-
c(0.919,0.834,0.379,0.712,0.489,0.586,0.235,0.482,0.183,0.480,0.619,0.364,0.9
73)
ll10<-c(0.406,0.180,-0.076,0.063,-0.072,0.229,0.001,-0.028,-
0.040,0.046,0.070,-0.060,0.478)

names(means10)<-rep(" ",13)
plotCI(y=means10,x=1:13, ui=ul10,li=ll10,ylim = c(-0.5,1),gap=0,xlab="Studies
",xlim=c(1,29),main="DFU",
      ylab ="Risk Difference ",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:29, cex = 2,lwd=2,font=2,las=2,labels =
c(names(means10),rep(" ",16)),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)
abline(h=0,col="gray",lty=2,lwd=2)

means11<-c(0.21,0.48,0.22,0.20,0.60,0.60,0.45,0.55)
ul11<-c(0.392,0.666,0.382,0.383,0.796,0.796,0.623,0.710)
ll11<-c(0.048,0.284,0.061,0.025,0.330,0.330,0.267,0.343)
plotCI(y=means11,x=14:21, ui=ul11,li=ll11,gap=0,err="y",lwd =
2,pch=19,col="red",add=T)

means12<-c(0.17,0.23,0.26,0.10,0.19,0.09)
ul12<-c(0.641,0.446,0.478,0.446,0.321,0.197)
ll12<-c(-0.148,-0.008,0.040,-0.253,0.054,-0.023)
plotCI(y=means12,x=22:27, ui=ul12,li=ll12,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)

means13<-c(0.05,0.21)
ul13<-c(0.332,0.438)
ll13<-c(-0.277,-0.012)
plotCI(y=means13,x=28:29, ui=ul13,li=ll13,gap=0,err="y",lwd =
2,pch=19,col="brown",add=T)

legend(locator(1),legend=c("Dermal vs Basic","Dermal vs Advanced", "Multi-
layered vs Basic", "Multi-layered vs
Advanced"),lty=c(1,1,1,1),lwd=c(2,2),col=c("black","red","blue","brown"),
pch=c(19,19,19,19),bty="n")

means10<-c(0.20,0.35,0.23)
ul10<-c(0.373,0.577,0.575)
ll10<-c(0.034,0.081,-0.131)

names(means10)<-rep(" ",3)
plotCI(y=means10,x=1:3, ui=ul10,li=ll10,ylim = c(-0.5,1),gap=0,xlab="Studies
",xlim=c(1,12),main="VLU",
      ylab ="Risk Difference ",err="y",lwd = 2,yaxt ="n",xaxt ="n", bty="n",
cex.axis=1,cex.lab=1.2,pch=19,font=2)
axis(side = 1, at = 1:12, cex = 2,lwd=2,font=2,las=2,labels =
c(names(means10),rep(" ",9)),lwd.ticks=0)
axis(side = 2,lwd = 2,font=2)
abline(h=0,col="gray",lty=2,lwd=2)
```

```

means11<-c(-0.04,0.12)
ul11<-c(0.323,0.246)
ll11<-c(-0.425,-0.009)
plotCI(y=means11,x=4:5, ui=ul11,li=ll11,gap=0,err="y",lwd =
2,pch=19,col="red",add=T)

means12<-c(0.25,0.12,0.14,0.20)
ul12<-c(0.455,0.257,0.258,0.378)
ll12<-c(0.045,-0.021,0.025,0.030)
plotCI(y=means12,x=6:9, ui=ul12,li=ll12,gap=0,err="y",lwd =
2,pch=19,col="blue",add=T)

means13<-c(0.11,0.03)
ul13<-c(0.245,0.311)
ll13<-c(-0.017,-0.237)
plotCI(y=means13,x=10:11, ui=ul13,li=ll13,gap=0,err="y",lwd =
2,pch=19,col="brown",add=T)

means14<-0.60
ul14<-0.905
ll14<-0.019
plotCI(y=means14,x=12, ui=ul14,li=ll14,gap=0,err="y",lwd =
2,pch=19,col="magenta",add=T)

legend(locator(1),legend=c("Dermal vs Basic","Dermal vs Advanced", "Multi-
layered vs Basic", "Epidermal vs Advanced","Epidermal vs
Basic"),lty=c(1,1,1,1,1),lwd=c(2,2,2,2),col=c("black","red","blue","brown","m
agenta"), pch=c(19,19,19,19,19),bty="n")

```

Appendix 6: Results of Economic Literature Review

Table A3: Results of Economic Literature Review for Diabetic Foot Ulcers—Summary

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
Allen et al, 2000, France ⁹⁰	Cost-effectiveness analysis Markov model Societal perspective Discount rate NA 12 mo FF, cost year NR	DFUs	Intervention: Dermagraft + SC Comparator: SC alone (type of dressings NR)	Mean per person Dermagraft + SC: 101.47 ulcers healed/ 100 patients SC alone: 86.64 ulcers healed/ 100 patients Mean difference Dermagraft vs. SC: 17.83 ulcers healed/ 100 patients	Mean per person Dermagraft + SC: 54,384 FF (unit cost: 2,600 FF/sheet × 7 applications/person; total skin substitute cost: 18,200/person) SC alone: 47,418 FF Mean difference Dermagraft + SC vs. SC alone: 6,967 FF	Reference case Dermagraft + SC vs. SC alone: 38,784 FF/ additional ulcer healed PSA Not conducted
