

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Sucrose Octasulfate–Impregnated Dressings for Adults With Difficult-to-Heal Noninfected Diabetic Foot Ulcers and Difficult-to-Heal Noninfected Venous Leg Ulcers

A Health Technology Assessment

MONTH 20XX

Key Messages

What Is This Health Technology Assessment About?

Diabetic foot ulcers and venous leg ulcers are wounds in the foot and leg, respectively. Diabetic foot ulcers are a common complication for people who have diabetes mellitus that is difficult to manage and can lead to amputation in the lower limb. Venous leg ulcers usually occur when there is underlying venous reflux or obstruction and the veins do not circulate blood properly. This can eventually lead to blood plasma leaking into the skin tissue, causing inflammation, edema, dermatitis, and ulceration.

As part of standard comprehensive wound care, diabetic foot ulcers and venous leg ulcers are often treated with dressings, which are products with specific properties that promote wound healing. However, there may be times when ulcers do not heal in a timely manner despite standard wound care. This can cause pain and hamper a patient's quality of life. In addition, the use of health care services and costs of treatment for these ulcers are important and challenging issues for the health care system. Therefore, there is a need to improve the healing process of these ulcers by appropriately managing the wound and using dressings that are more effective at healing ulcers.

This health technology assessment looked at how safe, effective, and cost-effective sucrose octasulfate-impregnated dressings are for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers. It also looked at the budget impact of publicly funding sucrose octasulfate-impregnated dressings and at the experiences, preferences, and values of people with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers.

What Did This Health Technology Assessment Find?

Sucrose octasulfate-impregnated dressings are safe and improve the healing of difficult-to-heal noninfected neuroischemic diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers compared with dressings that do not contain sucrose octasulfate.

Compared with dressings that are free of sucrose octasulfate, sucrose octasulfate-impregnated dressings may be a cost-effective option for difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers. We estimate that publicly funding sucrose octasulfate-impregnated dressings in Ontario for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers would lead to total cost savings of \$3.91 million and \$3.38 million, respectively, over the next 5 years.

Diabetic foot ulcers and venous leg ulcers negatively impacted patients' daily lives, including mobility, employment, social activities, and mental health. Patients experienced various forms of treatment to heal their ulcers, but it is not clear that the patient perspective evidence directly included experience with sucrose octasulfate-impregnated dressings, as most patients were not familiar with the medical terminology for different types of wound dressings.

Acknowledgements

This report was developed by a multidisciplinary team from Ontario Health. The primary clinical epidemiologist was Shayan Sehatzadeh, the secondary clinical epidemiologist was Milica Jokic, the primary medical librarian was Corinne Holubowich, the secondary medical librarian was Caroline Higgins, the primary health economist was Jennifer Guo, the secondary health economist was Xuanqian Xie, and the primary patient engagement analyst was Samrawit Lemma.

The medical editor was Kesiah Stoker. Others involved in the development and production of this report were Molly Li, Claude Soulodre, Susan Harrison, Sarah McDowell, Chunmei Li, Jigna Mistry, 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:

- David H. Keast, Parkwood Institute Research and Lawson Health Research Institute
- Lyndsay Orr, Ontario Health
- Valerie Winberg, Ontario Woundcare Interest Group
- Uργο Medical

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

TBD

Abstract

Background

Diabetic foot ulcers and venous leg ulcers may not always heal in a timely manner despite proper wound care. Treatments that improve the healing rate of these ulcers would improve clinical outcomes for patients and may result in downstream cost savings for the health care system. We conducted a health technology assessment of sucrose octasulfate-impregnated dressings for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding sucrose octasulfate-impregnated dressings, 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 trials (RoB 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 analyzed the budget impact of publicly funding sucrose octasulfate-impregnated dressings for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers in Ontario. We did not conduct a primary economic evaluation because there is existing evidence to approximate the cost-effectiveness of sucrose octasulfate-impregnated dressings in Ontario. We leveraged 4 previous health technology assessments to explore the perspectives and experiences of patients with diabetic foot ulcers and venous leg ulcers, as well as the perspectives and experiences of their care partners.

Results

We included 3 randomized controlled trials and 2 subsequent publications of these randomized controlled trials in the clinical evidence review. Compared with dressings that do not contain sucrose octasulfate, sucrose octasulfate-impregnated dressings result in faster wound closure in patients with difficult-to-heal noninfected neuroischemic diabetic foot ulcers (GRADE: Moderate) and reduce ulcer size and improve health-related quality of life in the domains of pain/discomfort and anxiety/depression for patients with difficult-to-heal noninfected venous leg ulcers (GRADE: Moderate). The use of sucrose octasulfate-impregnated dressings with noninfected wounds is considered safe (GRADE: Moderate).

The economic evidence showed that, compared with dressings that do not contain sucrose octasulfate, sucrose octasulfate-impregnated dressings are highly likely to be cost-effective for both difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers and would lead to cost savings due to faster and increased complete wound healing. The annual budget impact of publicly funding sucrose octasulfate-impregnated dressings in Ontario over the next 5 years would range from cost savings of \$0.93 million in year 1 to \$0.62 million in year 5 for adults with difficult-to-heal noninfected diabetic foot ulcers, and cost savings of \$0.8 million in year 1 to \$0.53 million in year 5 for adults with difficult-to-heal noninfected venous leg ulcers. Overall, we estimate that publicly funding sucrose octasulfate-impregnated dressings in Ontario for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers would lead to total cost savings of \$3.91 million and \$3.38 million, respectively, over the next 5 years.

Patients with diabetic foot ulcers and venous leg ulcers discussed the effects of living with these wounds, as well as their treatment journey. They spoke about the burden of their condition and its negative impact on their daily lives, including mobility, employment, social activities, and mental health. Patients also spoke about the variety of treatment options available and the financial barriers to accessing these treatments.

Conclusions

Sucrose octasulfate–impregnated dressings are safe and improve the healing of difficult-to-heal noninfected neuroischemic diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers compared with dressings that do not contain sucrose octasulfate. We estimate that publicly funding sucrose octasulfate–impregnated dressings in Ontario would result in cost savings for both difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers. Evidence from patient engagement suggests that people with diabetic foot ulcers or venous leg ulcers face negative impacts on their quality of life, especially related to mobility. Patients spoke about their challenges, including long and difficult care journeys, as well as trying different treatment options to heal their ulcers and avoid amputation. It is not clear if the participants had direct experience with sucrose octasulfate–impregnated dressings, so we could not draw specific conclusions about these dressings from the preferences and values evidence.

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Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of sucrose octasulfate-impregnated dressings for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers. It also evaluates the budget impact of publicly funding sucrose octasulfate-impregnated dressings and the experiences, preferences, and values of people with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers.

Background

Health Condition

Diabetic foot ulcers and venous leg ulcers are wounds in the foot and leg, respectively. They may be confined to the different layers of the skin, or they may reach muscle, tendon, and deeper tissues.¹ Ulcers normally have a predictable course of healing; however, there may be times when they do not heal in a timely manner despite proper and standard wound care.

Diabetic foot ulcers are a common complication for people who have diabetes mellitus that is difficult to manage. These wounds are usually located in the areas of the foot that encounter pressure and repetitive trauma. Diabetic foot ulcers may be painless because of reduced sensation in the feet due to nerve damage in the limb (peripheral neuropathy), which is caused by high blood glucose levels over the long term. People with diabetic foot ulcers may also have ischemia in their legs (lack of adequate blood flow due to peripheral arterial disease). Peripheral arterial disease occurs when 1 or more arteries that supply blood to the legs or feet are partially or fully blocked because of conditions such as atherosclerosis. It is suggested that in middle- and high-income countries, up to 50% of people with diabetic foot ulcers also have peripheral arterial disease.² Diabetic foot ulcers that are associated with uncorrected ischemia in the leg have shown higher rates of lower-limb amputation than those in which ischemia has been corrected.³ An adequate and thorough examination of the lower limb is necessary to evaluate the presence of peripheral arterial disease. Assessment for peripheral arterial disease should include a pulse assessment as well measurement of the ankle-brachial pressure index (ABPI) and/or the toe-brachial pressure index (TBPI). In patients with a diabetic foot ulcer who have ischemia in their legs (neuroischemic foot ulcer), treating the ulcer will not be sufficient to heal the wound, because the underlying ischemia must first be corrected. In addition to wounds dressings and addressing ischemia, pressure offloading, management of any infection and blood sugar management are critical to support wound healing.

Venous leg ulcers are wounds that appear typically below the knee and mainly above the ankle.⁴ They occur when the veins cannot circulate blood properly (venous reflux or obstruction) and there is a lack of calf muscle activation. Venous insufficiency may be present with or without peripheral arterial disease. Venous reflux or obstruction and lack of calf muscle activation can lead to poor venous return and venous hypertension. The sustained high pressure in the leg veins causes them to stretch and dilate. These changes lead to distention of the capillaries, which allows blood plasma to leak into the skin tissue, causing inflammation, edema, dermatitis, and finally, ulceration.

Clinical Need and Population of Interest

In a recent study conducted in Ontario, the prevalence of diabetic foot ulcers among adults with diabetes was 1.7%.⁵ Neuroischemic diabetic foot ulcers are the most common type of ulcer among people with diabetes.⁶

Population-based prevalence studies that used clinical validation reported a prevalence rate of open lower-limb ulcers ranging from 0.12% to 1.1% of the population.⁷ The estimated prevalence of active venous leg ulcers is 0.8 to 1 per 1,000 population.⁸ We did not identify any studies on the prevalence of active venous leg ulcers specific to the Ontario population.

When diabetic foot ulcers or venous leg ulcers do not close within a reasonable period, quality of life – including physical, mental, and social aspects – is usually hampered. A study conducted in Ontario found that for patients with leg ulcers, higher levels of pain, younger age, larger size and longer duration of ulcers, and limited mobility were associated with poorer health-related quality of life.⁹ Diabetic foot ulcers may lead to frequent infection, necrosis of tissues, and even amputation. Complications from diabetic foot ulcers alone led to more than 2,000 amputations across Canada from 2011 to 2012.¹⁰

The use of health care services and costs of treatment for these ulcers are important and challenging issues for the health care system. Therefore, the search continues for interventions that can help to heal these ulcers faster. Treatment strategies that focus on improving healing rate and reducing healing time would improve clinical outcomes for patients and may result in downstream cost savings for the health care system.

Current Treatment Options

Standard wound care for diabetic foot ulcers and venous leg ulcers includes wound debridement (removal of necrotic tissues), infection control, offloading (not bearing weight on the limb with the ulcer) and glycemic control for patients with diabetic foot ulcers, and compression bandages and wraps and calf muscle exercise for patients with venous leg ulcers. Wounds are often covered by necrotic tissues and/or biofilm (a structured community of microbial cells enclosed in polymeric matrix) and may be complicated by a concomitant infection.¹¹ Therefore, wounds usually need regular debridement to remove nonviable tissue and promote wound healing.

As part of standard wound care, diabetic foot ulcers and venous leg ulcers are often treated with dressings for moisture management. A variety of dressings have been used in clinical practice. Selection of the appropriate wound dressing to heal diabetic foot ulcers and venous leg ulcers requires an understanding of the type and characteristics of the ulcer such as the presence of local infection, amount of wound exudate, and depth of the wound. However, as the ulcer progresses toward closure, the ideal dressing type may also change, depending on several factors such as the environment of the wound bed and the depth of the wound.

In clinical practice, wounds are assessed after 4 weeks of treatment for evidence of progression toward healing. Normal healing is characterized as wound area reduction of 30% to 40% every 3 to 4 weeks.¹² All dressings require regular cleaning, but the frequency depends on many factors, such as the amount of exudate, type of secretion, presence of infection, and surrounding wound environment. Sometimes a secondary dressing is used as a therapeutic or protective layer to secure or enhance the therapeutic effect of the primary dressing.

Wounds normally heal in a sequenced and timely manner by undergoing 4 major phases: hemostasis, inflammation, proliferation, and remodelling. In wounds that do not heal in a timely manner, usually the inflammation phase is prolonged, which disrupts the balance between deposition and degradation of extracellular matrix components.¹¹ The prolonged inflammation phase ultimately results in an elevated level of proteases in the wound exudate. Proteases are enzymes involved in degrading proteins by breaking them down into peptides and amino acids. In the wound bed, different proteases act on different proteins, including extracellular matrix or connective tissue proteins such as collagen and elastin. Proteases are generally classified into 4 major groups based on their functionality. However, only 2 of these groups are considered important extracellularly: serine proteases and matrix metalloproteinases (MMPs).¹³

MMPs are necessary for normal healing and are released by inflammatory cells at the inflammation phase of wound healing to provide the initial debridement of damaged extracellular matrix proteins and tissues. In healable wounds, MMPs are balanced by tissue inhibitors of metalloproteinases. Loss of this balance results in an excess of MMPs. When MMPs are excessively elevated, they begin to degrade proteins such as growth factor and extracellular matrix proteins, and impair wound healing.¹⁴

Advanced therapies such as negative pressure wound therapy (NPWT), skin substitutes, and growth factor therapies including platelet-rich plasma, stem cells, and cell- and tissue-based products can be used in addition to standard wound care.¹⁵⁻¹⁷

Health Technology Under Review

Dressings are devices with specific properties that can be applied to a wound to create and maintain a suitable environment to promote wound healing. It has been proposed that dressings impregnated with sucrose octasulfate (an MMP modulator) neutralize the excessive amount of MMPs produced in the wound bed and shorten the time to wound closure.¹⁸

The potassium salt of sucrose octasulfate has been used in a range of dressings known as Technology Lipido-Colloid Nano-Oligosaccharide Factor (TLC-NOSF) dressings, which include UrgoStart Plus Pad, UrgoStart Plus Border, and UrgoStart Contact/Interface/Tul (Laboratoires Urgo Medical, France).^{19,20}

Regulatory Information

The following sucrose octasulfate–impregnated wound dressings are approved for use in Canada:

- UrgoStart Plus Pad (licence number 103053, class II) is a soft-adherent TLC-NOSF matrix combined with polyacrylate polyabsorbent fibres. The polyabsorbent fibres clean the wound from slough, exudate, and bacterial residue.²¹
- UrgoStart Plus Border (licence number 103052, class II) is a soft-adherent TLC-NOSF matrix combined with polyacrylate polyabsorbent fibres, a super-absorbent layer, and a vapour-permeable waterproof outer film silicon adhesive border.²²
- UrgoStart Contact layer (licence numbers 103051 and 109191, class II) is a nonadhesive, nonocclusive matrix with TLC-NOSF technology combined with a polyester mesh.²³ We did not find any information in the US Food and Drug Administration database about UrgoStart products containing sucrose octasulfate or TLC-NOSF as wound dressing.

Ontario and International Context

Ontario

Current treatment options for diabetic foot ulcers and venous leg ulcers in Ontario include the use of dressings available through regional formularies, which vary across different hospitals and Home and Community Care Support Services.

In Ontario, some hospitals have wound care programs. At the time of writing this report, there are 14 Home and Community Care Support Services that provide wound care to patients who have been referred by primary care providers, nurse practitioners, or specialists in ambulatory settings, or have been discharged from hospitals. Long-term care facilities also provide wound care for their residents.

At the time of writing this report, there is no provincial formulary for wound products, and each of the hospitals, Home and Community Care Support Services, and facilities that provide wound care have different wound care formularies with costs covered by the provincial budget.

In 2021, the Ontario Health Technology Assessment Committee (OHTAC) recommended publicly funding skin substitutes for adults with difficult-to-heal neuropathic diabetic foot ulcers.²⁴ Skin substitutes are made up of artificial or natural materials that provide temporary or permanent coverage for skin wounds. These products act as a protective coverage and barrier against infective microorganisms and help to reduce pain and promote wound healing.²⁵ Skin substitutes may be considered if the use of dressings, in addition to standard care, is not effective to heal the wound.

International

The International Working Group on the Diabetic Foot (IWGDF) supports the use of sucrose octasulfate-impregnated dressings as an adjunctive treatment, in addition to best standard of care, for noninfected, neuroischemic diabetic foot ulcers that are difficult to treat.²⁶

The National Institute for Health and Care Excellence (NICE) concludes in their medical technologies guidance (updated April 2023) that the evidence supports adopting sucrose octasulfate-impregnated dressings to treat diabetic foot ulcers and venous leg ulcers, after any modifiable factors such as infection have been treated, because these dressings are associated with increased wound healing compared with noninteractive dressings.¹⁹

The Australian guideline on wound healing interventions to enhance healing of foot ulcers recommends that for diabetic foot ulcers not healing after 4 to 6 weeks, sucrose octasulfate-impregnated dressings can be considered as an adjunctive treatment in noninfected, neuroischemic diabetic foot ulcers.²⁷

Equity Context

In Ontario, certain populations are at higher risk of developing type 2 diabetes, such as Indigenous people and people of African, Asian, and Hispanic ancestry.²⁸ At the time of developing this health technology assessment, there is limited access to sucrose octasulfate-impregnated dressings in Ontario as it is available in only a few wound care facilities. This may contribute to unequal access to sucrose octasulfate-impregnated dressings and inequity in outcomes for patients who may benefit from wound care with these dressings.