Guest et al, 2017, United States ⁸⁷	Cost-effectiveness analysis Markov model Public payer perspective (Medicare) Discount rate NA 12 mo USD, 2016	Neuropathic DFUs (mean duration at baseline: 21.8 wk)	Intervention: Oasis Ultra + SC Comparator: SC alone (silver dressing, hydrogel, wet-to-dry dressing, alginate dressing, Manuka honey + triple antibiotic dressing)	Mean per person Oasis + SC: 4.43 ulcer-free mo SC alone: 3.11 ulcer-free mo Mean difference Oasis + SC vs. SC alone: 1.32 ulcer-free mo ^b	Mean per person Oasis + SC: \$13,857.61 (unit cost: \$527/sheet × 5.73 applications/person; total skin substitute cost: \$3,019.84/person) SC alone: \$13,962.23 Mean difference Oasis + SC vs. SC alone: −\$104 ^b	Reference case Oasis + SC vs. SC alone: Dominant ^c (−\$79.38/ ulcer-free mo) (Results also reported for \$/healed ulcer, \$/avoided complicated ulcer, and \$/avoided amputation) PSA Probability of Oasis + SC being cost-effective: 98% at a WTP of \$2,500/ulcer-free mo

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
Guest et al, 2018, United Kingdom ⁸⁶	Cost-utility analysis Decision tree Public payer perspective (NHS) Discount rate NA 4 mo £, 2015/16	Difficult-to-heal DFUs with duration > 6 mo	Intervention: Collagen-containing dressing + SC Comparator: SC alone (type of dressing NR)	Mean per person Collagen-containing dressing + SC: 0.163 QALYs SC alone: 0.156 QALYs Mean difference Collagen-containing dressing + SC vs. SC alone: 0.007 QALYs	Mean per person Collagen-containing dressing + SC: £2,255 (unit cost: £10.41/sheet × 13 applications/person; total skin substitute costs: £135/person) SC alone: £2,897 Mean difference Collagen-containing dressing + SC vs. SC alone: -£642	Reference case Collagen-containing dressing + SC vs. SC alone: Dominant (-£91,714/QALY) PSA Probability of collagen-containing dressing + SC being cost-effective: 99% at a WTP of £20,000/QALY
Redekop et al, 2003, Netherlands ⁸⁸	Cost-effectiveness analysis Markov model Societal perspective Discount rate NA 12 mo €, 1999	Neuropathic DFUs with duration of ≥ 2 wk (mean duration at baseline: 11.5 mo)	Intervention: Apligraf + SC Comparator: SC alone (type of dressing NR)	Mean per person Apligraf + SC: 7.78 ulcer-free mo SC alone: 6.25 ulcer-free mo Mean difference Apligraf + SC vs. SC alone: 1.53 ulcer-free mo	Mean per person Apligraf + SC: €4,656 (unit cost: €817/sheet × 2 applications/person; total skin substitute cost: 1,634/person) SC alone: €5,310 Mean difference Apligraf + SC vs. SC alone: -€654	Reference case Apligraf + SC vs. SC alone: Dominant (-€427.45/ulcer-free mo) ^b PSA Not conducted

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
Steinberg et al, 2002, United States ⁸⁹	Cost-effectiveness analysis Randomized controlled trial Private or public payer perspective Discount rate NA 6 mo USD, 2000	Neuropathic DFUs with duration of ≥ 2 wk (mean duration at baseline: 11.3 mo) Total N: 112 (Apligraf); 96 (control) Mean age: 56.8 y % Male: NR	Intervention: Apligraf + SC Comparator: SC alone (saline gauze)	Mean per person Apligraf + SC: 2.3 ulcer-free mo SC alone: 1.5 ulcer-free mo Mean difference Apligraf + SC vs. SC alone: 0.8 ulcer-free mo	Mean per person Apligraf + SC: \$7,366 (unit cost: \$1,435/sheet $\times$ 3.9 applications/person; total skin substitute cost: \$5,598/person) SC alone: \$2,020 Mean difference Apligraf + SC vs. SC alone: \$5346	Reference case Apligraf + SC vs. SC alone: \$6,683/ulcer-free mo PSA Not conducted

Abbreviations: DFU, diabetic foot ulcer; FF, French franc; NA, not applicable; NHS, National Health Service; NR, not reported; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SC, standard care; WTP, willingness-to-pay; y, year(s).

^aUncertainty was classified into one of five categories based on the Ontario Decision Framework: highly likely to be cost-effective (80–100% probability of being cost-effective), moderately likely to be cost-effective (60–79% probability), uncertain if cost-effective (40–59% probability), moderately likely not to be cost-effective (20–39% probability), or highly likely not to be cost-effective (0–19% probability).¹³⁸

^bCalculated.

^cDominant = less costly and more effective.

Table A4: Results of Economic Literature Review for Venous Leg Ulcers—Summary

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention(s) and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
AETMIS, 2001, Canada ⁹⁶	Cost-effectiveness analysis Decision tree Societal and health care payer perspectives Discount rate NA 12 mo USD, cost year NR	VLUs	Interventions: Apligraf + SC simultaneously for all VLUs; SC alone, followed by Apligraf + SC for ulcers resistant to first round of treatment with SC alone (i.e., difficult-to-heal VLUs) Comparator: SC alone	Mean per 8,000 persons <i>Societal and health care payer perspectives</i> Apligraf + SC simultaneously: 498,003 ulcer-days Apligraf + SC for difficult-to-heal VLUs: 1,236,589 ulcer-days SC alone: 1,428,411 ulcer-days Mean difference <i>Societal and health care payer perspective</i> Apligraf + SC simultaneously vs. SC alone: 930,437 ulcer-days averted Apligraf + SC for difficult-to-heal VLUs vs. SC alone: 191,851 ulcer-days averted	Mean per 8,000 persons <i>Societal perspective</i> Apligraf + SC simultaneously: \$37,008,280 Apligraf + SC for difficult-to- heal VLUs: \$16,637,937 SC alone: \$12,496,939 <i>Health care payer perspective</i> Apligraf + SC simultaneously: \$36,188,157 Apligraf + SC for difficult-to- heal VLUs: \$15,955,830 SC alone: \$11,630,664 (unit cost: \$950/sheet × 3.34 applications/ person; total skin substitute cost: \$3,173/person) Mean difference <i>Societal perspective</i> Apligraf + SC simultaneously vs. SC alone: \$24,511,341 Apligraf + SC for difficult-to- heal VLUs vs. SC alone: \$4,140,998 <i>Health care payer perspective</i> Apligraf + SC simultaneously vs. SC alone: \$24,577,493 Apligraf + SC for difficult-to- heal VLUs vs. SC alone: \$4,325,166	Reference case <i>Societal perspective</i> Apligraf + SoC simultaneously vs SoC alone: \$26.34/ulcer-day averted Apligraf + SoC for difficult-to-heal ulcers vs SoC alone: \$21.58/ulcer-day averted <i>Health care payer perspective</i> Apligraf + SC simultaneously vs. SC alone: \$26.39/ulcer-day averted Apligraf + SC for difficult-to-heal ulcers vs. SC alone: \$22.54/ulcer-day averted PSA Not conducted

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention(s) and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
Carter et al, 2014, United States ⁹³	Cost-effectiveness analysis Markov model Payer perspective Discount rate NA 12 mo USD	VLUs (mean duration at baseline: 7.2 wk for ECM group and 6.9 wk for SC group)	Interventions: Oasis + SC; Apligraf + SC; Dermagraft + SC Comparator: SC alone	Mean per person Oasis + SC: 31 ulcer-free wk Apligraf + SC: 29 ulcer-free wk Dermagraft + SC: 27 ulcer-free wk SC alone: 24 ulcer-free wk Mean difference Oasis vs. SC alone: 7 ulcer-free wk Apligraf vs. SC alone: 5 ulcer-free wk Dermagraft vs. SC alone: 3 ulcer-free wk	Mean per person Oasis + SC: \$6,732 Apligraf + SC: \$10,638 Dermagraft + SC: \$11,237 SC alone: \$6,133 Mean difference Oasis + SC vs. SC alone: \$599 Apligraf + SC vs. SC alone: \$4,505 Dermagraft + SC vs. SC alone: \$5,104	Reference case Oasis + SC vs. SC alone: \$86/ulcer-free wk Apligraf + SC vs. SC alone: \$901/ulcer-free wk Dermagraft + SC vs. SC alone: \$1,701/ulcer-free wk PSA Oasis consistently had the highest average effectiveness and lowest cost
Guest et al, 2018, United Kingdom ⁹¹	Cost-utility analysis Decision tree Public payer perspective (NHS) Discount rate NA 6 mo £, 2015/16	VLUs	Intervention: Collagen- containing dressing + SC Comparator: SC alone (type of dressings NR)	Mean per person Collagen-containing dressing + SC: 0.373 QALYs SC alone: 0.331 QALYs Mean difference Collagen-containing dressing + SC vs. SC alone: 0.042 QALYs	Mean per person Collagen-containing dressing + SC: £3,789 (unit cost: £10.41 × 3 applications/person; total skin substitute costs: £32.00/person) SC alone: £6,328 Mean difference Collagen-containing dressing + SC vs. SC alone: -£2,539	Reference case Collagen-containing dressing + SC vs. SC alone: dominant ^b (-£60,452.38/QALY) PSA Probability of collagen-containing dressing being cost- effective: 99% at a WTP of \$20,000/QALY

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention(s) and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
Harding et al, 2000, United Kingdom ¹⁰⁰	Cost-effectiveness analysis Meta-analysis Perspective NR Discount rate NA 12 wk £, 1999	VLUs	Interventions: Apligraf; hydrocolloid dressing (Granuflex) Comparator: SC alone (saline gauze)	Mean per person Apligraf: 45% healed at 12 wk Granuflex: 52% healed at 12 wk SC: 40% healed at 12 wk Mean difference NR	Mean per person Apligraf: ~£7,000 Granuflex: ~£1,000 SC: ~£1,500 Mean difference NR	Reference case Hydrocolloid vs. SC: £541/healed wound Granuflex vs. Apligraf: £6741/healed wound PSA Not conducted