Expert Consultation

We engaged with experts in the specialty area of wound care 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 (CRD42023447482), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of sucrose octasulfate–impregnated dressings, compared with dressings that do not contain sucrose octasulfate, for the treatment of adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers?

Methods

Clinical Literature Search

We performed a clinical literature search on June 30, 2023, to retrieve studies published from January 1, 2019, until the search date. When we conducted the literature search, we consulted the National Institute for Health and Care Excellence’s (NICE) report that was published in 2019 and updated in 2023.¹⁹ As the NICE report identified studies up to 2019, we used their included studies that met our eligibility criteria and also searched the literature from 2019 to the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, 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. Methodological filters were used to limit retrieval to systematic reviews, meta-analyses, health technology assessments, and randomized controlled trials. 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 until October 16, 2023. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Because randomized controlled trials are of highest-quality evidence and studies with such a design were found during scoping, we included only randomized controlled trials for this review. During our scoping process, we identified work by NICE, published in 2019 and updated in 2023,¹⁹ that was relevant to our research question. We leveraged their report by using their included studies that met our eligibility criteria and identified studies that were published since January 1, 2019, through our literature search.

Inclusion Criteria

- English-language full-text publications
- Studies identified through the 2019 NICE report that met our eligibility criteria, as well as randomized controlled trials published since January 1, 2019, to the search date
- Randomized controlled trials, health technology assessments of randomized controlled trials, and systematic reviews of randomized controlled trials that reported outcomes of interest for this review

Exclusion Criteria

- Nonsystematic reviews, observational studies, single-arm studies, case reports, conference abstracts, letters, editorials, and commentaries
- Animal and in vitro studies

Participants

Inclusion Criteria

- Adults (≥18 years old) with type 1 or type 2 diabetes mellitus with a difficult-to-heal or chronic noninfected diabetic foot ulcer
- Adults (≥18 years old) with a difficult-to-heal or chronic noninfected venous leg ulcer

Exclusion Criteria

- People < 18 years old
- People with localized or spreading infection

Interventions

Inclusion Criteria

- Sucrose octasulfate–impregnated dressings, not in combination with other interactive dressings, used as an adjunct to standard care

Exclusion Criteria

- Dressings that do not contain sucrose octasulfate

Comparators

Inclusion Criteria

- Dressings that do not contain sucrose octasulfate

Exclusion Criteria

- Nondressing treatments

Outcome Measures

- Complete wound closure
- Time to complete wound closure
- Absolute wound area reduction
- Relative wound area reduction
- Amputation due to diabetic foot ulcer
- Health-related quality of life
- Adverse events

Literature Screening

Two reviewers screened all titles and abstracts using Covidence.³⁰ All disagreements were discussed and resolved. We then obtained the full texts of studies that appeared to be 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 of included studies for any additional relevant studies not identified through the search. We reported citation flow and reasons for exclusion of full-text articles according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.³¹

Data Extraction

A single reviewer extracted relevant data on study design and characteristics; risk-of-bias items; population, intervention, comparator, outcome, time, and setting (PICOTS); and results.

Equity Considerations

We used PROGRESS-Plus, a health equity framework recommended by the Campbell and Cochrane Equity Methods Group,³² to explore potential inequities for this health technology assessment. Factors that may lead to disadvantage or inequities in the framework include place of residence; race, ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes. We sought but did not identify any equity considerations relevant to the research question across different populations defined by the PROGRESS-Plus categories.³³ However, equity considerations may exist that were not identified as part of our analysis.

Statistical Analysis

We analyzed the results of studies on diabetic foot ulcers and venous leg ulcers separately. We did not conduct a meta-analysis, as there was only 1 study for diabetic foot ulcers and the 2 studies on venous leg ulcers used different comparisons. Therefore, we provided a narrative summary of the results.

Subgroup Analysis

We reported a subgroup analysis that was performed based on the duration of the ulcers.

Critical Appraisal of Evidence

A single reviewer assessed risk of bias using the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Appendix 2).³⁴

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 for each outcome.

Results

Clinical Literature Search

The database search of the clinical literature yielded 54 citations published between January 1, 2019, and June 30, 2023, including grey literature searches and after duplicates were removed. Database alerts (monitored until October 16, 2023) did not identify any new randomized controlled trials. In total, including studies identified through the 2019 NICE report, we identified 5 studies that met our inclusion criteria.³⁶⁻⁴⁰ See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the PRISMA flow diagram for the clinical literature search.

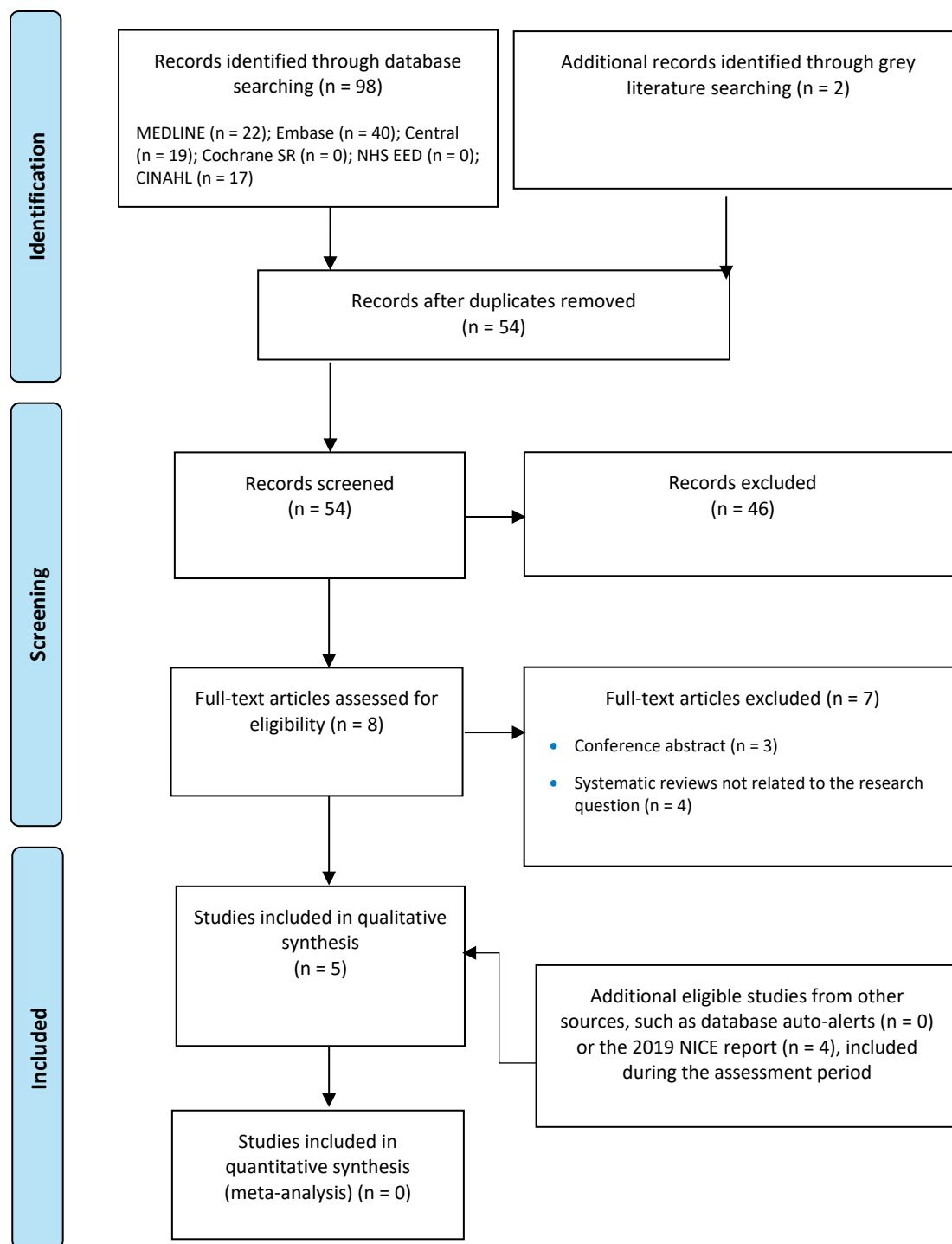


Figure 1: PRISMA Flow Diagram – Clinical Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 54 citations published between January 1, 2019, and June 30, 2023, including grey literature searches and after duplicates were removed. We screened the abstracts of the 54 identified studies and excluded 46. We assessed the full text of 8 articles and excluded a further 7. In the end, we included 5 articles in the qualitative synthesis.

Abbreviations: NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.³¹

Characteristics of Included Studies

We identified 3 randomized controlled trials that compared the effectiveness and safety of sucrose octasulfate-impregnated dressings with dressings that did not contain this agent.^{36,39,40} Another publication reported on the health-related quality of life of patients included in 1 of these randomized controlled trials.³⁸ We also identified 1 post hoc analysis that reported on the primary outcome for subgroups of patients included in 1 of these randomized controlled trials.³⁷ Table 1 shows study and participant characteristics, and Table 2 shows the characteristics of ulcers treated in these trials.

Table 1: Characteristics of Studies Included in the Clinical Literature Review

Author, year, country, intervention, comparator	Study design				Participants
	Study period	Sample size, n	Treatment duration, wk	Assessment time	Age, mean (SD), y
Edmonds et al, 2018, ³⁶ and Lázaro-Martinez et al, 2019, ³⁷ France, Spain, Italy, Germany, and UK	March 2013 to March 2016	—	20	2 weeks after randomization, then monthly	—
I: SOS		126			64.2 (11.2)
C: TLC		114			64.9 (10.7)
Meaume et al, 2012 ³⁹ and 2017, ³⁸ France	March 2009 to July 2010	—	8	Every 2 weeks	—
I: SOS		93			72.6 (13)
C: TLC		94			74.4 (12.1)
Schmutz et al, 2008, ⁴⁰ France and UK	October 2004 to June 2006	—	12	Every week for the first week and then every 2 weeks until week 12	—
I: SOS		57			71.5 (13.1)
C: ORC		60			71 (13.9)

Abbreviations: C, comparator; I, intervention; ORC, oxidized regenerated cellulose; SD, standard deviation; SOS, sucrose octasulfate; TLC, Technology Lipido-Colloid.

Table 2: Characteristics of Ulcers Treated in Randomized Controlled Trials Included in the Clinical Literature Review

Author, year, intervention, comparator	Ulcer type	Wound area at baseline		Wound duration at baseline	
		Area, mean (SD)/median (IQR), cm ²	Number of patients with given wound area, n	Duration, mean (SD)/median (IQR), mo	Number of patients with given wound duration, n
Edmonds et al, 2018 ³⁶ (EXPLORER trial)	Noninfected neuroischemic DFUs > 1 cm ² , grade IC (superficial) or IIC (penetrating to tendon or capsule)	—	—	—	—
I: SOS		5.3 (9.1)/2.9 (1.4–5.2)	>5 cm ² 25 (20%)	7.3 (6.5)/5 (2–11)	≥6 months 55 (44%)
C: TLC		4.2 (6.0)/2.1 (1.2–3.9)	>5 cm ² 18 (16%)	7.1 (6.5)/4 (2–11)	≥6 months 46 (40%)
Meaume et al, 2012 ³⁹ (CHALLENGE trial)	Noninfected VLU	—	—	—	—
I: SOS		17 (15.6)/12.9 (2.3–86.9)	>10 cm ² 54 (58.1%)	15.6 (9.1)/12 (3–35)	>12 months 54 (58.1%)
C: TLC		16.6 (15.8)/10.5 (2.7–85.3)	>10 cm ² 48 (51.1%)	15.1 (8.7)/12 (6–36)	>12 months 49 (52.7%)
Schmutz et al, 2008 ⁴⁰	Noninfected VLUs	—	—	—	—
I: SOS		11.4 (10.1)/9	>10 cm ² 26 (45.6%)	10.4 (7.1)/8	≥6 months 31 (54.4%)
C: ORC		10.4 (8.4)/7.9	>10 cm ² 22 (36.7%)	12.1 (7.7)/12	≥6 months 35 (58.3%)

Abbreviations: C, comparator; DFU, diabetic foot ulcer; I, intervention; IQR, interquartile range; ORC, oxidized regenerated cellulose; SD, standard deviation; SOS, sucrose octasulfate; TLC, Technology Lipido-Colloid; VLU, venous leg ulcer.

Risk of Bias in the Included Studies

We assessed the risk of bias for the studies included in this review using the RoB 2 tool and determined that the risk of bias was low in the trials by Edmonds et al³⁶ (EXPLORER trial) and Meaume et al³⁹ (CHALLENGE trial). There was some concern about the risk of bias in the trial by Schmutz et al⁴⁰ because it was an open-label trial in which participants and health care providers were not blinded to the allocated treatment. Detailed risk-of-bias assessments are provided in Appendix 2.

Diabetic Foot Ulcers

Only 1 randomized controlled trial, which was an international double-blind randomized controlled trial studying diabetic foot ulcers (EXPLORER), compared the effectiveness of a dressing containing sucrose octasulfate potassium salt (i.e., Technology Lipido-Colloid Nano-Oligosaccharide Factor [TLC-NOSF]) with a dressing that did not contain sucrose octasulfate (i.e., UrgoTul, a lipido-colloid dressing).³⁶ Standard wound care was provided in the same manner for both groups, and all patients received an offloading device. The authors reported a high level of patient adherence to offloading devices throughout the study period.

A total of 289 patients were enrolled, of which 240 were eligible for inclusion. Most participants were outpatients (93% in the sucrose octasulfate group and 94% in the control group). All participants were older than 18 years of age and had a noninfected neuroischemic diabetic foot ulcer of grade IC

(ischemic, noninfected superficial wound) or IIC (ischemic, noninfected penetrating to tendon or capsule). Eligibility criteria included a diabetic foot ulcer size between 1 and 30 cm and wound duration between 1 and 24 months. The most common location of diabetic foot ulcers was plantar (47%), and in 81% of cases, the wounds were superficial.³⁷ The median size of the wounds was 2.3 cm².³⁷ Dressing changes were performed 2 to 4 times per week; the mean number of dressing changes per week was 3.1 (standard deviation [SD] 1.8). At the start of the study, eligibility criteria included an ankle-brachial pressure index (ABPI) score of 0.9 or less. However, after the trial started, the protocol was amended to also include patients with an ABPI score greater than 0.9 to account for falsely high ABPI values that result from medial arterial calcification, a common complication in diabetes that might misleadingly rule out the presence of peripheral arterial disease. From 240 eligible patients, 59 were recruited before the amendment of the vascular assessment protocol (35 in the intervention group and 24 in the control group). The baseline mean ABPI score was 0.88 in both groups.

Thirty-seven of 240 patients (15%) withdrew during the treatment period, with no difference between the allocated groups.

Statistical analyses were performed for the intention-to-treat population, which included all randomly assigned patients with at least 1 post-treatment follow-up measurement. The median duration of the treatment period was 115 days (interquartile range [IQR] 56–141) for the intervention group and 135 days (IQR 56–141) for the control group. The mean duration of follow-up was 54.1 days (SD 9.2) in the intervention group and 53.2 days (SD 11.4) in the control group, with no difference between the 2 groups.

Baseline demographic characteristics and medical history of the patients were similar between the 2 groups.

Complete Wound Closure

In the EXPLORER trial, wound closure was defined as 100% re-epithelialization without exudate, confirmed at least 10 days after wound closure was first assessed. Wound closure, the primary outcome of the study, was achieved in 60 of 126 patients (48%) in the intervention group and 34 of 114 patients (30%) in the control group at week 20, resulting in a difference of 18 percentage points (95% confidence interval [CI], 5–30) in the intention-to-treat population. The adjusted odds ratio (OR) was 2.60 (95% CI, 1.43–4.73; $P = .002$). The estimated mean time to wound closure was 120 days (95% CI, 110–129) in the intervention group and 180 days (95% CI, 163–198) in the control group, resulting in a mean difference of 60 days (95% CI, 47–75; $P = .029$) (Table 3). The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A4).

Table 3: Complete Wound Closure and Wound Area Reduction for Diabetic Foot Ulcers – Sucrose Octasulfate–Impregnated Dressing Versus Lipido-Colloid Dressing

Author, year	Complete wound closure, n/total	Estimated time to complete wound closure, mean (95% CI), d	Absolute wound area reduction, cm ²	Relative wound area reduction, %
Edmonds et al, 2018 ³⁶ (EXPLORER trial)	SOS: 60/126 (48%)	SOS: 120 (110–129)	Mean (SD)	Mean (SD)
	Control: 34/114 (30%)	Control: 180 (163–198)	SOS: 3.2 (5.2)	SOS: 72 (47)
	OR, 2.60 (95% CI, 1.43–4.73)	Mean difference, 60 (47–75)	Control: 2.3 (5.5)	Control: 42 (115)
	P = .002	P = .029	P = NA	P = NA
			Median (IQR)	Median (IQR)
			SOS: 1.8 (0.9–3.8)	SOS: 98 (58–100)
			Control: 1.2 (0.6–2.4)	Control: 90 (29–100)
			P = .022	P = .024

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not available; OR, odds ratio; SD, standard deviation; SOS, sucrose octasulfate.

Subgroup Analysis

The investigators of the EXPLORER trial performed a post hoc analysis of wound duration for the outcome of complete wound closure. This analysis was based on 2 and 4 categories of wound duration.

Complete Wound Closure Based on 2 Categories of Wound Duration

In the EXPLORER trial, wound duration was <6 months for most patients (139 of 240 [58%]). Complete wound closure at week 20 was achieved in 73 of 139 patients (53%) with a wound duration of <6 months versus 21 of 101 patients (22%) with a wound duration of ≥6 months. The OR for comparison between the intervention and control groups for a wound duration of <6 months was 2.79 (95% CI, 1.33–5.89), indicating that sucrose octasulfate is effective for ulcers with shorter duration. The OR for comparison between the intervention and control groups for a wound duration of ≥6 months was 1.90 (95% CI, 0.63–6.16), indicating no difference between the groups when ulcers are in a more chronic state.

Complete Wound Closure Based on 4 Categories of Wound Duration

In a post hoc analysis of the EXPLORER trial, Lázaro-Martínez et al³⁷ stratified the data of complete wound closure based on wound duration into 4 categories and showed the association between wound duration and complete wound closure rate.³⁷ The authors demonstrated that older diabetic foot ulcers had a lower closure rate than more recently developed wounds, while the absolute differences between wound closure rates of the intervention and control groups were always in favour of the intervention group regardless of wound duration.

At week 20, complete wound closure was achieved as follows: 57% of the wounds with a duration of ≤2 months, 49% of the wounds with a duration of 3 to ≤5 months, 23% of the wounds with a duration of 6 to ≤11 months, and 19% of the wounds with a duration of >11 months. Table 4 shows the details of the post hoc subgroup analysis of wound duration.

Table 4: Subgroup Analysis: Complete Wound Closure According to Duration of Diabetic Foot Ulcer

Author, year	≤2 mo	3 to ≤5 mo	6 to ≤11 mo	>11 mo
Lázaro-Martinez et al, 2019 ³⁷	All: 57% SOS: 71% Control: 41% RR, 1.7 (95% CI, 1.1–2.8)	All: 49% SOS: 59% Control: 38% RR, 1.6 (95% CI, 1.0–2.5)	All: 23% SOS: 29% Control: 16% RR, 1.8 (95% CI, 0.6–6)	All: 19% SOS: 22% Control: 15% RR, 1.5 (95% CI, 0.5–4.7)

Abbreviations: CI, confidence interval; RR, relative risk; SD, standard deviation; SOS, sucrose octasulfate.

The authors concluded that the 30-percentage point difference between the 2 groups for a wound duration of ≤2 months supports the initiation of treatment with sucrose octasulfate as early as possible to achieve optimal effect.

Wound Area Reduction

The mean absolute wound area reduction from the start of treatment to week 20 was 3.2 cm² (SD 5.2) in the intervention group and 2.3 cm² (SD 5.5) in the control group (*P* value not reported). The median absolute wound area reduction was 1.8 cm² (IQR 0.9–3.8) in the intervention group and 1.2 cm² (IQR 0.6–2.4) in the control group (*P* = .022).

The mean relative wound area reduction from the start of treatment to week 20 was 72% (SD 47%) in the intervention group and 42% (SD 115%) in the control group (*P* value not reported). The median wound area reduction was 98% (IQR 58%–100%) in the intervention group and 90% (IQR 29%–100%) in the control group (*P* = .024). The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A4).

At week 20, more patients in the intervention group had a wound area reduction of at least 50% than in the control group (*P* = .029).

Amputation

Amputations in the affected limb were minor and occurred in 1 patient (1%) in the intervention group and 2 patients (2%) in the control group (*P* value not reported). These amputations did not affect the wound site and did not lead to withdrawal from the study because the wound site was not affected. The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A4).

Health-Related Quality of Life

Health-related quality of life was assessed using the EQ-5D-5L quality-of-life questionnaire at baseline and at the end of treatment. The questionnaire included 5 domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. There was no statistically significant difference between the 2 groups except for the domain of usual activities in which the intervention group had higher scores than the control group, indicating lower quality of life in that domain (*P* = .041). At the end of treatment, scores for all domains were similar between the 2 groups. However, scores remained poor overall because of restrictions in mobility and usual activities. At the end of treatment, the mean quality-of-life index was 0.63 (SD 0.30) in the intervention group and 0.69 (SD 0.32) in the control group

($P = .245$), and the mean visual analogue scale (VAS) scores were 67 (SD 21) in the intervention group and 69 (SD 22) in the control group ($P = .539$). The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A4).

Adverse Events

Adverse events occurred in 40 patients (32%) in the intervention group and in 47 patients (41%) in the control group. The total number of adverse events in the intervention and control groups were 64 and 66, respectively. Only 2 events in the intervention group and 6 events in the control group were deemed to be possibly or probably related to the dressing or procedure. The most frequent adverse event in both groups was local infection of the target wound, which occurred in 25 patients (20%) in the intervention group and in 32 patients (28%) in the control group. Three patients (2%) in the intervention group and 4 patients (4%) in the control group died during the study period, but none of the deaths were related to the dressing or procedure. The occurrence of adverse events was the reason for discontinuation for 1 patient (1%) in the intervention group and 3 patients (2.6%) in the control group. The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A4).

Venous Leg Ulcers

Two randomized controlled trials compared the effectiveness of sucrose octasulfate–impregnated dressings with dressings that did not contain this agent for the treatment of venous leg ulcers.^{39,40} The CHALLENGE trial³⁹ compared the effectiveness of a dressing containing sucrose octasulfate potassium salt (i.e., TLC-NOSF) with a dressing that did not contain this agent (i.e., UrgoTul, a lipido-colloid dressing). The study by Schmutz et al⁴⁰ compared the effectiveness of a dressing containing sucrose octasulfate potassium salt (i.e., TLC-NOSF) with a dressing containing oxidized regenerated cellulose and collagen.

Sucrose Octasulfate–Impregnated Dressing Versus Lipido-Colloid Dressing

The CHALLENGE trial³⁹ was a double-blind randomized controlled trial with a short study duration (8 weeks). Eligibility criteria included venous leg ulcer size between 5 and 50 cm² and wound duration between 6 and 36 months despite appropriate treatment. Eligibility criteria also included an ABPI score between 0.8 and 1.3, and ulcers that had at least 50% of their surface covered with granulation tissue without any black necrotic tissue on the surface of the ulcer. Standard wound care was provided in the same manner for both groups. Dressings were changed on average 6 ± 3 times every 2 weeks in both groups. All analyses were conducted on the intention-to-treat population, defined as patients who received the allocated dressing at least once.

A total of 187 patients with a noninfected venous leg ulcer were eligible for inclusion and were randomly allocated to either the treatment group ($n = 93$) or the control group ($n = 94$). Participants were older than 18 years and were mostly outpatients (81.3%). Female sex was predominant among the study population (65.2%). Demographic data and ulcer characteristics were balanced between the 2 groups.

Wound duration in most patients in both groups was >1 year (intervention 58.1%, control 52.7%), and most ulcers were recurrent (intervention 54.8%, control 52.1%). More than half of the patients had a wound size of >10 cm² (intervention 58.1%, control 51.1%). The mean ulcer size was 17 cm² (SD 15.6) in the intervention group and 16.6 cm² (SD 15.8) in the control group, with no difference between the

2 groups. Nearly 92% of patients were wearing a compression therapy system before randomization, and their compliance with prescribed compression therapy after randomization was very good, with 96.4% of the patients still wearing the compression therapy system at week 6. The mean ABPI score was 1.05 (SD 0.14) in the intervention group and 1.03 (SD 0.12) in the control group. Venous leg ulcers were evaluated every 2 weeks until week 8, even if the dressing had not been used for any reason.

In the intervention group, 1 patient was lost to follow-up and 3 patients discontinued the intervention (1 withdrew consent, 1 withdrew because of adverse events, and 1 died). In the control group, 1 patient was lost to follow-up and 5 patients discontinued the intervention (2 withdrew consent, 2 withdrew because of adverse events, and 1 died). Eleven patients (11.8%) in the intervention group and 11 patients (11.7%) in the control group switched to another wound dressing, mainly because of the occurrence of a local adverse event. The mean duration of follow-up was 54.1 days (SD 9.2) in the intervention group and 53.2 days (SD 11.4) in the control group, with no difference between the 2 groups.

Table 5 shows clinical outcomes of the CHALLENGE trial after 8 weeks of treatment.

Table 5: Complete Wound Closure and Wound Area Reduction for Venous Leg Ulcers – Sucrose Octasulfate–Impregnated Dressing Versus Lipido-Colloid Dressing

Author, year	Complete wound closure, n/total	Estimated time to reach wound area reduction >40%, median (95% CI), d	Absolute wound area reduction, cm ²	Relative wound area reduction, %
Meaume et al, 2012 ³⁹ (CHALLENGE trial)	SOS: 6/93 (6.45%) Control: 7/94 (7.45%) P = NR	SOS: 43 (37.2–48.8) Control: 63 (57.8–68.1) P = .002	Mean (SD) SOS: 6.9 (11.4) Control: 2.5 (11.9) P = .003	Mean (SD) SOS: 45.2 (47.9) Control: 21.4 (81) P = .002

Abbreviations: CI, confidence interval; NR, not reported; SD, standard deviation; SOS, sucrose octasulfate.

Complete Wound Closure

By the end of the study, 6 patients in the intervention group and 7 patients in the control group had 100% re-epithelization and did not need further dressing (*P* value not reported). Time to achieve complete wound closure was not reported. The quality of evidence (GRADE) for this outcome was rated as Low, downgraded for inconsistency and indirectness (Appendix 2, Table A5).

Wound Area Reduction

Relative wound area reduction was the primary outcome and was defined as $(\text{Area}_{\text{last}} - \text{Area}_{\text{t0}}) / \text{Area}_{\text{t0}} \times 100$. At the end of treatment, the mean relative wound area decreased by 45.2% (SD 47.9%) in the intervention group and by 21.4% (SD 81%) in the control group (*P* = .002). The median relative wound area decreased by 58.3% in the intervention group and by 31.6% in the control group, resulting in a median difference of 26.7% (95% CI, 38.3%–15.1%; *P* = .002). The superior effect of the intervention group was observed after 2 weeks and increased steadily thereafter. The mean absolute wound area reduction was 6.9 cm² (SD 11.4) in the intervention group and 2.5 cm² (SD 11.9) in the control group (*P* = .003). No *P* value was reported for the median difference.

A wound area reduction of $\geq 40\%$ was observed in 61 of 93 patients (65.6%) in the intervention group compared with 37 of 94 patients (39.4%) in the control group (OR 2.9 [95% CI, 1.6–5.3]; $P = .000$). A wound area reduction of $\geq 60\%$ was observed in 42 of 93 patients (45.2%) in the intervention group compared with 26 of 94 patients (27.7%) in the control group (OR 2.2 [95% CI, 1.2–4]; $P = .013$). At the end of the trial, 70 of 86 ulcers (81.4%) were considered to be “improved” in the intervention group compared with 54 of 82 ulcers (65.9%) in the control group ($P = .022$).

The median time to reach a wound area reduction of $>40\%$ was 43 days (95% CI, 37.2–48.8) in the intervention group compared with 63 days (95% CI, 57.8–68.1) in the control group ($P = .002$). The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A5).

Subgroup Analysis

The investigators of the CHALLENGE trial performed subgroup analysis based on 2 categories of wound duration (i.e., ≤ 1 year and >1 year) for the primary outcome (relative wound area reduction), but no P value was reported. Fifty-four patients in the intervention group and 50 patients in the control group had ulcers for >1 year, and the median wound area reduction for these patients was 55.2% in the intervention group and 23.1% in the control group (median difference 32% [95% CI, 48.7%–15.4%]).

Thirty-nine patients in the intervention group and 44 patients in the control group had ulcers for ≤ 1 year. The median wound area reduction for these patients was 63.3% in the intervention group and 38.1% in the control group (median difference 25.3% [95% CI, 49.5%–1.01%]).

Health-Related Quality of Life

The principal investigator of the CHALLENGE trial reported health-related quality of life in a separate publication.³⁸ In this trial, patients completed the EQ-5D questionnaire at baseline and at week 8 or before the discontinuation of treatment. The questionnaire included 5 domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A VAS was also part of the questionnaire. At baseline, there was no statistically significant difference in any of the 5 domains of EQ-5D between the 2 groups. Pain/discomfort was the most impaired domain, and self-care was the least affected. At the final visit, the questionnaire was completed by 80 patients (86%) in the intervention group and 78 patients (83%) in the control group.

At the end of the trial, EQ-5D scores for 2 domains (pain/discomfort and anxiety/depression) were statistically significantly lower in the intervention group than in the control group, indicating better quality of life in the intervention group in these domains. The mean score for pain/discomfort was 1.53 (SD 0.52) in the intervention group versus 1.74 (SD 0.65) in the control group ($P = .022$), and the mean score for anxiety/depression was 1.35 (SD 0.53) in the intervention group versus 1.54 (SD 0.59) in the control group ($P = .037$). The VAS scores were not different between the 2 groups at the end of the trial (intervention 72.1 [SD 17.5], control 67.3 [SD 18.7]; $P = .072$) (Table 6).

The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A5).

Table 6: Health-Related Quality of Life Scores for Patients With Venous Leg Ulcers – Sucrose Octasulfate–Impregnated Dressing Versus Lipido-Colloid Dressing

Author, year	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression	VAS
Meaume et al, 2017 ³⁸ (CHALLENGE study)	Baseline SOS: 1.56 (0.52) Control: 1.59 (0.51)	Baseline SOS: 1.25 (0.48) Control: 1.27 (0.49)	Baseline SOS: 1.55 (0.62) Control: 1.5 (0.6)	Baseline SOS: 1.82 (0.6) Control: 1.95 (0.52)	Baseline SOS: 1.53 (0.64) Control: 1.61 (0.63)	Baseline SOS: 65.84 (17.68) Control: 65.63 (17.38)
	Final visit SOS: 1.55 (0.52) Control: 1.56 (0.52)	Final visit SOS: 1.23 (0.44) Control: 1.27 (0.55)	Final visit SOS: 1.54 (0.61) Control: 1.51 (0.59)	Final visit SOS: 1.53 (0.52) Control: 1.74 (0.65)	Final visit SOS: 1.35 (0.53) Control: 1.54 (0.59)	Final visit SOS: 72.1 (17.5) Control: 67.3 (18.7)
	<i>P</i> = .86	<i>P</i> = .55	<i>P</i> = .74	<i>P</i> = .022	<i>P</i> = .037	<i>P</i> = .072

Abbreviations: SOS, sucrose octasulfate; VAS, visual analogue scale.

Adverse Events

A total of 66 local adverse events occurred in 29 patients (31.2% [95% CI, 22–41.6]) in the intervention group (34 adverse events) and 27 patients (28.7% [95% CI, 19.9–38]) in the control group (32 adverse events), with no difference between the 2 groups (Table 7). Ten of the adverse events in the intervention group and 13 in the control group were considered by the investigators to most probably be dressing related.

Periwound eczema was the most frequently reported adverse event (15.05% in the intervention group and 9.57% in the control group). Infection occurred in 7.53% of patients in the intervention group and 6.38% of patients in the control group. Occurrence of local adverse event was the reason for discontinuation of the dressings in 11 patients (11.8%) in the intervention group and in 12 patients (12.8%) in the control group. Table 7 shows the occurrence of local adverse events in this trial.

The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for inconsistency (Appendix 2, Table A5).

Table 7: Local Adverse Events in Patients With Venous Leg Ulcers – Sucrose Octasulfate–Impregnated Dressing Versus Lipido-Colloid Dressing

Author, year	Periwound eczema, %	Infection, %	Skin irritation, %	Overgranulation, %	Pain, %	Other, %
Meaume et al, 2012 ³⁹ (CHALLENGE trial)	SOS: 15.05 Control: 9.57	SOS: 7.53 Control: 6.38	SOS: 2.16 Control: 4.26	SOS: 3.23 Control: 2.13	SOS: 1.08 Control: 0	SOS: 7.53 Control: 11.7

Abbreviation: SOS, sucrose octasulfate.

Sucrose Octasulfate–Impregnated Dressings Versus Oxidized Regenerated Cellulose and Collagen Dressings

The study by Schmutz et al⁴⁰ was an open-label randomized controlled trial with a study duration of 12 weeks. The study compared a sucrose octasulfate–impregnated dressing with a dressing containing oxidized regenerated cellulose and collagen (Promogran) in 117 patients with noninfected venous leg ulcers. Oxidized regenerated cellulose is another matrix metalloproteinase (MMP) modulating agent that forms a gel upon contact with wound fluids and absorbs and inhibits the activity of MMPs. This study was conducted in 22 hospital units in France and 5 wound specialist centres in the UK, and 82% of participants were outpatients.