Kerstein et al, 2001, United States ⁹⁸	Cost-effectiveness analysis Decision tree Perspective NR Discount rate NR 6 wk, 12 wk USD, 2000	VLUs (Pressure ulcers not summarized in this table)	Interventions: Apligraf + SC; hydrocolloid dressing (Duoderm) + SC Comparator: SC alone (saline gauze)	Mean per person Apligraf + SC: 22% of ulcers healed at 6 wk; 45% of ulcers healed at 12 wk Duoderm + SC: 27% of ulcers healed at 6 wk; 51% of ulcers healed at 12 wk SC alone: 19% of ulcers healed at 6 wk; 39% of ulcers healed at 12 wk Mean difference NR	Mean per person Apligraf + SC: \$15,053/ patient healed Duoderm + SC: \$1,873/ patient healed SC alone: \$2,939/patient healed (Unit cost: \$1,226/sheet × 5 applications/person; total skin substitute cost: \$6,130.02/person) Mean difference NR	Reference case Costs to heal VLUs were highest with Apligraf and lowest for 12 wk hydrocolloid management PSA Not conducted

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention(s) and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
Meaume and Gemmen, 2002, France ⁹⁵	Cost-effectiveness analysis Meta-analysis Health care payer perspective (French health insurance plan) Discount rate NA 12 wk €, 2000	VLUs (Pressure ulcers not summarized in this table)	Interventions: Hydrocolloid dressing (DuoDERM) + SC (saline gauze); Apligraf + SC Comparator: SC alone	Mean per person <i>Europe results</i> <i>(French results were</i> <i>similar)</i> Duoderm + SC: 51% healed in 12 wk Apligraf + SC: 45% healed in 12 wk SC alone: 35% healed in 12 weeks Mean difference NR	Mean per person <i>Europe results (French results</i> <i>were similar)</i> Duoderm + SC: €1,436/ulcer healed Apligraf + SC: €11,396/ulcer healed SC alone: €2,763/ulcer healed Mean difference NR	Reference case <i>Europe results</i> <i>(French results were</i> <i>similar)</i> Duoderm + SC vs. Apligraf + SC: cost- effective Hydrocolloid + SC vs. SC alone: cost- effective Apligraf + SC vs SC alone: cost-effective PSA Not conducted
Romanelli et al, 2016, United States ⁹²	Cost-effectiveness analysis Markov model Payer perspective Discount rate NA 32 wk USD, 2015	Difficult-to-heal VLUs with duration > 6 mo (Results reported separately for mixed arterial/venous leg ulcers)	Intervention: Oasis + SC Comparator: SC alone	Mean per person Oasis + SC: 26 ulcer-free wk SC alone: 22 ulcer-free wk Mean difference Oasis + SC vs. SC alone: 4 ulcer-free wk	Mean per person Oasis + SC: \$2,527 (unit cost: \$430.12/sheet; number of applications NR) SC alone: \$2,540 Mean difference Oasis + SC vs. SC alone: –\$13	Reference case Oasis + SC vs. SC alone: dominant (–\$3.75/ulcer-free wk) PSA Probability of Oasis + SC being cost- effective: 95% at a WTP of \$2,000/ulcer-free wk

Author, Year, Country	Analytic Technique, Study Design, Perspective, Discount Rate, Time Horizon, Currency, Cost Year	Population	Intervention(s) and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness ^a
Schonfeld et al, 2000, United States ⁹⁹	Cost-effectiveness analysis Semi-Markov Private health care payer perspective Discount rate NA 12 mo Currency and cost year NR	Difficult-to-heal VLU with duration of ≥ 12 mo	Intervention: Apligraf + SC (without Unna Boot ^d) Comparator: SC alone (with Unna Boot)	Mean per person Apligraf: 48.1% healed at 12 mo SC: 25.2% healed at 12 mo Mean difference Apligraf + SC vs. SC alone: 22.9%	Mean per person Apligraf + SC: \$20,041 SC alone: \$27,493 (Unit cost: \$975/sheet × 3.34 applications/person, with each application also requiring additional professional fee of \$450/application; total skin substitute cost: \$4,759.50) Mean difference Apligraf + SC vs. SC alone: −\$7,452	Reference case Apligraf + SC vs. SC alone: Dominant PSA Not conducted
Sibbald et al, 2001, Canada ⁹⁷	Cost-effectiveness analysis Decision tree Societal and health care payer perspectives Discount rate NA 3 mo, 6 mo CAD, 1996/97	Difficult-to-heal VLU with a duration of ≥ 4 wk	Intervention: Apligraf + SC Comparator: SC alone	Mean per person, 3-mo model Apligraf: 45 mean ulcer-days/patient SC: 67 mean ulcer-days/patient Mean difference, 3-mo model Apligraf vs SC: −22 mean ulcer-days/patient (Results of 6-mo model not summarized in this table)	Mean per person, 3-mo model Apligraf + SC: \$1,758 (societal); \$1,701 (health care payer) SC: \$1,454 (societal); \$1,386 (health care payer) (Unit cost: \$950/sheet × 1 application/person) Mean difference, 3-mo model Apligraf + SC vs. SC alone: \$304 (societal); \$316 (health care payer) (Results of 6-mo model not summarized in this table)	Reference case, 3-mo model Apligraf + SC vs. SC alone: \$14/ulcer day averted (Results of 6-mo model not summarized in this table) PSA Not conducted

Abbreviations: NA, not applicable; NHS, National Health Service; NR, not reported; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SC; standard care; VLU, venous leg ulcer; WTP, willingness-to-pay.

^aUncertainty was classified into one of five categories based on the Ontario Decision Framework: highly likely to be cost-effective (80–100% probability of being cost-effective), moderately likely to be cost-effective (60–79% probability), uncertain if cost-effective (40–59% probability), moderately likely to not be cost-effective (20–39% probability), or highly likely to not be cost-effective (0–19% probability).¹³⁸

^bDominant = less costly and more effective.

Appendix 7: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A5: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Skin Substitutes

Author, Year, Country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment ^a
AETMIS, 2001, Canada ⁹⁶	Yes	Yes	Yes	Yes; health care and societal perspectives	Yes	No	No	Yes	Partially applicable
Allen et al, 2000, France ⁹⁰	Yes	Yes	Partially; non-Canadian health care system	Yes; societal perspective	Yes	No	No	No; societal costs not reported despite reporting societal perspective	Partially applicable
Carter et al, 2014, United States ⁹³	Yes	Yes	Partially; non-Canadian health care system	Yes; payer perspective	Yes	No	No	Yes	Partially applicable
Guest et al, 2017, United States ⁸⁷	Yes	Yes	Partially; non-Canadian health care system	Yes; public payer perspective (Medicare)	Yes	No	No	Yes	Partially applicable
Guest, et al, 2018, United Kingdom ⁸⁶	Yes	Partially; focused on collagen dressing terms	Partially; non-Canadian health care system	Yes; public payer perspective (NHS)	Yes	No	Yes	No	Partially applicable
Guest et al, 2018, United Kingdom ⁹¹	Yes	Partially; focused on collagen dressing terms	Partially; non-Canadian health care system	Yes; public payer perspective (NHS)	Yes	No	Yes	No	Partially applicable
Harding et al, 2000, United Kingdom ¹⁰⁰	Yes	No; SC was saline-moistened gauze	No; non-Canadian health care system	Unclear; not reported	No	No	No	No	Partially applicable
Kerstein et al, 2001, United States ⁹⁸	Yes	Yes	No	No	Yes	No	No	No	Partially applicable
Meaume and Gemmen, 2002, France ⁹⁵	Yes	Yes	Partially; non-Canadian health care system	Yes; payer perspective	Yes	No	No	No	Partially applicable

Author, Year, Country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment ^a
Redekop et al, 2003, Netherlands ⁸⁸	Yes	Yes	Partially; non-Canadian health care system	Yes; societal perspective	Yes	No	No	No; societal costs not reported despite reporting societal perspective	Partially applicable
Romanelli et al, 2016, United States ⁹²	Yes	Yes	Partially; non-Canadian health care system	Yes; payer perspective	Yes	No	No	Yes	Partially applicable
Schonfeld et al, 2000, United States ⁹⁹	Yes	Yes	No; US private health care system	Yes; US private payer perspective	Yes	No	No	No	Partially applicable
Sibbald et al, 2001, Canada ⁹⁷	Yes	Yes	Yes	Yes; health care and societal perspectives	Yes	No	No	Yes	Partially applicable
Steinberg et al, 2002, United States ⁸⁹	Yes	Yes	Partially; non-Canadian health care system	No	Yes	No	No	Yes	Partially applicable

Abbreviations: NHS, National Health Service; SC, standard care.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

^aOverall judgment may be “directly applicable,” “partially applicable,” or “not applicable.”