Patients were randomized into 2 groups: 57 patients in the intervention group and 60 patients in the control group. The cause of leg ulcer was venous in 54.7% of patients (intervention 56.1%, control 53.3%). Although the trial was for venous leg ulcers, 28.2% of patients had arterial disease as the cause of leg ulcer (intervention 29.8%, control 26.7%).

At inclusion, all ulcers were appropriately debrided and patients in both groups received compression therapy. The adherence rate with prescribed compression therapy was high (93%). Analyses were performed based on intention to treat, as well as per protocol.

Baseline demographic and ulcer characteristics were similar between the 2 groups. The majority of ulcers (56%) had a wound duration of >6 months (median 10 months), and 61% were recurrent ulcers. The mean wound area at baseline was 10.9 cm² (SD 9.3), and in 41% of patients, the size of the wound was >10 cm². Sixty-eight percent of the wounds were considered to be nonhealing (intervention 64.9%, control 71.7%). The mean ABPI score was 1.01 (SD 0.10) in the intervention group and 1.03 (SD 0.17) in the control group.

Relative wound area reduction was the primary outcome of the study, and absolute wound area reduction was the secondary outcome. By the end of the study, the target ulcer was closed in 10 patients in the intervention group and in 8 patients in the control group (*P* value not reported). The quality of evidence (GRADE) for this outcome was rated as Very low, downgraded for risk of bias, inconsistency, and indirectness (Appendix 2, Table A6).

In this trial, the median relative wound area reduction and the mean absolute wound area reduction showed greater improvement in the intervention group than in the control group. The mean absolute wound area reduction was 2.3 cm² (SD 10.2) in the intervention group (median 4.2 cm²) and 0.2 cm² (SD 10.4) in the control group (median 1 cm²) (*P* = .010). The median relative wound area reduction was 54.4% in the intervention group and 12.9% in the control group (*P* = .028). Overall, 56% of wounds in the intervention group and 35% of wounds in the control group reached 40% reduction in the wound area, favouring the intervention (*P* = .022). The quality of evidence (GRADE) for this outcome was rated as Low, downgraded for risk of bias and inconsistency (Appendix 2, Table A6).

The estimated time to reach a 40% reduction in wound surface area was not different between the intervention and control groups (*P* = .06). The quality of evidence (GRADE) for this outcome was rated as Low, downgraded for risk of bias and inconsistency (Appendix 2, Table A6).

Subgroup Analysis

This study reported the effect of wound duration on the outcomes of absolute and relative wound area reduction. There was no difference between the 2 groups in either absolute or relative wound area reduction for wounds with a duration of ≤6 months, but for wounds with a duration of >6 months, the intervention group had statistically significantly better absolute and relative wound area reduction (Table 8). The subgroup analysis of this trial showed a different direction than the analysis of the trial of diabetic foot ulcers, as diabetic foot ulcers demonstrated better wound closure for wounds with a shorter duration.

In the trial by Schmutz et al,⁴⁰ 15 patients (57.7%) in the intervention group and 12 patients (48.8%) in the control group who had a wound duration of ≤6 months had ≥40% reduction in ulcer size ($P = .488$), but 17 patients (54.8%) in the intervention group and 9 patients (25.7%) in the control group who had a wound duration of >6 months had ≥40% reduction in ulcer size, which favoured the intervention group ($P = .016$).

Table 8: Complete Wound Closure and Wound Area Reduction for Venous Leg Ulcers – Sucrose Octasulfate–Impregnated Dressing Versus Oxidized Regenerated Cellulose and Collagen Dressing

Author, year	Complete wound closure, N	Estimated time to complete wound closure, mean (95% CI), d	Absolute wound area reduction, mean (SD)/median, cm ²	Relative wound area reduction, mean (SD), %
Schmutz et al, 2008 ⁴⁰	SOS: 10 Control: 8 $P = \text{NR}$	Not reported Median time to reach a 40% reduction in ulcer size SOS: 42 Control: 84 $P = .06$	SOS: 2.3 (10.2)/4.2 Control: 0.2 (10.4)/1.0 $P = .010$	Median SOS: 54.4% Control: 12.9% $P = .028$
Subgroup analysis				
			Wound duration ≤6 mo SOS: 3.4 (5.8) Control: 1.7 (11.4) Median SOS: 4.6 Control: 1.9 $P = .559$	Wound duration ≤6 mo SOS: 36.5 (80.2) Control: 21.6 (86) Median SOS: 63.5 Control: 28.3 $P = .608$
			Wound duration >6 mo SOS: 1.3 (12.9) Control: 0.9 (9.6) Median SOS: 4.1 Control: 0.6 $P = .019$	Wound duration >6 mo SOS: 26.5 (72.9) Control: 1 (70.3) Median SOS: 44.3 Control: 7.7 $P = .044$

Abbreviations: CI, confidence interval; SD, standard deviation; SOS, sucrose octasulfate.

Adverse Events

Local adverse events occurred in 14 patients (24.5%) in the intervention group (16 events) and in 23 patients (38.3%) in the control group (27 events). The nature of local adverse events differed between the 2 groups. Overgranulation was more frequent in the intervention group (intervention 7%,

control 1.7%), but infection was more frequent in the control group (intervention 7%, control 10%; *P* value not reported). Pain between dressing changes was also more frequent in the control group (intervention 8.8%, control 20%; *P* value not reported). Perilesional skin irritation was similar in both groups. Occurrence of adverse events was the reason for discontinuation for 6 patients in the intervention group and 14 patients in the control group (*P* value not reported). The quality of evidence (GRADE) for this outcome was rated as Moderate, downgraded for risk of bias (Appendix 2, Table A6).

Discussion

The evidence for the effectiveness and safety of sucrose octasulfate–impregnated dressings is mainly derived from 2 well-conducted double-blind randomized controlled trials, as well as the results of an open-label randomized trial that demonstrated consistent results.

We determined that the quality of evidence (GRADE) for complete wound closure³⁹ for patients with venous leg ulcers is Low, which differs from the Moderate quality of evidence (GRADE) for the same outcome for patients with diabetic foot ulcers. The Low quality of evidence (GRADE) is because the study duration was not sufficient to observe a difference between the intervention and control groups. It may also be partially due to the larger ulcer size (mean 17 cm²) of the venous leg ulcers compared with the diabetic foot ulcers (mean 4–5 cm²).³⁶ Intuitively, larger ulcers may need more time to close.

In the 2 trials of venous leg ulcers,^{39,40} the intervention group had a statistically significantly larger reduction in wound surface area than the control group. Thus, more complete wound closures might have been observed in the intervention group if more time had been allotted for the trial, but we cannot consider this judgement as definitive until trials with longer duration of treatment are published.

Although the majority of patients (58%) in the EXPLORER trial had diabetic foot ulcers for <6 months, the majority of patients in the CHALLENGE trial (55%) had venous leg ulcers for >1 year and the majority of patients in the study by Schmutz et al⁴⁰ (56%) had venous leg ulcers for >6 months, and neither of the 2 studies on venous leg ulcers showed a difference between the intervention and control groups for the outcome of complete wound closure. The longer wound duration, larger wound size, and shorter duration of these trials may have contributed to the lack of difference between the intervention and control groups for the outcome of complete wound closure. However, the statistically significant reduction in wound size in the intervention group compared with the control group in both trials is a positive outcome and seems to be promising.

The EXPLORER trial³⁶ and the CHALLENGE trial³⁹ both compared sucrose octasulfate–impregnated dressings with only 1 type of dressing (i.e., UrgoTul, a lipido-colloid dressing). However, this control dressing has shown an effect similar to that of DuoDERM in an earlier randomized controlled trial.⁴¹ DuoDERM is a hydrocolloid dressing and is approved for use in Canada. The trial by Schmutz et al⁴⁰ compared sucrose octasulfate with Promogran, which also inhibits the activity of MMPs. Several trials have investigated the effectiveness of Promogran for the treatment of venous leg ulcers.⁴²⁻⁴⁵

In the trials included in this review, regular dressing change (every 3 days or more frequently if required), wound inspection, wound cleaning, and standard care (including regular debridement, offloading for diabetic foot ulcers, and compression bandages for venous leg ulcers) were provided to participants, and the investigators reported high rates of patient adherence to the standard care interventions. Therefore, for sucrose octasulfate–impregnated dressings to be effective in healing

noninfected diabetic foot ulcers or noninfected venous leg ulcers, they must be used along with these interventions and patient concordance with the prescribed interventions is important.

Strengths and Limitations

The strength of our clinical review is its systematic approach to include 2 high-quality randomized controlled trials and 1 open-label randomized trial, which increases the confidence about the reliability of the results. However, the review is limited by the small number of published randomized controlled trials, which did not allow for the examination of comparative effectiveness of sucrose octasulfate-impregnated dressings with other types of dressings.

Conclusions

For patients with difficult-to-heal noninfected neuroischemic diabetic foot ulcers, treatment with sucrose octasulfate-impregnated dressings compared with lipido-colloid dressings:

- Likely increases complete wound closure rate and results in greater wound surface area reduction (GRADE: Moderate)
- Likely decreases time to complete wound closure (GRADE: Moderate)
- Likely results in little to no difference in health-related quality of life (GRADE: Moderate)
- Can be considered safe (GRADE: Moderate)

For patients with difficult-to heal noninfected venous leg ulcers, treatment with sucrose octasulfate-impregnated dressings compared with lipido-colloid dressings:

- May have a similar complete wound closure rate at 8 weeks (GRADE: Low)
- Likely results in greater wound surface area reduction at 8 weeks (GRADE: Moderate)
- May decrease time to reach a wound surface area reduction of >40% (GRADE: Low)
- Likely improves health-related quality of life in the domains of pain/discomfort and anxiety/depression (GRADE: Moderate)
- Can be considered safe (GRADE: Moderate)

For patients with difficult-to-heal noninfected venous leg ulcers, treatment with sucrose octasulfate-impregnated dressings compared with dressings containing oxidized regenerated cellulose and collagen:

- May have a similar complete wound closure rate (GRADE: Very low)
- May have similar time to reach a wound surface area reduction of 40% (GRADE: Low)
- May result in greater wound surface area reduction (GRADE: Low)
- Can be considered safe (GRADE: Low)

Economic Evidence

Research Question

What is the cost-effectiveness of sucrose octasulfate-impregnated dressings, compared with dressings that do not contain sucrose octasulfate, for the treatment of adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers?

Methods

Economic Literature Search

We performed an economic literature search on July 5, 2023, 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. Since no previous systematic review of economic evidence was found during the scoping period, we did not use a date limit.

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until October 16, 2023. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database 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
- Cost-benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost-utility analyses

Exclusion Criteria

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

Participants

Inclusion Criteria

- Adults (≥18 years old) with type 1 or type 2 diabetes mellitus with a difficult-to-heal or chronic noninfected diabetic foot ulcer
- Adults (≥18 years old) with a difficult-to-heal or chronic noninfected venous leg ulcer

Exclusion Criteria

- People < 18 years old
- People with localized or spreading infection

Interventions

Inclusion Criteria

- Sucrose octasulfate–impregnated dressings, not in combination with other interactive dressings, used as an adjunct to standard care

Exclusion Criteria

- Dressings that do not contain sucrose octasulfate

Comparators

Inclusion Criteria

- Dressings that do not contain sucrose octasulfate

Exclusion Criteria

- Nondressing treatments

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs])
- 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. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The 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 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.⁴⁶ 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 2 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 49 citations published from database inception until July 5, 2023, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources, including database alerts (monitored until October 16, 2023). In total, we identified 5 studies (3 cost-effectiveness analyses and 2 cost–utility analyses) that met our inclusion criteria. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

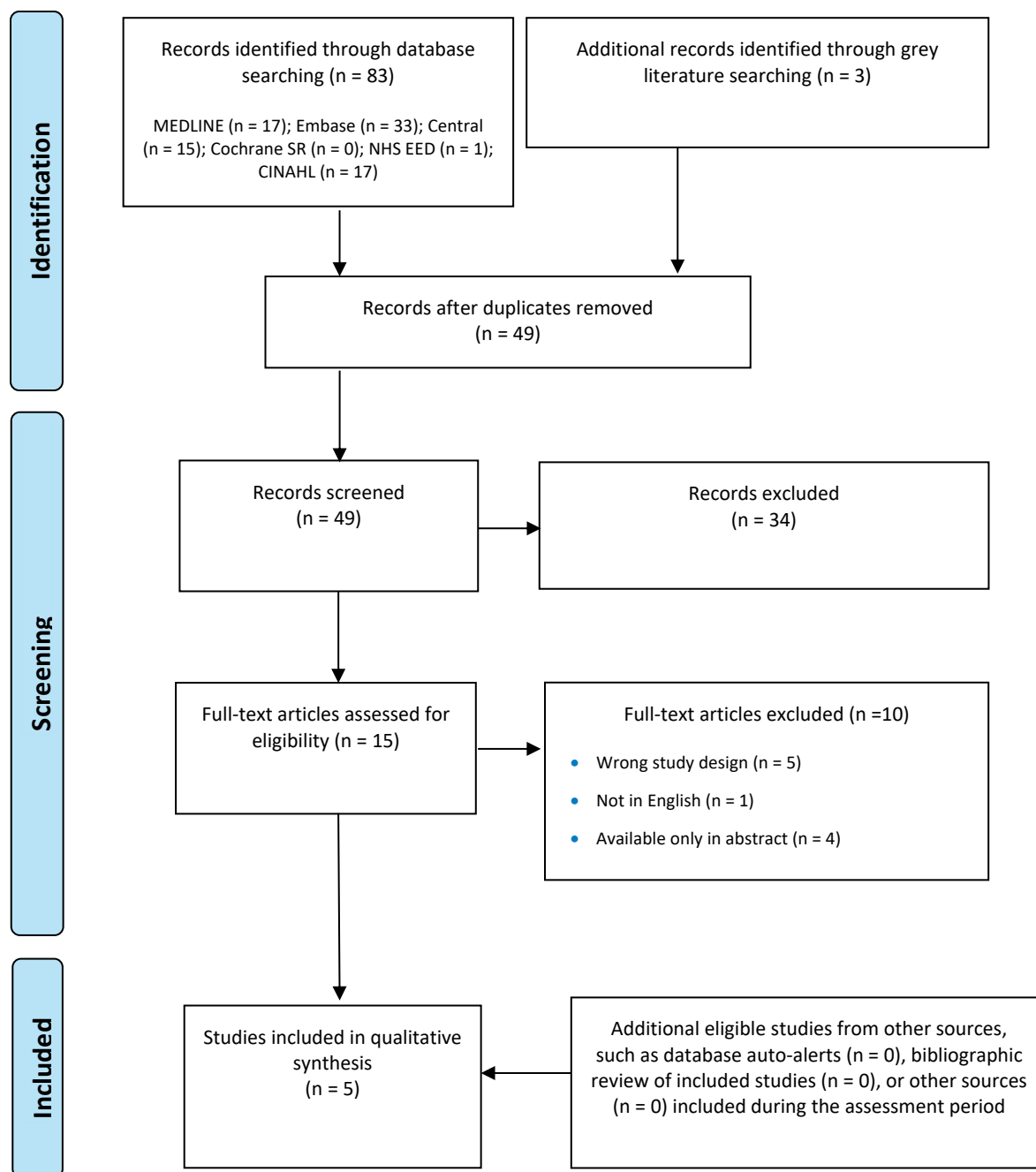


Figure 2: PRISMA Flow Diagram – Economic Search Strategy

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 49 citations published from database inception to July 5, 2023, including grey literature and after duplicates were removed. We screened the abstracts of the 49 identified studies and excluded 34. We assessed the full text of 15 articles and excluded a further 10. In the end, we included 5 articles in the qualitative synthesis.

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

Source: Adapted from Page et al.³¹

Overview of Included Economic Studies

We identified 5 model-based economic evaluations (see Table 9).⁴⁷⁻⁵¹ Three were cost-effectiveness analyses,⁴⁹⁻⁵¹ and 2 were cost-utility analyses.^{47,48} Three studies focused on the population with diabetic foot ulcers,⁴⁷⁻⁴⁹ 1 study focused on the population with venous leg ulcers,⁵⁰ and the remaining study conducted separate analyses for both populations.¹⁹

The studies were conducted from the perspectives of the public payer or all payers in Canada,⁴⁷ France,⁴⁸ Germany,^{49,50} and the UK.¹⁹ The time horizon of the studies ranged from 8 weeks to 40 years.

All studies derived their key clinical parameter inputs from either the EXPLORER³⁶ or the CHALLENGE³⁹ randomized controlled trial, which evaluated sucrose octasulfate-impregnated dressings versus dressings that do not contain sucrose octasulfate (sucrose octasulfate-free dressings) for patients with noninfected diabetic foot ulcers or venous leg ulcers, respectively.