Table A6: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Skin Substitutes

Author, Year, Country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment ^b
AETMIS, 2001, Canada ⁹⁶	Yes	Yes	No; QALYs not included	Yes	Yes	Yes	Yes	Yes	Yes	No; PSA not conducted	No	Minor limitations
Allenet et al, 2000, France ⁹⁰	Yes	Yes	No; QALYs not included	Yes	Partially; original study treatment effects extrapolated from 32 wk to 52 wk	Yes	Yes	Yes	Yes	No; PSA not conducted	Unclear; disclosure not provided	Minor limitations
Carter et al, 2014, United States ⁹³	Yes	Yes	No; QALYs not included	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes; study was funded by Healthpoint Biotherapeutics, and authors were affiliated with Smith and Nephew Inc.	Minor limitations
Guest et al, 2017, United States ⁸⁶	Yes	Yes	No; QALYs not included	Yes	Partially; treatment effect was extrapolate from 12 wk to 12 mo	Yes	Yes	Unclear; source of cost of skin substitute not reported	Yes	No; cost of skin substitute not used in SA	Unclear; authors did not declare COI, but authors had affiliation with Smith and Nephew Inc.	Potentially serious limitations

Author, Year, Country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment ^b
Guest et al, 2018, United Kingdom ⁸⁶	No; amputation and death not included	Yes	Yes	No; clinical inputs obtained from systematic search focused on "collagen-containing dressing"	Yes	No; amputation not costed	Yes	No; cost of collagen dressing was £10.41, very low, source unclear	Yes	No; cost of skin substitute not used in SA	Unclear; authors did not declare COI, but study was sponsored and funded by Acelyty and KCI USA Inc.	Potentially serious limitations
Guest et al, 2018, United Kingdom ⁸⁷	No; death not included	Yes	Yes	No; clinical inputs obtained from systematic search focused on "collagen-containing dressing"	Yes	Yes	Yes	No; cost of collagen dressing was £10.41, very low, source unclear	Yes	Yes	Unclear; authors did not declare COI, but study was funded by Acelyty	Potentially serious limitations
Harding et al, 2000, United Kingdom ¹⁰⁰	Unclear	No	No	No	No	No	No	No	No	No	Yes; study was conducted by ConvaTec	Potentially serious limitations
Kerstein et al, 2001, United States ⁹⁸	Unclear	Yes	No; QALYs not included	Yes	Yes	Yes	Yes	Yes	No	No; PSA not conducted	Yes; study was supported by grant from ConvaTec	Potentially serious limitations
Meaume and Gemmen, 2002, France ⁹⁵	Yes	Yes	No; QALYs not included	Unclear	Yes	No	No	No	Partially	No	Yes; study was sponsored by a grant from ConvaTec	Potentially serious limitations

Author, Year, Country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment ^b
Redekop et al, 2003, Netherlands ⁸⁸	Yes	Yes	No; QALYs not included	Yes	No; number of skin substitute applications used in clinical trial different from that used in economic model	Yes	Yes	No	Yes	No; PSA not conducted	Yes; study was funded by and authors had affiliation with Novartis Pharma AG	Potentially serious limitations
Romanelli et al, 2016, United States ⁹²	Partially; amputation and death not reflected	Yes	No; QALYs not included	Yes	Yes	Yes	Yes	Yes	Yes	No; PSA not conducted	Unclear; study did not declare COI, but authors were affiliated with Smith and Nephew Inc.	Minor limitations
Schonfeld et al, 2000, United States ⁹⁹	Yes	Yes	No; QALYs not included	Yes	Yes	Yes	Yes	Yes	Yes	No; PSA not conducted	Yes; study was funded by Novartis	Minor limitations
Sibbald et al, 2001, Canada ⁹⁷	Yes	Yes	No; QALYs not included	Unclear; based on one study, not selected through a systematic review	Yes	Yes	Yes	Yes	Yes	No; PSA not conducted	Unclear; study did not declare COI, but authors were affiliated with Innovus Research Inc.	Minor limitations

Author, Year, Country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs ^a obtained from the best available sources?	Do the clinical inputs ^a match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropria te incremen tal analysis presente d, or can it be calculate d from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment ^b
Steinberg, 2002, United States ⁸⁹	NA	Yes	No; QALYs not included	Yes	Yes	Yes	Yes	Yes	Yes	No; PSA not conducted	Yes; study was funded by and authors were affiliated with Novartis Pharmaceutical Corp	Minor limitations

Abbreviations: COI, conflict of interest; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SA, sensitivity analysis.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

^aClinical inputs include relative treatment effects, natural history, and utilities.

^bOverall judgment may be “minor limitations,” “potentially serious limitations,” or “very serious limitations.”