Across all studies, sucrose octasulfate-impregnated dressings were found to be dominant (i.e., less costly and more effective) or cost-saving compared with sucrose octasulfate-free dressings. Results remained robust in the 3 studies that conducted probabilistic sensitivity analysis.^{47,48,51} In the Canadian study by Wen et al,⁴⁷ the probability of sucrose octasulfate-impregnated dressings being cost-effective at a willingness-to-pay of \$50,000 per QALY was 86%, which suggests that the intervention is highly likely to be cost-effective.⁵²

Results also remained robust across most one-way deterministic sensitivity analyses conducted across the studies. Key drivers of study results were largely attributed to effectiveness (i.e., healing rate) or cost of sucrose octasulfate-impregnated dressings. For instance, the NICE health technology assessment¹⁹ found that sucrose octasulfate-impregnated dressings were no longer cost-saving for the population with diabetic foot ulcers when healing rates with these dressings were reduced by 50% compared with what was estimated from the EXPLORER trial.³⁶ For the population with venous leg ulcers, Augustin et al⁵³ found that the breakeven point between the intervention and comparator arms occurred when the unit price of sucrose octasulfate-impregnated dressings was increased by over 170% (from €9.98 to €27.29), or when the healing rate in the intervention arm was reduced by 34% (from 65.6% to 43.15%) compared with what was observed in the CHALLENGE trial.³⁹ Additionally, Maunoury et al⁴⁸ conducted a subgroup analysis based on wound duration (i.e., ≤2 months, 3–5 months, 6–11 months, >11 months) at the start of treatment in the EXPLORER trial³⁶ and found results to be robust across all subgroups.

Lastly, we did not find any economic studies that evaluated the cost-effectiveness of sucrose octasulfate-impregnated dressings in equity-deserving populations.

Table 9: Characteristics of Studies Included in the Economic Literature Review

Author, year, country, intervention, comparator	Analysis				Study population	Results		
	Technique	Design (model)	Approach or perspective	Time horizon (discount rate)		Health outcomes	Costs	Cost-effectiveness
Wen et al, 2022, ⁴⁷ Canada	Cost–utility analysis	Markov model	Canadian public payer	5 y (1.5%)	Difficult-to-heal noninfected DFUs	Mean QALY difference, I vs C: 0.16	Mean cost difference, I vs C: –\$5,878 Currency, cost year: CAD, 2000	I vs C: Dominant PSA results found that the probability of SOS-impregnated dressings being cost-effective at WTP of \$50,000 per QALY is 86%. Results remained robust in one-way DSA, whereby parameters were varied by ±20%.
I: SOS-impregnated dressing (i.e., UrgoStart)	—	—	—	—	—	Mean QALY: 2.94	Mean cost: \$18,317	
C: Dressing with the same appearance but SOS free (e.g., UrgoTul)	—	—	—	—	—	Mean QALY: 2.78	Mean cost: \$24,195	
Maunoury et al, 2021, ⁴⁸ France	Cost–utility analysis	Markov microsimulation model	French societal perspective	50 y (2.5%)	Difficult-to-heal noninfected DFUs	Mean QALY difference, I vs C: 0.16 I vs C: 0.50 Lys	Mean cost difference, per 1,000 people, I vs C: –€35,489 Currency, cost year: EUR, 2019	I vs C: Dominant Results remained robust in PSA, one-way DSA, and across all subgroups ^a in subgroup analyses.
I: SOS-impregnated dressing (i.e., UrgoStart)	—	—	—	—	—	Mean QALY: 4.44	Mean cost, per 1,000 people: €281,360	
C: Dressing with the same appearance but SOS free (e.g., UrgoTul)	—	—	—	—	—	Mean QALY: 4.28	Mean cost, per 1,000 people: €316,849	
NICE, 2019, ¹⁹ UK	Cost-effectiveness analysis	Markov model	UK public payer	1 y (NA)	Difficult-to-heal noninfected DFUs	Mean difference, I vs C: NR	Mean cost difference, I vs C: –£435 Currency, cost year: £, NR	Intervention had cost savings of £342 per patient versus the comparator. Results were robust across one-way DSA, except when healing rates with the SOS-impregnated dressings were reduced by 50% compared with those observed in the EXPLORER trial. ³⁶ PSA was conducted, but the results of CEAC or CE plane were not presented.
I: SOS-impregnated dressing (i.e., UrgoStart)	—	—	—	—	—	Mean effectiveness measure: NR	Mean cost: £2,667	
C: Dressing with the same appearance but SOS free (e.g., UrgoTul)	—	—	—	—	—	Mean effectiveness measure: NR	Mean cost: £3,102	

Author, year, country, intervention, comparator	Analysis					Results		
	Technique	Design (model)	Approach or perspective	Time horizon (discount rate)	Study population	Health outcomes	Costs	Cost-effectiveness
NICE, 2019, ¹⁹ UK	Cost-effectiveness analysis	Markov model	UK public payer	1 y (NA)	Difficult-to-heal noninfected VLU ^b	Mean difference, I vs C: NR	Mean cost difference, I vs C: -£886 Currency, cost year: £, NR	Intervention had cost savings of £541 per patient versus the comparator. SOS-impregnated dressings were robust across all one-way DSAs. PSA was conducted, but the results of CEAC or CE plane were not presented.
I: SOS-impregnated dressing (i.e., UrgoStart)	—	—	—	—	—	Mean effectiveness measure: NR	Mean cost: £927	
C: Dressing with the same appearance but SOS free (e.g., UrgoTul)	—	—	—	—	—	Mean effectiveness measure: NR	Mean cost: £1,813	
Lobmann et al, 2019, ⁴⁹ Germany	Cost-effectiveness analysis	Decision tree and Markov model	German public payer	100 wk (NR)	Difficult-to-heal noninfected DFUs	Mean healing rate difference, I vs C: 12%	Mean cost difference, I vs C: -€2,566.52 Currency, cost year: EUR, NR	Intervention is dominant. Results remained robust across all one-way DSAs, whereby parameters were varied by ±20%. PSA not conducted.
I: SOS-impregnated dressing (i.e., UrgoStart)	—	—	—	—	—	Mean healing rate: 94%	Mean cost: €5,882.87	
C: Dressing with the same appearance but SOS free (e.g., UrgoTul)	—	—	—	—	—	Mean healing rate: 81%	Mean cost: €8,449.39	
Augustin et al, 2016, ⁵⁰ Germany	Cost-effectiveness analysis	Decision tree	German public payer	8 wk (NA)	Difficult-to-heal noninfected VLUs ^b	Mean response rate difference, I vs C: 26.2%	Mean cost difference, I vs C: €31.32 Currency, cost year: €, NR	I vs C: -€485.64 per responder One-way DSA found that the breakeven point between the intervention and comparator arms occurred when the unit price of SOS-impregnated dressings was increased to over 170%, or when the response rate in the intervention arm was reduced from 65.6% (in the CHALLENGE trial) to 43.15%. PSA was not conducted.
I: SOS-impregnated dressing (i.e., UrgoStart)	—	—	—	—	—	Mean response rate ^c : 65.6%	Mean cost: €557.51	
C: Dressing with the same appearance but SOS free (e.g., UrgoTul)	—	—	—	—	—	Mean response rate ^c : 39.4%	Mean cost: €526.19	

Abbreviations: C, comparator; CE, cost-effectiveness; CEAC, cost-effectiveness acceptability curve; DFU, diabetic foot ulcer; DSA, deterministic sensitivity analysis; I, intervention; Lys, life-years; NA, not applicable; NR, not reported; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SOS, sucrose octasulfate; VLU, venous leg ulcer; WTP, willingness-to-pay.

^aSubgroup analysis was conducted based on wound duration (i.e., ≤2 months, 3–5 months, 6–11 months, >11 months) at the start of treatment in the EXPLORER trial.³⁶

^bAlthough the population of interest was reported as leg ulcers in these 2 studies,^{50,51} the primary clinical source used was the CHALLENGE trial,³⁹ which focused on venous leg ulcers.

^cResponse to treatment is defined as at least 40% wound area reduction after 8 weeks of treatment.⁵⁰

Applicability and Limitations of the Included Studies

Appendix 4 (Tables A7 and A8) provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. One study was deemed directly applicable to the research question,⁴⁷ and the remaining 4 studies were deemed partially applicable.⁴⁸⁻⁵¹ We assessed the limitations of these studies and found that 3 studies had minor limitations^{47,48,51} and 2 studies had potentially serious limitations.^{49,50} One study was relevant to the Ontario setting.⁴⁷

Discussion

Sucrose octasulfate-impregnated dressings were found to be more effective and less costly than sucrose octasulfate-free dressings across all studies and perspectives. However, these studies share some common limitations.

For studies evaluating the intervention for the population with diabetic foot ulcers, key clinical parameter inputs were derived from the EXPLORER trial,³⁶ a multicentre double-blind randomized controlled trial with a treatment phase of 20 weeks. Yet, all studies adopted a time horizon longer than 20 weeks, and as such, the extrapolation of treatment effect beyond the observation period in the trial may be associated with some uncertainty about the model validity. Transition probabilities for clinical parameters such as wound closure, amputation, and mortality beyond 20 weeks were sourced from a range of other studies or expanded to a longer timeframe based on model assumptions.

Additionally, except for the NICE health technology assessment¹⁹ on sucrose octasulfate-impregnated dressings for diabetic foot ulcers, all other studies evaluating the intervention for this population did not differentiate between minor and major amputation health states. This may underestimate costs for both treatment arms in these studies and overestimate the health-related quality-of-life outcomes for both the intervention and comparator in the 2 cost-utility analyses.^{47,48}

For the 2 studies evaluating sucrose octasulfate-impregnated dressings for the population with venous leg ulcers,^{51,53} key clinical parameter inputs were derived from the CHALLENGE trial,³⁹ a double-blind randomized controlled trial with a treatment phase of 8 weeks.

One study, Augustin et al,⁵⁰ restricted its time horizon to the observation period of the trial.³⁹ However, because the 8-week treatment phase of the trial³⁹ was not long enough to observe complete wound closure, its primary outcome was relative wound area reduction. Augustin et al⁵⁰ used the study's secondary outcome, at least 40% wound area reduction by the end of the treatment phase, as a proxy for wound healing. This may introduce some uncertainties when interpreting the study outcome, as not all wounds that meet this end point achieve complete wound closure. Furthermore, using the secondary outcome in the CHALLENGE trial³⁹ as a proxy for wound healing may overestimate transition probabilities from open to closed ulcers.

On the other hand, the NICE health technology assessment¹⁹ evaluating this intervention for venous leg ulcers adopted a longer time horizon and used relative wound area reduction as a proxy for wound healing, which may be biased toward smaller wounds and underestimate healing time.¹⁹ The NICE health technology assessment¹⁹ transformed this measure into 1-week healing rates and expanded the treatment effect to 1 year, while also calibrating the model based on the assumption that a proportion of patients in both treatment arms will not heal. The lack of follow-up data on complete wound healing beyond 8 weeks is a key limitation of these 2 studies,^{50,51} and their results should be interpreted with this limitation in mind.

Overall, all economic evaluations used model structures that appropriately reflect the nature of the respective diseases under treatment and comparator dressings. Despite some common limitations across the studies, all studies used the best available sources for clinical and cost inputs. Moreover, results were consistent across all studies and remained largely robust across a range of sensitivity analyses, which may convey higher confidence in the results showing sucrose octasulfate–impregnated dressings as dominant or cost-saving compared with sucrose octasulfate–free dressings.

Additionally, while most of the studies received financial support from the manufacturer (i.e., Urgo Medical) of the sucrose octasulfate–impregnated dressings (i.e., UrgoStart), at least 2 studies evaluating the intervention for diabetic foot ulcers^{47,51} and 1 study evaluating the intervention for venous leg ulcers¹⁹ did not have any potential conflict of interest.

Conclusions

We found 5 economic analyses that evaluated sucrose octasulfate–impregnated dressings for people with difficult-to-heal noninfected diabetic foot ulcers or difficult-to-heal noninfected venous leg ulcers, which were either directly or partially applicable to our research question. All studies found sucrose octasulfate–impregnated dressings to be dominant (less costly and more effective) or cost-saving compared with sucrose octasulfate–free dressings. Despite some common limitations, the consistency of these findings across all studies and perspectives, in addition to the robustness of results against a range of sensitivity analyses, may convey higher confidence in the cost-effectiveness results in favour of sucrose octasulfate–impregnated dressings in our populations of interest.

Primary Economic Evaluation

The published economic evaluations identified in our economic literature review provided sufficient evidence to approximate the cost-effectiveness of sucrose octasulfate-impregnated dressings compared with dressings that do not contain sucrose octasulfate for our populations of interest.

For the population with difficult-to-heal noninfected diabetic foot ulcers, results were consistent across all studies and perspectives and remained largely robust across a range of sensitivity analyses. Of these studies, the most recent cost-utility analysis was the study by Wen et al,⁴⁷ which used a Canadian perspective, sourced all costs from Canadian sources, and had minor limitations. Because their findings were consistent with all previous published economic evaluations and consistent across both public payer and societal perspectives from various other countries, we have high confidence in the cost-effectiveness results estimated by Wen et al⁴⁷ and their direct applicability to the perspective of the Ontario public payer.

For the population with difficult-to-heal noninfected venous leg ulcers, results were similarly consistent across all studies and perspectives and remained largely robust across various sensitivity analyses. However, no study adopted a Canadian perspective. A common limitation for all studies is that their key clinical parameters were derived from the 8-week treatment phase of the CHALLENGE trial,³⁹ which was not long enough to observe complete wound closure in both treatment arms. However, the outcome measures from this trial³⁹ were nonetheless used as a proxy for wound healing in the existing economic evaluations. Despite this limitation, we consider the use of these proxy outcomes as reasonable in the absence of follow-up data beyond 8 weeks for sucrose octasulfate-impregnated dressings versus noninteractive dressings that do not contain sucrose octasulfate. Because the CHALLENGE trial³⁹ remains the best available clinical evidence to date for this intervention for the population with venous leg ulcers, we do not expect that conducting a primary economic evaluation of our own will provide meaningful results and conclusions different to that of existing published economic evaluations.^{50,51}

For these reasons, we decided to forgo conducting a primary economic evaluation for sucrose octasulfate-impregnated dressings compared with dressings that do not contain sucrose octasulfate for the treatment of adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding sucrose octasulfate-impregnated dressings for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers?

Methods

Analytic Framework

We estimated the budget impact of publicly funding sucrose octasulfate-impregnated dressings using the cost difference between 2 scenarios: (1) current clinical practice without public funding for sucrose octasulfate-impregnated dressings (the current scenario), and (2) anticipated clinical practice with public funding for sucrose octasulfate-impregnated dressings (the new scenario). Figure 3 presents the model schematic.

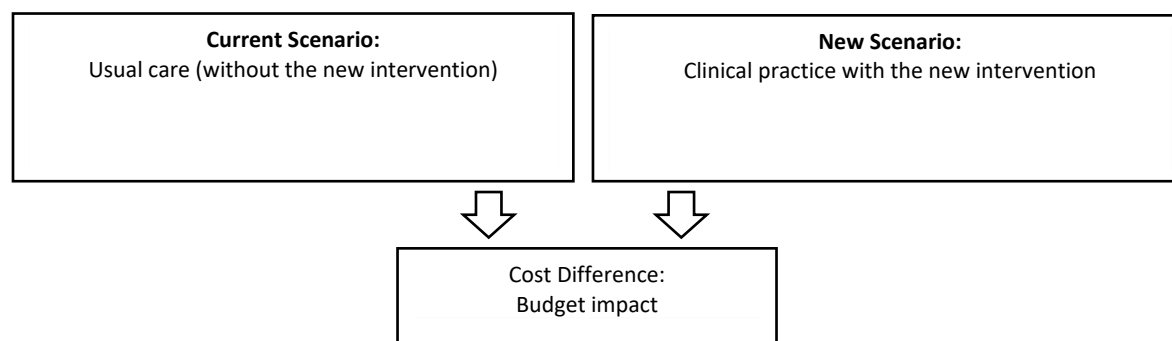


Figure 3: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. The current scenario would explore resource use and total costs without public funding for sucrose octasulfate-impregnated dressings. The new scenario would explore resource use and total costs with public funding for sucrose octasulfate-impregnated dressings. The budget impact would represent the difference in costs between the 2 scenarios.

Key Assumptions

Our main assumptions are as follows:

- The frequency of dressing changes for sucrose octasulfate-impregnated dressings and sucrose octasulfate-free dressings is 3 times per week. This assumption closely reflects both the dressing change protocol in the EXPLORER and CHALLENGE trials^{36,39} and what we anticipate would feasibly take place in the Home and Community Care Support Services setting should sucrose octasulfate-impregnated dressings be added to the wound dressing formulary (V. Winberg, MN, email communication, September 12, 2023; L. Orr, PhD, telephone communication, September 14, 2023).

Draft – do not cite. Report is a work in progress and could change following public consultation.

- All individuals with diabetic foot ulcers and venous leg ulcers present with a single ulcer, as bilateral or multiple ulcers on a single person are considered less common.^{54,55}
- All individuals are offered and comply with the standard best practices in the management of diabetic foot ulcers or venous leg ulcers (see Current Intervention Mix for further details). This assumption is for simplicity and may not reflect the current state in Ontario.
- Ulcers that are infected will receive treatment, after which they become noninfected. This assumption is for simplicity; we did not further distinguish between infected and noninfected difficult-to-heal wounds.

Populations of Interest

We estimated our populations of interest using published epidemiology data. Table 10 lists the input parameters we used to estimate our populations with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers.

We estimated our populations of interest based on the adult population (≥ 18 years old) in Ontario projected by the Ontario Ministry of Finance for 2022 to 2026.⁵⁶ For diabetic foot ulcers, we estimated our expected population of interest for each year using the following parameters derived from the literature:

- Prevalence of diabetes in Canada (8.9%)⁵⁷
- Prevalence of diabetic foot ulcers among adults (≥ 18 years old) with diabetes (1.7%)⁵
- Proportion of diabetic foot ulcers that are difficult to heal (28.5%) (calculated from Nube et al⁵⁸)

For venous leg ulcers, we estimated our expected population of interest for each year using the following parameters derived from the literature:

- Prevalence of venous leg ulcers in Ontario (0.9 per 1,000 population)⁸
- Proportion of venous leg ulcers that are difficult to heal (34.2%) (calculated from Rajhathy et al⁵⁹)

Table 10: Input Parameters for Estimating Populations of Interest

Input parameter	Value	Source
Adults (≥18 years old) in Ontario, 2022 (year 1), n	12,334,046	Calculated from Ministry of Finance ⁵⁶
Projected annual growth rate of adults (≥18 years old) in Ontario		
2023 (year 2)	1.04%	Calculated from Ministry of Finance ⁵⁶
2024 (year 3)	1.03%	Calculated from Ministry of Finance ⁵⁶
2025 (year 4)	1.02%	Calculated from Ministry of Finance ⁵⁶
2026 (year 5)	1.02%	Calculated from Ministry of Finance ⁵⁶
Prevalence of diabetes in Canada (general population), %	8.9%	PHAC, 2022 ⁵⁷
Prevalence of DFUs among adults (≥18 years old) with diabetes, %	1.7%	Aronson et al, 2021 ⁵
Proportion of DFUs that are difficult to heal, %	28.5% ^a	Calculated from Nube et al, 2016 ⁵⁸
Prevalence of VLUs	0.9 per 1,000 population ^b	Hopman et al, 2013 ⁸
Proportion of VLUs that are difficult to heal, %	34.2% ^c	Calculated from Rajhathy et al, 2020 ⁵⁹

Abbreviations: DFU, diabetic foot ulcer; PHAC, Public Health Agency of Canada; VLU, venous leg ulcer.

^aEstimate based on the average of the range of healing rates (66%–77%) of diabetic foot ulcers under standard care from large cohort studies.⁵⁸

^bBased on the average of prevalence rates ranging from 0.8 to 1 per 1,000 population.⁸

^cBased on findings that suggest that 65.8% of people with venous leg ulcers achieved complete wound closure by 6 months under standard care.⁵⁹

Our estimated annual volume of difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers in the adult population in Ontario is summarized in Table 11.

Table 11: Estimated Annual Volume of Difficult-to-Heal Noninfected^a Diabetic Foot Ulcers and Difficult-to-Heal Noninfected^a Venous Leg Ulcers

	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^b
Difficult-to-heal noninfected ^a DFUs in the adult (≥18 years old) population in Ontario	5,319	5,512	5,680	5,807	5,911	28,230
Difficult-to-heal noninfected ^a VLUs in the adult (≥18 years old) population in Ontario	3,796	3,935	4,055	4,145	4,219	20,151

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

^aWe assumed that ulcers that are infected will receive treatment, after which they would become noninfected.

^bResults may appear inexact due to rounding.

Current Intervention Mix

In the current scenario, wound dressing products are provided by some Ontario hospitals for inpatients, by long-term care facilities, or by the 14 Home and Community Care Support Services to patients who have been referred by primary care providers, nurse practitioners, or specialists in ambulatory settings (A. Shantz, MCIScWH, telephone communication, April 25, 2023).

Currently, there is no provincial formulary in Ontario for wound products. Instead, each of the hospitals, Home and Community Care Support Services, and facilities that provide wound care have their own wound care formularies. In general, dressings that are not on these formularies are not covered by the

provincial budget (A. Shantz, MClScWH, telephone communication, April 25, 2023). To our knowledge, sucrose octasulfate–impregnated dressings are not currently on any of the hospital or regional formularies for wound care in Ontario.

In this analysis, we considered diabetic foot ulcers and venous leg ulcers “difficult to heal” if they did not achieve normal healing, which is characterized as wound area reduction of 30% to 40% every 3 to 4 weeks.¹²

For the management of noninfected diabetic foot ulcers, the standard best practices include the following^{60,61}:

- Maintaining healthy lifestyle choices (e.g., proper nutrition, glycemic control, exercise, not smoking)
- Routine wound cleaning and debridement (100% conservative sharp debridement) and dressing changes with a first-line wound care dressing
- Use of pressure-relieving (offloading) devices (e.g., total contact casts, removable cast walkers)

For the management of noninfected venous leg ulcers, the standard best practices include the following^{60,62}:

- Routine calf muscle pump exercise and meticulous skin care (D. H. Keast, MD, written communication, September 3, 2023)
- Routine wound cleaning and debridement (100% conservative sharp debridement) and dressing changes with a first-line wound care dressing
- Use of compression therapy (i.e., compression bandages or wraps)

In the current scenario, we assumed that people with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers would continue to receive and comply with standard best practices in wound care, either using a first-line wound care dressing or switching to another dressing that does not contain sucrose octasulfate (sucrose octasulfate–free dressing), which may or may not be as clinically effective as sucrose octasulfate–impregnated dressings (there is a lack of published evidence).

Uptake of the New Intervention and New Intervention Mix

If publicly funded, we expect that the uptake of sucrose octasulfate–impregnated dressings will be 10% in year 1, and then gradually decrease by 1% each year to 6% in year 5. This assumption reflects the typical trend of a new wound dressing product introduced to wound dressing formularies in Ontario. This trend begins with more orders of the product in the first year because of the initial marketing and education, after which there is a gradual decline in orders (L. Orr, PhD, telephone communication, September 14, 2023).

However, our estimated uptake of sucrose octasulfate–impregnated dressings is associated with some uncertainty. This is because there is a wide range of wound dressings that patients with difficult-to-heal wounds can be switched to, based on health care provider discretion. The choice of dressing that a health care provider offers patients with difficult-to-heal wounds may depend on various factors,

including level of exudate in the wound, the type of medications the patient is taking, comorbidities, and skin contact allergies (V. Winberg, MN, telephone communication, April 6, 2023). The available evidence on the clinical effectiveness of wound dressings currently on wound care formularies varies widely, and there are limited head-to-head studies comparing them.

In the new intervention mix, we expect that sucrose octasulfate-impregnated dressings would be one type of wound dressing that health care providers can offer to patients whose wounds have not healed under standard care using a first-line wound dressing. We expect that in the new scenario, patients that have been switched from a first-line wound dressing to another wound dressing (either a sucrose octasulfate-impregnated dressing or a sucrose octasulfate-free dressing) may be switched again to yet another wound dressing if the wound continues to not heal.

Tables 12 and 13 summarize the estimated number of people with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers receiving standard care (using sucrose octasulfate-free dressings) and sucrose octasulfate-impregnated dressings in the current and new scenarios.

Table 12: Uptake of New Intervention and Standard Care in Ontario – Diabetic Foot Ulcers

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Standard care, n ^a	5,319	5,512	5,680	5,807	5,911	28,230
New scenario^b						
Uptake rate of new intervention, %	10	9	8	7	6	—
New intervention, n ^{a,b}	532	496	454	407	355	2,244
Standard care, n ^a	4,787	5,016	5,226	5,401	5,556	25,986

^aResults may appear inexact due to rounding.

^bThe volume of interventions was calculated from the total number multiplied by the uptake rate of the new intervention. For example, in the new scenario, the total volume in year 1 is 5,319 and the uptake rate of sucrose octasulfate-impregnated dressings is 10%, so the volume of sucrose octasulfate-impregnated dressings in year 1 is 532 (5,319 × 10%).

Table 13: Uptake of New Intervention and Standard Care in Ontario – Venous Leg Ulcers

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Standard care, n ^a	3,796	3,935	4,055	4,145	4,219	20,151
New scenario^b						
Uptake rate of new intervention, %	10	9	8	7	6	—
New intervention, n ^{a,b}	380	354	324	290	253	1,601
Standard care, n ^a	3,417	3,581	3,730	3,855	3,966	18,549

^aResults may appear inexact due to rounding.

^bThe volume of interventions was calculated from the total number multiplied by the uptake rate of the new intervention. For example, in the new scenario, the total volume in year 1 is 3,796 and the uptake rate of sucrose octasulfate-impregnated dressings is 10%, so the volume of sucrose octasulfate-impregnated dressings in year 1 is 380 (3,796 × 10%).

Resources and Costs

In our standalone budget impact analysis, we included the weekly cost of dressings (sucrose octasulfate-impregnated dressings and sucrose octasulfate-free dressings) and the weekly cost of standard best practices in the management of diabetic foot ulcers and venous leg ulcers (minus the cost of dressings). Table 14 summarizes the costs and other parameters used in our budget impact analysis.

We estimated the average duration of treatment and percentage of patients who achieved complete wound closure from clinical studies identified in the clinical evidence review (the EXPLORER trial³⁶ for difficult-to-heal noninfected diabetic foot ulcers and the CHALLENGE trial³⁹ for difficult-to-heal noninfected venous leg ulcers). Individuals with difficult-to-heal noninfected diabetic foot ulcers using sucrose octasulfate-impregnated dressings were assumed to receive these dressings 3 times per week for an average of 120 days, or 17 weeks.³⁶ Following this period, 48% of wounds were assumed to achieve complete wound closure.³⁶ The remaining proportion of unhealed wounds were assumed to be switched to sucrose octasulfate-free dressings and incur costs associated with diabetic foot ulcer management and sucrose octasulfate-free dressings for the remainder of the year. Individuals with difficult-to-heal noninfected diabetic foot ulcers using sucrose octasulfate-free dressings were assumed to receive these dressings 3 times per week for an average of 180 days, or 26 weeks.³⁶ Following this period, 30% of wounds were assumed to achieve complete wound closure.³⁶ The remaining proportion of unhealed wounds were assumed to continue accruing costs associated with diabetic foot ulcer management and sucrose octasulfate-free dressings for the remainder of the year.³⁶

Individuals with difficult-to-heal noninfected venous leg ulcers using sucrose octasulfate-impregnated dressings were assumed to receive these dressings 3 times per week for an average of 107.5 days, or 15 weeks.³⁹ This duration was estimated based on information from the CHALLENGE trial,³⁹ which reported that a wound area reduction of $\geq 40\%$ was observed in 65.6% of patients and the median time to reach a wound area reduction of $\geq 40\%$ was 43 days.³⁹ We made a simplifying assumption that these patients would likely achieve complete wound closure if they continue with the treatment and the healing rate is linear ($107.5 \text{ days} = 43 \text{ days}/40\%$). Following this period, the remaining proportion of unhealed wounds were assumed to be switched to sucrose octasulfate-free dressings and incur costs associated with venous leg ulcer management and sucrose octasulfate-free dressings for the remainder of the year.³⁹ Similarly, we derived that individuals with difficult-to-heal noninfected venous leg ulcers using sucrose octasulfate-free dressings would receive these dressings 3 times per week for an average of 157.5 days ($63 \text{ days}/40\%$), or 23 weeks. Following this period, 39.4% of wounds were assumed to achieve complete wound closure.³⁹ The remaining proportion of unhealed wounds were assumed to continue accruing costs associated with venous leg ulcer management and sucrose octasulfate-free dressings for the remainder of the year.

Although sucrose octasulfate-impregnated dressings are available in several formats and sizes, for simplicity, we used the unit cost of a small-sized dressing (\$10) that is most common for diabetic foot ulcers and the unit cost of a medium-sized dressing (\$20) that is most common for venous leg ulcers (Urgo Medical, email communication, September 1, 2023). Therefore, the weekly costs of sucrose octasulfate-impregnated dressings are \$30 (\$10 per application for 3 applications per week) and \$60 (\$20 per application for 3 applications per week) for difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers, respectively.

We derived the costs associated with the standard best practices in the management of diabetic foot ulcers and venous leg ulcers from a Canadian costing analysis of the various debridement methods used

for cleaning the wound beds of diabetic foot ulcers, venous leg ulcers, and pressure ulcers.⁶³ Because sucrose octasulfate–impregnated dressings would be largely applied in either a Home and Community Care Support Services community nursing clinic or home care setting, we assumed that our populations of interest would most likely be receiving weekly conservative sharp debridement (which can be performed by registered nurses) rather than other debridement methods, such as surgical or ultrasonic debridement, which can only be performed in an acute environment. In practice, mechanical debridement through saline irrigation may also be performed, but this is not typically the best standard of care (L. Orr, PhD, telephone communication, September 14, 2023). Based on this costing study, we calculated that the weekly cost associated with standard best practices in the management of diabetic foot ulcers and venous leg ulcers, minus dressing cost, was \$232 (inflated to 2023 CAD). This cost includes wound debridement performed by the health care provider, dressing changes once every 3 to 4 days, and treatments for complications, such as pain medications for 50% of patients and medications for 50% to 60% of patients who may experience an infection.⁶³

The cost of sucrose octasulfate–free dressings was derived from the same costing study, in which the dressing was a 10 cm × 10 cm dressing that was either a hydrogel dressing (50%) or a hydrocolloid dressing (50%).⁶³ Based on the assumption that dressing changes would occur 3 times per week, the weekly cost of sucrose octasulfate–free dressings was approximately \$9.56. Because the size of a 10 cm × 10 cm dressing suits most diabetic foot ulcers and venous leg ulcers⁶³ and owing to the relatively low cost of sucrose octasulfate–free dressings, we assumed the same cost of sucrose octasulfate–free dressings for both diabetic foot ulcers and venous leg ulcers.

Lastly, while pressure-relieving (i.e., offloading) devices and compression therapy (i.e., compression bandages or wraps) are part of standard best practices for the treatment of diabetic foot ulcers and venous leg ulcers, respectively, we did not account for these costs because they are unlikely to differ substantially between people using sucrose octasulfate–impregnated dressings or sucrose octasulfate–free dressings.

Table 14: Resource Use and Budget Impact Analysis Parameters

Variable	Value	Reference
SOS-impregnated dressings, size small (\$10 per dressing), weekly cost (3 applications per week)	\$30	Urgo Medical, email communication, September 1, 2023
SOS-impregnated dressings, size medium (\$20 per dressing), weekly cost (3 applications per week)	\$60	Urgo Medical, email communication, September 1, 2023
SOS-free dressings, weekly cost (3 applications per week)	\$9.56	Woo et al, 2015 ⁶³
DFU or VLU management, weekly cost	\$232	Woo et al, 2015 ⁶³
SOS-impregnated dressing outcomes for DFUs		
Proportion of DFUs achieving wound closure	48%	Edmonds et al, 2018 ³⁶ (EXPLORER trial)
Time required to achieve complete wound closure	17 wk (120 d)	Edmonds et al, 2018 ³⁶ (EXPLORER trial)
SOS-free dressing outcomes for DFUs		
Proportion of DFUs achieving wound closure	30%	Edmonds et al, 2018 ³⁶ (EXPLORER trial)
Time required to achieve complete wound closure	26 wk (180 d)	Edmonds et al, 2018 ³⁶ (EXPLORER trial)
SOS-impregnated dressing outcomes for VLUs		
Proportion of VLUs achieving wound closure ^a	65.6%	Assumption based on Meaume et al, 2012 ³⁹ (CHALLENGE trial)
Time required to achieve complete wound closure	15 wk (107.5 d)	Assumption based on Meaume et al, 2012 ³⁹ (CHALLENGE trial)
SOS-free dressing outcomes for VLUs		
Proportion of VLUs achieving wound closure ^a	39.4%	Assumption based on Meaume et al, 2012 ³⁹ (CHALLENGE trial)
Time required to achieve complete wound closure	23 wk (157.5 d)	Assumption based on Meaume et al, 2012 ³⁹ (CHALLENGE trial)

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

^aAssuming that patients who achieved $\geq 40\%$ wound area reduction by end of trial would continue healing and have wound closure later.