Appendix 8: Minor and Major Lower-Extremity Amputation Data Inputs

Table A7: Minor and Major Lower-Extremity Amputations as Defined in This Report

CCI Code	Description
Minor Lower-Extremity Amputation (Partial Foot or Toe)	
1.WA.93.^	Amputation, ankle joint
1.WE.93.^	Amputation, tarsal bones and intertarsal joints (hindfoot, midfoot)
1.WI.93.^	Amputation, first metatarsal bone and first metatarsophalangeal joint
1.WJ.93.^	Amputation, tarsometatarsal joints, other metatarsal bones and other metatarsophalangeal joints (forefoot)
1.WK.93.^	Amputation, first phalanx of foot
1.WM.93.^	Amputation, other interphalangeal joints of toe
1.WN.93.^	Amputation, first interphalangeal joint of toe
Major Lower-Extremity Amputation (Above the Ankle)	
1.VC.93.^	Amputation, femur
1.VG.93.^	Amputation, knee joint
1.VQ.93.^	Amputation, tibia and fibula

Abbreviation: CCI, Canadian Classification of Health Interventions.

Source: *Canadian Classification of Health Interventions, Version 2015*.¹⁶³

Table A8: Physician Fees for Minor and Major Lower-Extremity Amputations, by Amputation Type

Procedure	Schedule of Benefits Code ^a	Surgeon Fee	Assistant Surgeon ^b				Anaesthesiologist ^c			Total Amount	
			Unit Fee	Basic Units	Time Units	Total	Unit Fee	Basic Units	Time Units		Total
Major Lower-Extremity Amputation											
Femur (through femur) ^d	R626	\$306.30	\$12.25	6	8	\$171.50	\$15.29	7	8	\$229.35	\$707.17
Knee (Gritti-Stokes or callander) ^d	R625	\$305.25		6	8	\$171.50		7	8	\$229.35	\$706.10
Tibia fibula ^d	R624	\$306.30		6	8	\$171.50		7	8	\$229.35	\$707.17
Average cost of major lower-extremity amputation											\$706.80
Minor Lower-Extremity Amputation											
Metatarsal/phalanx disarticulation ^d	R620	\$155.90	\$12.25	6	8	\$171.50	\$15.29	6	8	\$214.06	\$580.10
Ray (single) ^d	R621	\$217.15		6	8	\$171.50		6	8	\$214.06	\$602.71
Ankle joint (symes) ^d	R623	\$285.80		6	8	\$171.50		7	8	\$229.35	\$686.65
Transmetatarsal/transtarsal ^d	R622	\$235.75		6	8	\$171.50		7	8	\$229.35	\$636.60
Toe (terminal symes) ^e	R619	\$144.80		6	4	\$122.50		6	4	\$152.90	\$420.20
Average cost of minor lower-extremity amputation											\$577.52

^aOntario Schedule of Benefits: Physician Services Under the Health Insurance Act (effective April 1, 2020)¹³¹

^bThe surgical assistant service is calculated by adding the number of basic and time units and multiplying that total by the unit fee. The assistant unit fee is \$12.25. The number of basic units is listed opposite the service that describes the procedure. Time units are calculated for each 15 minutes. The unit value of each 15-minute period during the first hour or less is 1 unit; after the first hour is 2 units; and after 2.5 hours is 3 units.¹³¹

^cThe anaesthesiologist service is calculated by adding the number of basic and time units and multiplying that total by the unit fee. The anaesthesiologist unit fee is \$15.29. The number of basic units is listed opposite the service that describes the procedure. Time units are calculated for each 15 minutes. The unit value of each 15-minute period during first hour or less is 1 unit; after the first hour up to and including the first 1.5 hours is 2 units; and after 1.5 hours is 3 units.¹³¹

^dThe duration of the procedure is estimated to be 90 minutes.¹³²

^eThe duration of the procedure is estimated to be 60 minutes.¹³²

Table A9: Physicians Fees for Initial Consultation and Follow-Up Visit Following Minor and Major Lower-Extremity Amputations

Procedure	Schedule of Benefits Code ^a	Surgeon Fee
Initial consult	A035	\$90.30
Subsequent visit	C032	\$31.00

^aOntario Schedule of Benefits: Physician Services Under the Health Insurance Act (effective April 1, 2020).¹³¹

Table A10: Ontario Case Costing 2017/18 Hospitalization Costs Associated With Major Lower-Extremity Amputations

	Direct and Indirect Costs					Length of Stay, Days			
	Cases	Average	SD	Min	Max	Average	SD	Min	Max
1VQ93LA (amputation, tibia and fibula)	570	\$34,674	\$69,179	\$2,109	\$957,805	25.5	49	1	701
1VG93LA (amputation, knee joint)									
1VC93LA (amputation, femur)									

Abbreviations: SD, standard deviation.

^aDirect costs are costs that are directly related to the provision of care to the patient and include nursing (including operating Room and intensive care unit), diagnostic imaging, pharmacy, and labs. Indirect costs are overhead expenses relating to the running of hospitals and include administration, finance, human resources, plant operations, etc.