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

The scenarios examined in our sensitivity analyses were as follows:

- Scenario 1: Low population estimate for difficult-to-heal noninfected diabetic foot ulcers. In this scenario, we applied the low growth projections of the Ontario adult population over the next 5 years from the Ministry of Finance⁵⁶ and assumed that a lower proportion of diabetic foot ulcers would be difficult to heal (23%).⁵⁸

- Scenario 2: High population estimate for difficult-to-heal noninfected diabetic foot ulcers. In this scenario, we applied the high growth projections of the Ontario adult population over the next 5 years from the Ministry of Finance.⁵⁶ We assumed that diabetic foot ulcers would occur in a higher proportion of people with diabetes (2.5%)⁶⁴ and that a higher proportion of diabetic foot ulcers would be difficult to heal (34%).⁵⁸
- Scenario 3: Low uptake of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected diabetic foot ulcers, at 6% in year 1, 5% in year 2, and stable at 4% for the remaining years.
- Scenario 4: High uptake of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected diabetic foot ulcers, at 15% in year 1 and decreasing gradually by 1% each year to 11% in year 5.
- Scenario 5: Lower cost of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected diabetic foot ulcers, at 75% of the unit cost in the reference case.
- Scenario 6: Higher cost of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected diabetic foot ulcers, at 125% of the unit cost in the reference case.
- Scenario 7: Low population estimate for difficult-to-heal noninfected venous leg ulcers. In this scenario, we applied the low growth projections of the Ontario adult population over the next 5 years from the Ministry of Finance⁵⁶ and assumed that a lower proportion of venous leg ulcers would be difficult to heal (26%).⁶⁵
- Scenario 8: High population estimate for difficult-to-heal noninfected venous leg ulcers. In this scenario, we applied the high growth projections of the Ontario adult population over the next 5 years from the Ministry of Finance⁵⁶ and assumed a higher prevalence of venous leg ulcers (1.8 per 1,000 population).⁶⁶
- Scenario 9: Low uptake of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected venous leg ulcers, at 6% in year 1, 5% in year 2, and stable at 4% for the remaining years.
- Scenario 10: High uptake of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected venous leg ulcers, at 15% in year 1 and decreasing gradually by 1% each year to 11% in year 5.
- Scenario 11: Lower cost of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected venous leg ulcers, at 75% of the unit cost in the reference case.
- Scenario 12: Higher cost of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected venous leg ulcers, at 125% of the unit cost in the reference case.

Results

Reference Case

Tables 15 and 16 summarize the total costs associated with sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers, respectively, in the adult population in Ontario over the next 5 years.

For the population with difficult-to-heal noninfected diabetic foot ulcers, we estimated that the budget impact would be annual cost savings between \$0.93 million in year 1 and \$0.62 million in year 5, for total cost savings of \$3.91 million over 5 years.

Table 15: Budget Impact Analysis Results – Diabetic Foot Ulcers

Scenario	Budget impact, \$ million ^a					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Current scenario	54.61	56.60	58.32	59.62	60.69	289.84
SOS-free dressing costs	2.25	2.33	2.40	2.45	2.50	11.92
DFU management costs	52.36	54.27	55.92	57.17	58.19	277.91
New scenario	53.68	55.73	57.53	58.91	60.07	285.92
New intervention	4.53	4.23	3.87	3.47	3.02	19.12
SOS-impregnated dressing costs	0.27	0.25	0.23	0.21	0.18	1.14
SOS-free dressing costs	0.09	0.09	0.08	0.07	0.06	0.39
DFU management costs	4.17	3.89	3.56	3.19	2.78	17.59
Standard care	49.14	51.50	53.66	55.45	57.05	266.80
SOS-free dressing costs	2.02	2.12	2.21	2.28	2.35	10.98
DFU management costs	47.12	49.38	51.45	53.17	54.70	255.82
Budget impact ^{b,c}	-0.93	-0.86	-0.79	-0.71	-0.62	-3.91
SOS-impregnated dressing costs	0.27	0.25	0.23	0.21	0.18	1.14
SOS-free dressing costs	-0.13	-0.12	-0.11	-0.10	-0.09	-0.56
DFU management costs	-1.07	-0.99	-0.91	-0.81	-0.71	-4.50

Abbreviations: DFU, diabetic foot ulcer; SOS, sucrose octasulfate.

^aIn 2023 Canadian dollars.

^bNegative costs indicate savings.

^cResults may appear inexact due to rounding.

For the population with difficult-to-heal noninfected venous leg ulcers, we estimated that the budget impact would be annual cost savings between \$0.8 million in year 1 and \$0.53 million in year 5, for total cost savings of \$3.38 million over 5 years.

Table 16: Budget Impact Analysis Results – Venous Leg Ulcers

Scenario	Budget impact, \$ million ^a					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Current scenario	35.61	36.91	38.03	38.88	39.57	188.99
SOS-free dressing costs	1.46	1.52	1.56	1.60	1.63	7.78
VLU management costs	34.14	35.39	36.46	37.28	37.95	181.22
New scenario	34.81	36.16	37.35	38.27	39.04	185.62
New intervention	2.76	2.57	2.36	2.11	1.84	11.64
SOS-impregnated dressing costs	0.35	0.33	0.30	0.27	0.23	1.48
SOS-free dressing costs	0.05	0.04	0.04	0.03	0.03	0.19
VLU management costs	2.36	2.21	2.02	1.81	1.58	9.97
Standard care	32.05	33.58	34.99	36.16	37.20	173.97
SOS-free dressing costs	1.32	1.38	1.44	1.49	1.53	7.16
VLU management costs	30.73	32.20	33.55	34.67	35.67	166.82
Budget impact ^{b,c}	-0.80	-0.75	-0.68	-0.61	-0.53	-3.38
SOS-impregnated dressing costs	0.35	0.33	0.30	0.27	0.23	1.48
SOS-free dressing costs	-0.10	-0.09	-0.09	-0.08	-0.07	-0.43
VLU management costs	-1.05	-0.98	-0.90	-0.80	-0.70	-4.43

Abbreviations: SOS, sucrose octasulfate; VLU, venous leg ulcer.

^aIn 2023 Canadian dollars.

^bNegative costs indicate savings.

^cResults may appear inexact due to rounding.

Sensitivity Analyses

Tables 17 and 18 summarize the results of the scenario analyses conducted for the populations with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers, respectively. Compared with the reference case analysis, scenarios that considered a lower estimate of the populations of interest (scenarios 1 and 7), a lower uptake rate of sucrose octasulfate-impregnated dressings (scenarios 3 and 9), or a higher cost of sucrose octasulfate-impregnated dressings (scenarios 6 and 12) resulted in lower cost savings.

Conversely, scenarios that considered a higher estimate of the populations of interest (scenarios 2 and 8), a higher uptake rate of sucrose octasulfate-impregnated dressings (scenarios 4 and 10), and a lower cost of sucrose octasulfate-impregnated dressings (scenarios 5 and 11) resulted in higher cost savings.

Table 17: Budget Impact Analysis Results – Sensitivity Analyses: Diabetic Foot Ulcers

Scenario	Budget impact, \$ million ^{a,b,c}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Reference case	-0.93	-0.86	-0.79	-0.71	-0.62	-3.91
Scenario 1: Low estimate of population of interest	-0.75	-0.69	-0.62	-0.55	-0.48	-3.08
Scenario 2: High estimate of population of interest	-1.63	-1.54	-1.43	-1.29	-1.13	-7.03
Scenario 3: Low uptake of SOS-impregnated dressings	-0.56	-0.48	-0.40	-0.40	-0.41	-2.25
Scenario 4: High uptake of SOS-impregnated dressings	-1.39	-1.35	-1.29	-1.21	-1.13	-6.37
Scenario 5: Lower cost of SOS-impregnated dressings	-0.99	-0.93	-0.85	-0.76	-0.66	-4.20
Scenario 6: Higher cost of SOS-impregnated dressings	-0.86	-0.80	-0.73	-0.66	-0.57	-3.62

Abbreviation: SOS, sucrose octasulfate.

^aIn 2023 Canadian dollars.

^bNegative costs indicate savings.

^cResults may appear inexact due to rounding.

Table 18: Budget Impact Analysis Results – Sensitivity Analyses: Venous Leg Ulcers

Scenario	Budget impact, \$ million ^{a,b,c}					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total ^{b,c}
Reference case	-0.80	-0.75	-0.68	-0.61	-0.53	-3.38
Scenario 7: Low estimate of population of interest	-0.61	-0.56	-0.50	-0.45	-0.39	-2.51
Scenario 8: High estimate of population of interest	-1.60	-1.52	-1.41	-1.27	-1.11	-6.92
Scenario 9: Low uptake of SOS-impregnated dressings	-0.56	-0.41	-0.34	-0.35	-0.36	-2.02
Scenario 10: High uptake of SOS-impregnated dressings	-1.20	-1.16	-1.11	-1.05	-0.98	-5.50
Scenario 11: Lower cost of SOS-impregnated dressings	-0.89	-0.83	-0.76	-0.68	-0.59	-3.75
Scenario 12: Higher cost of SOS-impregnated dressings	-0.71	-0.67	-0.61	-0.55	-0.48	-3.01

Abbreviation: SOS, sucrose octasulfate.

^aIn 2023 Canadian dollars.

^bNegative costs indicate savings.

^cResults may appear inexact due to rounding.

Discussion

Sucrose octasulfate-impregnated dressings are associated with additional costs that may be partially offset by a reduction in overall resource use in the management of diabetic foot ulcers and venous leg ulcers due to a higher rate of healing and faster time to complete wound closure compared with sucrose octasulfate-free dressings. For instance, for difficult-to-heal noninfected diabetic foot ulcers, we estimated that the additional cost associated with sucrose octasulfate-impregnated dressings would be \$1.14 million for the next 5 years. However, there would be likely a reduction in costs related to the use of sucrose octasulfate-free dressings (savings of \$0.56 million) and diabetic foot ulcer management (savings of \$4.50 million).

Similarly, for difficult-to-heal noninfected venous leg ulcers, we estimated that the additional cost associated with sucrose octasulfate-impregnated dressings would be \$1.48 million for the next 5 years.

However, there would also likely be a reduction in costs related to the use of sucrose octasulfate–free dressings (savings of \$0.43 million) and venous leg ulcer management (savings of \$4.43 million). It is important to note that we extrapolated the key clinical outcomes used in our budget impact analysis for difficult-to-heal noninfected venous leg ulcers from the relative wound area reduction outcomes reported the CHALLENGE trial,³⁹ because it provided the best available evidence on sucrose octasulfate–impregnated dressings for the population with venous leg ulcers. Specifically, we used the percentage of wounds that achieved a wound area reduction of $\geq 40\%$ and the median time to reach this wound area reduction outcome as proxies for rate of healing and time to complete wound closure, respectively. Therefore, there is some uncertainty associated with the use of this parameter in our budget impact analysis. However, a wound area reduction of 30% may be considered predictive of progress toward closure.⁵⁹

Overall, there are per-person cost savings associated with sucrose octasulfate–impregnated dressings for both difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers. As such, higher uptake of sucrose octasulfate–impregnated dressings is expected to lead to greater budget impact savings for the province.

Equity Considerations

In Ontario, diabetes has been found to be more prevalent among certain ethnic and socioeconomic populations. As such, there may be a greater proportion of difficult-to-heal diabetic foot ulcers within these subpopulations compared with the general adult population in Ontario. For instance, compared with the prevalence of diabetes in the general population (8.9%),⁵⁷ the prevalence of diabetes was found to be higher in the South Asian, Indigenous, and Black populations in Ontario, at 15.3%,⁵⁷ 15.1%,⁶⁷ and 12.9%,⁵⁷ respectively. Additionally, the risk of diabetes has been shown to have an inverse association with income quintiles in a population-based study in Ontario.⁶⁸

Additionally, the frequency of sucrose octasulfate–impregnated dressing changes should occur once every 3 days.^{36,39} As such, in practice, individuals with difficult-to-heal diabetic foot ulcers who are using sucrose octasulfate–impregnated dressings, and who are not receiving wound care in their place of residence, would be required to visit a Home and Community Care Support Services community nursing clinic approximately 3 times per week (L. Orr, PhD, telephone communication, September 14, 2023). This travel may be a barrier to accessing sucrose octasulfate–impregnated dressings.

Strengths and Limitations

We derived estimates for our budget impact largely from published Canadian literature, where available.^{5,57,59,63} Additionally, we incorporated the best available evidence on the effectiveness outcomes of sucrose octasulfate–impregnated dressings compared with sucrose octasulfate–free dressings for both difficult-to-heal diabetic foot ulcers and difficult-to-heal venous leg ulcers.^{36,39} Our results, showing per-person cost savings and overall budget impact cost savings in both populations of interest, were consistent with previously published literature on the cost-effectiveness of sucrose octasulfate–impregnated dressings compared with sucrose octasulfate–free dressings.^{47,48,50,51,69} We further explored changes to the budget impact in scenarios that accounted for lower and higher population and uptake estimates. Finally, we validated our assumptions and estimates with clinical experts in the specialty area of wound care in Ontario.

There are some limitations associated with our analyses.

First, our analyses assumed that all individuals would be offered and would adhere with the standard best practices in the management of diabetic foot ulcers or venous leg ulcers. This is a simplifying and optimistic assumption that may not reflect the current state in Ontario. In practice, there are access barriers and challenges to patient adherence for the treatment and management of wounds (e.g., offloading, compression, regular appropriate debridement, regular dressing changes) over time. These factors affect both healing rates and time to complete wound closure with sucrose octasulfate-impregnated dressings, which in turn would affect the budget impact.

Second, we estimated the unit cost of a sucrose octasulfate-free dressing, assuming that it is 10 cm × 10 cm and is either a hydrogel dressing (50%) or a hydrocolloid dressing (50%), from a costing analysis on the costs of various wound debridement methods in Canada.⁶³ However, there are a wide range of sucrose octasulfate-free dressings available in the wound dressing formularies in Ontario, which further complicates the prediction of which sucrose octasulfate-free dressing a health care provider may choose. However, we do not expect the differences in cost between these dressings to be substantial. As such, our estimated cost of sucrose octasulfate-free dressings is a reasonable estimate that is generalizable to Ontario.

Third, in our budget impact of sucrose octasulfate-impregnated dressings for difficult-to-heal diabetic foot ulcers, we did not account for potential downstream savings that may be associated with a reduction of amputations. This is because the EXPLORER trial³⁶ found that the amputation rates were similar between the sucrose octasulfate-impregnated dressing and sucrose octasulfate-free dressing treatment groups (see Clinical Evidence Review), but no statistical analysis was reported. This may be due to the short treatment duration across studies. However, if the higher rate of healing and faster time to complete wound closure for difficult-to-heal diabetic foot ulcers treated with sucrose octasulfate-impregnated dressings can lead to a reduction in amputations, we can expect greater budget impact savings for the province.

Overall, further research is needed to determine longer-term outcomes of sucrose octasulfate-impregnated dressings, in particular for the population with difficult-to-heal venous leg ulcers.

Conclusions

We estimate that publicly funding sucrose octasulfate-impregnated dressings in Ontario for adults with difficult-to-heal noninfected diabetic foot ulcers would lead to annual cost savings between \$0.93 million in year 1 and \$0.62 million in year 5, for total cost savings of \$3.91 million over 5 years. We estimate that publicly funding sucrose octasulfate-impregnated dressings in Ontario for adults with difficult-to-heal noninfected venous leg ulcers would lead to annual cost savings between \$0.8 million in year 1 and \$0.53 million in year 5, for total cost savings of \$3.38 million over 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of adults who have lived experience of difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers, as well as the preferences and perceptions of these patients and their care partners.

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 care partners, 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).⁷⁰⁻⁷² 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 seek the engagement of people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we leveraged 4 previous health technology assessments to explore the perspectives and experiences of patients with diabetic foot ulcers and venous leg ulcers, as well as the perspectives and experiences of their care partners. From direct engagement with 54 participants across the previous health technology assessments, as well as consultation with clinical experts, we learned that patients are not always familiar with the medical terminology for different wound dressings. Hence, we made the decision to not conduct new patient engagement but instead leverage the extensive evidence from previous health technology assessments.

We leveraged the following 4 health technology assessments from Ontario Health:

1. Fibreglass Total Contact Casting, Removable Cast Walkers, and Irremovable Cast Walkers to Treat Diabetic Neuropathic Foot Ulcers (2017)⁷³
2. Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcers (2017)⁷⁴
3. Compression Stockings for the Prevention of Venous Leg Ulcer Recurrence (2019)¹⁵
4. Skin Substitutes for Adults With Diabetic Foot Ulcers and Venous Leg Ulcers (2021)⁶⁰

Direct Patient Engagement

Research Question

What are the underlying values, needs, impact, and preferences of adults with lived experience of difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers and their treatment options, including wound dressing?

Methods

Throughout the 4 health technology assessments, Ontario Health conducted direct engagement with 54 patients and care partners through qualitative interviews. Thirty-nine participants had lived experience of diabetic foot ulcers and 15 had lived experience of venous leg ulcers.

Interview questions sought to examine the lived experience of people with diabetic foot ulcers and venous leg ulcers and the impact of the condition on their daily activities and quality of life. Participants were asked about their decision-making and values related to treatment, their experiences with treatment, and the impact of their treatments. Participants were familiar with different treatment options; however, it is not clear if these participants had experience with sucrose octasulfate-impregnated dressings.