Source: Ontario Case Costing.¹³³

Appendix 9: Parameters Varied in the Economic Models

Table A11: Model Parameters Varied in the Probabilistic Analysis—Diabetic Foot Ulcers

Parameter	Mean Value	Duration	Distribution	Source
Clinical Parameters				
Treatment effect (risk difference)	33%	12 weeks	Beta (29.45–59.56)	15% of deterministic value
Unhealed DFU → Minor LEA	5.4%	1 year	Beta (24–425)	Jeffcoate et al, 2006 ¹²³
Unhealed DFU → Major LEA	5.3%	1 year	Beta (24–425)	Jeffcoate et al, 2006 ¹²³
Unhealed DFU → Dead	16%	2 years	Beta (276.96–1,454.04)	Vadiveloo et al, 2018 ¹²⁴
Healed DFU → Dead			Same as above	
Minor LEA → Dead	3%	4 weeks	Beta (119–3,663)	Gurney et al, 2018 ¹²⁵
Major LEA → Dead	11.1%	4 weeks	Beta (289–2,281)	Gurney et al, 2018 ¹²⁵
Post-minor LEA → Dead	41.4%	5 years	Beta (12–17)	Jones et al, 2008 ¹²⁶
Post-major LEA → Dead	63.6%	5 years	Beta (18–12)	Jones et al, 2008 ¹²⁶
Utility Values				
Healed ulcer	0.6	NA	Beta (17.18–10.85)	15% of deterministic value
Unhealed ulcer	0.44	NA	Beta (24.45–30.68)	15% of deterministic value
Minor/post-minor amputation	0.61	NA	Beta (16.72–10.08)	15% of deterministic value
Major/post-major amputation	0.31	NA	Beta (30.36–67.26)	15% of deterministic value
Cost Parameters				
Major LEA hospitalization	\$35,500		Gamma (150.10–236.51)	OCC ¹³³
Post-minor LEA	\$144.44/week		Gamma (23,804–0.25)	25% of deterministic value
Post-major LEA	\$114.46/week		Gamma (23,808–0.25)	25% of deterministic value

Abbreviations: DFU, diabetic foot ulcer; LEA, lower-extremity amputation; OCC, Ontario Case Costing.

Table A12: Model Parameters Varied in the Probabilistic Analysis—Venous Leg Ulcers

Parameter	Value	Duration	Distribution	Reference
Clinical Parameters				
Unhealed VLU → Healed VLU (skin substitute)	59%	16 weeks	Beta (32–32)	Bianchi et al, 2019 ⁶⁴
Unhealed VLU → Healed VLU (SC)	39%	16 weeks	Beta (20–44)	Bianchi et al, 2019 ⁶⁴
Unhealed VLU → Dead	37%	5 years	Beta (76.22–129.78)	Nelzen et al, 1999 ¹³⁵
Healed VLU → Dead			Same as above	
Utility Values				
Healed ulcer	0.73	NA	Beta (613.427–226.154)	Clegg et al, 2007 ¹³⁶
Unhealed ulcer	0.64	NA	Beta (353.402–198.149)	Clegg et al, 2007 ¹³⁶

Abbreviations: SC, standard care; VLU, venous leg ulcer.

Appendix 10: Letter of Information

LETTER OF INFORMATION



Ontario Health is conducting a review of **Skin Substitutes** for people with diabetic foot ulcers and venous leg ulcers. The purpose is to understand whether this device should be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers with experience with diabetic foot ulcers or venous leg ulcers that may or may not have used a skin substitute either currently or in the past, and people who could be considering it in the future.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30 minutes of your time for a phone
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 30 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US BEFORE SEPTEMBER 30, 2020:

Appendix 11: Interview Guide

HTA Interview Guide: Skin Substitutes

Intro

1. Explain HQO purpose, HTA process, and purpose of interview
2. I would like your permission to have an audio recording of this conversation so I can use your direct quotes and other information from this conversation to make a case for the decision makers. Your name or any other identifiers will not be placed in the report or the presentation and your privacy and your confidentiality will be protected. So do I have your permission to audio record this conversation?
3. DFU or VLU?
4. History of DFU/VLU - diagnosis and background
 - a. When were you diagnosed
 - b. Symptoms

Lived- Experience

5. Day-to-day routine
6. What is the impact of DFU/VLU and its progression on quality of life? (Loss of independence?, activities, work)
7. Impact on loved-ones/caregivers, work, etc?

Therapies

8. What current therapies/treatments are used and their impact?
9. Cost of therapies (example, standard of care, other skin substitutes)- covered by insurance vs out of pocket
10. Is accessibility to therapies/treatments an issue (are you able to take advantage of all potential therapies?)
11. Expectations of current therapies?

Note: HQO (Health Quality Ontario) is now part of Ontario Health.

Skin substitute

12. Information surrounding skin substitutes for DFU/VLU
13. Would you be open to trying skin substitutes for DFU/VLU?
14. Would this be accessible to you? (cost)
15. Ethical concerns
16. Decision-making
17. Application process
18. Management of skin substitute
19. Result, impact, change in quality of life (if applicable)
20. Side effects?

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ISSN 1915-7398 (online)
ISBN 978-1-4868-5317-5 (PDF)

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