One health technology assessment included a survey to understand the impact of diabetic foot ulcers on patients' and family members' quality of life and experiences with other health interventions designed to manage diabetic foot ulcers.

No relevant equity considerations were identified in this health technology assessment; as a result, we did not carry out specific engagement initiatives for distinct populations.

Results

Day-to-Day Impact of Living With Diabetic Foot Ulcers and Venous Leg Ulcers

Participants commonly reported that living with diabetic foot ulcers and venous leg ulcers substantially affected their day-to-day lives, including the daily burden of managing their condition. Most participants also reported that they had other diseases that added to their difficulties in managing their health. They reported that ulcers affected their mobility, employment, social activities, and emotional and mental health.

Mobility

Most participants reported reduced functionality of their leg because of their diabetic foot ulcers or venous leg ulcers. Issues with mobility posed restrictions in their daily lives and led to difficulty walking, exercising, and driving. Some also reported that they had to adapt to certain lifestyle changes to manage their condition and often get support from family and friends.

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

Participants reported that after they developed diabetic foot ulcers, performing work duties was a challenge and often required leaves of absence from work, modified work duties, and scheduling treatments around work. Some had to quit their jobs altogether, leading to financial burden. Both patients and care partners were impacted by the change in the patient's ability to work.

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

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 spiraling down into the abyss pretty quick.

Social Activities

People's social lives were also impacted by their diabetic foot ulcers, including limited ability to conduct day-to-day activities. They felt confined to their house because of limited mobility, which led to decreased interactions with their friends and family. Those with severe ulcers found it straining to participate in social activities.

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.

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

Participants described the effect of their diabetic foot ulcers on their emotional and mental health. Many expressed frustration about not being able to leave their house, leading to depression. Care partners also described the emotional burden of caring for a person with a venous leg ulcer.

Draft – do not cite. Report is a work in progress and could change following public consultation.

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 4 years. I was bedridden.

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 reported an increased awareness and vigilance about the status of their foot health. They emphasized stress regarding recurrence of the ulcer and fear of potential amputation. This emotional burden was expressed by both patients and family members.

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

Having these things is incredibly terrifying for people. Most [people with diabetes] will not admit that they have a problem until it becomes evident to the family around them, and they're forced into care.

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 in trying to deal with all of this and deal with the inevitable fear of this potential amputation looming over her head.

Frustration with slow healing was commonly reported.

It is frustrating at times; you think everything's healed up, but they say the integrity of the skin takes 2 full years to reach its strong point. Once it heals, then the 2-year period starts, but then if you open up a wound, then that stops and ... then you've gotta start all over again.

Patients reported that this emotional burden necessitated support from their family members. Because of the limitations imposed by patients' diabetic foot ulcers, families often helped transport patients to and from treatment centres and advocated for treatment options. Patients acknowledged the difficulties that their care partners faced.

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.

Treatment for Diabetic Foot Ulcers and Venous Leg Ulcers

People reported being familiar with different treatment options, 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 encountered these treatment options in the

community at hospitals, wound care clinics, and chiropody clinics, and in the home through nursing visits arranged by Home and Community Care Support Services. Participants were not able to comment on the type of wound dressings because they were unfamiliar with the medical terminology surrounding various dressings.

It started 7 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 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 2 days. The wounds were stable, but they were not getting better.

People reported that the main goal of any therapy was the successful healing of their diabetic foot ulcers or venous leg ulcers. They had higher willingness to try alternative treatment methods if recommended by their health care provider or if alternative treatments show an increased rate of healing.

This home care and the ulcer had been going on for 2½ years approximately. And this was a last-ditch effort for me, so I was going to do whatever had to be done to get this over with.

Well, it [removable cast] 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.

A few years ago, we tried the air cast. It didn't work. We tried orthopedic shoes. They didn't work. We tried different types of shoes. They didn't work. We even tried a sort of cap, like a brace, that keeps the foot straight, that comes down the back of the calf and under the foot. These were all specifically made to my foot and my leg, and they didn't work. I would have problems, then the wound would open up, then I'd be back in the cast again.

People also had a high tolerance toward treatments that were inconvenient, burdensome, or uncomfortable, as long as their ulcer was healing. Treatments took a long time and healing was often slow and inconsistent.

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.

Preventing amputation was the main decision-making factor regarding different wound treatment options. Some participants reported having experience with amputation, including single-toe, multiple-toe, foot, and below-the-knee amputation. They also spoke about the physical and emotional impacts of amputation on their lives.

You've had a member of your body attached to you for 66 years, and all of [a] 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.

When people were asked about their preferences on an alternate treatment for ulcers (skin substitutes), they reported that they would be open to using it if it was recommended by a physician or likely to heal their ulcer.

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 the treatment would increase the chances of their wound healing and reduce infection and scarring before they would consider trying it as an option.

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?

Cost

People reported cost as a barrier to accessing treatment for diabetic foot ulcers and venous leg ulcers. Many participants did not have private insurance or did not qualify for disability insurance and had to pay out of pocket for their treatment. Because of the extreme consequences of untreated ulcers, such as amputation, people resorted to out-of-pocket payment regardless of the financial burden. 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 had their treatment costs covered by public funding and private health insurance.

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.

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.

Discussion

People with diabetic foot ulcers and venous leg ulcers discussed the effects of living with these wounds and their treatment journey. Participants spoke about the burden of their condition and its negative impact on 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. Cost was noted as a barrier to accessing treatment for their ulcers. Patients experienced various forms of treatment to heal their ulcers, but it is not clear if they had direct

experience with sucrose octasulfate-impregnated dressings, as they were not familiar with the medical terminology for different types of wound dressings. Hence, we can not draw specific conclusions about sucrose octasulfate-impregnated dressings from this preference and values evidence.

Preferences and Values Evidence Conclusions

Evidence from direct patient engagement suggests that people with diabetic foot ulcers and venous leg ulcers face substantial negative effects on their quality of life, especially related to mobility. Patients spoke about their challenges, including long and difficult care journeys, as well as trying different treatment options to heal their ulcers and avoid amputation. It was not clear if the participants had direct experience with sucrose octasulfate-impregnated dressings, so we could not draw specific conclusions from this preferences and values evidence about these dressings. However, patients reported being open to this form of treatment if it meant that their ulcers would heal. Barriers to sucrose octasulfate-impregnated dressings could include 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

For adults with difficult-to-heal noninfected neuroischemic diabetic foot ulcers, sucrose octasulfate–impregnated dressings likely increase the complete wound closure rate and likely result in a greater reduction in wound surface area when compared with dressings that do not contain sucrose octasulfate (GRADE: Moderate). Sucrose octasulfate–impregnated dressings also likely decrease time to complete wound closure and result in little to no difference in health-related quality of life for adults with difficult-to-heal noninfected neuroischemic diabetic foot ulcers (GRADE: Moderate). For adults with difficult-to-heal noninfected venous leg ulcers, sucrose octasulfate–impregnated dressings likely result in a greater reduction in wound surface area at 8 weeks (GRADE: Moderate) and likely improve health-related quality of life in the domains of pain/discomfort and anxiety/depression (GRADE: Moderate) when compared with dressings that do not contain sucrose octasulfate. The use of sucrose octasulfate–impregnated dressings for difficult-to-heal noninfected neuroischemic diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers can be considered safe.

The economic evidence showed that, compared with dressings that do not contain sucrose octasulfate, sucrose octasulfate–impregnated dressings are highly likely to be cost-effective for both difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers and would lead to cost savings due to faster and increased complete wound healing. We estimate that publicly funding sucrose octasulfate–impregnated dressings in Ontario for adults with difficult-to-heal noninfected diabetic foot ulcers and difficult-to-heal noninfected venous leg ulcers would lead to total cost savings of \$3.91 million and \$3.38 million, respectively, over the next 5 years.

Evidence from direct patient engagement suggests that people with diabetic foot ulcers and venous leg ulcers face substantial negative effects on their quality of life, especially related to mobility. It was not clear if the participants had direct experience with sucrose octasulfate–impregnated dressings, so we could not draw specific conclusions about patient preferences and values about these dressings. However, patients reported being open to this form of treatment if it meant that their ulcers would heal.

Abbreviations

ABPI: ankle-brachial pressure index

CI: confidence interval

CINAHL: Cumulative Index to Nursing & Allied Health Literature

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

IQR: interquartile range

IWGDF: International Working Group on the Diabetic Foot

MMP: matrix metalloproteinase

NHS EED: National Health Service Economic Evaluation Database

NICE: National Institute for Health and Care Excellence

NPWT: negative pressure wound therapy

OHTAC: Ontario Health Technology Assessment Committee

OR: odds ratio

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

QALY: quality-adjusted life-year

RoB 2: Cochrane risk-of-bias tool for randomized trials

SD: standard deviation

TBPI: toe-brachial pressure index

TLC-NOSF: Technology Lipido-Colloid Nano-Oligosaccharide Factor

VAS: visual analogue scale

Glossary

Adverse event: An adverse event is any noxious, pathological, or unintended change in a physical or metabolic function, revealed by signs or symptoms or a change in the results of laboratory tests, in any phase of a clinical study, whether or not the change is considered treatment related.⁷⁵ It may involve the exacerbation of a pre-existing condition, intercurrent diseases, an accident, a drug interaction, or a significant worsening of the disease.

Budget impact analysis: A budget impact analysis is an evaluation of the financial impact of the introduction of a technology or service on the capital and operating budgets of a government or agency.⁷⁵

Cost–benefit analysis: A cost–benefit analysis is an economic evaluation consisting of comparing various options, in which costs and outcomes are quantified in common monetary units.⁷⁵

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: A cost-effectiveness acceptability curve is a graph illustrating the probability that a given option is efficient on the basis of the value assigned to an additional quality-adjusted life-year.⁷⁵

Cost-effectiveness analysis: A cost-effectiveness analysis is an economic evaluation consisting of comparing various options, in which costs are measured in monetary units, then aggregated, and outcomes are expressed in natural (nonmonetary) units.⁷⁵

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost-minimization analysis: A cost-minimization analysis is an economic evaluation consisting of comparing the costs of various options presumed to produce equivalent outcomes and determining the least costly of those options.⁷⁵

Cost–utility analysis: A cost–utility analysis is an economic evaluation consisting of comparing various options, in which costs are measured in monetary units and outcomes are measured in utility units, usually in terms of utility to the patient (using quality-adjusted life-years, for example).⁷⁵ This is a form of cost-effectiveness analysis in which the effectiveness of an option is adjusted on the basis of quality of life.

Decision tree: A decision tree is a graphical representation of the possible options and outcomes, used in decision analysis.⁷⁵

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.

Discount rate: The interest rate used to determine the present value of future costs and benefits.⁷⁵

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

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 5 questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are 3 response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes 5 response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.⁷⁶ It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

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 difference between the cost of an option and the cost of another option with which it is compared.⁷⁵

Incremental cost-effectiveness ratio: The incremental cost-effectiveness ratio is the additional cost of the more expensive intervention compared with the less expensive intervention, divided by the difference between the effects of the interventions on the patients (the additional cost per quality-adjusted life-year, for example).⁷⁵

Markov model: A Markov model is a type of quantitative modelling that involves a specified set of mutually exclusive and exhaustive health states for which there are transitional probabilities of moving from one state to another, including the probability of remaining in the same state.⁷⁵ Typically, states have a uniform time period, and transitional probabilities remain constant over time.

Microsimulation model: In economic evaluations, a microsimulation model (e.g., an individual-level or patient-level model) is used to simulate the health outcomes for a heterogeneous group of patients (e.g., patients of different ages or with different sets of risk factors) after receiving a particular health

care intervention. The health outcomes and health events of each patient are modelled, and the outcomes of several patients are combined to estimate the average costs and benefits accrued by a group of patients. In contrast, a cohort model follows a homogeneous cohort of patients (e.g., patients of the same age or with the same set of risk factors) through the model and estimates the proportion of the cohort who will experience specific health events.

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.

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 unit of outcome of an intervention where gains (or losses) of years of life subsequent to this intervention are adjusted on the basis of the quality of life during those years.⁷⁵ This parameter can provide a common unit for comparing cost utility across different interventions and health problems.

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.

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: A sensitivity analysis is a means for evaluating the robustness of a mathematical model by testing a plausible range of estimates of key independent variables to determine whether such variations result in meaningful changes in the model's results.⁷⁵

Social capital: Social capital refers to the connections among people's social networks and the reciprocity and trust that arise from them. More social capital is generally seen as better than less, but some kinds are more societally productive (for example, bridging) and others are more valuable for individuals (for example, bonding). It is also important to note that the effects of social capital are not always positive. For example, some communities' social bonding can make them exclusionary, wealth concentrated, and restrictive of freedoms.

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).

Time horizon: In economic evaluations, the time horizon is the timeframe 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.

Uptake rate: In instances where 2 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.

Visual analogue scale (VAS): The visual analogue scale (VAS) is a direct method of measuring people's preferences for various health states. Respondents are first asked to rank a series of health states from least to most preferable. Then, they are asked to place the health states on a scale with intervals reflecting the differences in preference among the given health states. The scale ranges from 0 (worst imaginable health) to 100 (best imaginable health). The value of a respondent's preference for each health state is given by their placement of each health state on the scale.

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: June 30, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and NHS Economic Evaluation Database; and EBSCO CINAHL

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 27, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 25>, Ovid MEDLINE(R) ALL <1946 to June 29, 2023>

Search Strategy:

- 1 Diabetic Foot/ (33931)
- 2 Foot Ulcer/ (8772)
- 3 Diabetic Neuropathies/ (37528)
- 4 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath* or neuro path*)) or ((neuroisch?em* or neuro isch?em* or neuropath* or neuro path*) adj4 ulcer*).ti,ab,kf. (96591)
- 5 Leg Ulcer/ (23730)
- 6 ((leg* or lower extremit*) adj2 ulcer*).ti,ab,kf. (21121)
- 7 Varicose Ulcer/ (17745)
- 8 (((venous or varicos*) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).ti,ab,kf. (23483)
- 9 Venous Insufficiency/ (12712)
- 10 (((venous or vein) adj2 insufficienc*) or CVI).ti,ab,kf. (23961)
- 11 or/1-10 (193473)
- 12 Matrix Metalloproteinase Inhibitors/ (10306)
- 13 ((matrix metalloproteinas* or matrix metallo-proteinase* or matrix metalloproteas* or matrix metallo-proteas* or MMP*) adj4 (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*).ti,ab,kf. (50586)
- 14 exp Matrix Metalloproteinases/ and (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*).ti,ab,kf. (46721)
- 15 (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligo* saccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*).ti,ab,kf. (306)
- 16 (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS adj4 (impregnat* or dressing* or bandag*))).ti,ab,kf. (335)
- 17 polyhydrat* ionogen*.ti,ab,kf. (15)
- 18 (urgostart* or urgo start* or (urgo adj3 medical)).ti,ab,kf. (92)

- 19 or/12-18 (78323)
- 20 11 and 19 (768)
- 21 limit 20 to yr="2019 -Current" (299)
- 22 21 use cctr,coch,cleed (20)
- 23 Clinical Trials as Topic/ (335916)
- 24 controlled clinical trials as topic/ (18481)
- 25 exp Randomized Controlled Trials as Topic/ (470342)
- 26 controlled clinical trial.pt. (95350)
- 27 randomized controlled trial.pt. (595477)
- 28 Pragmatic Clinical Trial.pt. (2232)
- 29 Random Allocation/ (225648)
- 30 Single-Blind Method/ (107439)
- 31 Double-Blind Method/ (513644)
- 32 Placebos/ (395261)
- 33 trial.ti. (1091284)
- 34 (random* or sham or placebo* or RCT*1).ti,ab,kf. (5072544)
- 35 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (785790)
- 36 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (6318)
- 37 or/23-36 (6117200)
- 38 21 and 37 (79)
- 39 38 use medall (16)
- 40 (Systematic Reviews or Meta Analysis).pt. (183245)
- 41 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (999612)
- 42 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (734225)
- 43 (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. (684906)
- 44 (evidence adj2 (review* or overview* or synthes#s)).ti,ab,kf. (103532)
- 45 (review of reviews or overview of reviews).ti,ab,kf. (2574)
- 46 umbrella review*.ti,ab,kf. (3121)
- 47 GRADE Approach/ (3203)
- 48 ((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. (659990)
- 49 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebSCO* or scopus).ab. (769551)
- 50 cochrane.ti,ab,kf. (325910)
- 51 (meta regress* or metaregress*).ti,ab,kf. (33593)
- 52 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (40138)
- 53 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (77784)
- 54 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (67642)
- 55 or/40-54 (1900369)
- 56 21 and 55 (37)
- 57 56 use medall (11)

- 58 22 or 39 or 57 (44)
- 59 exp Animals/ not Humans/ (16351366)
- 60 58 not 59 (43)
- 61 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6413378)
- 62 60 not 61 (43)
- 63 limit 62 to english language [Limit not valid in CDSR; records were retained] (41)
- 64 diabetic foot/ (33931)
- 65 foot ulcer/ (8772)
- 66 diabetic neuropathy/ (44609)
- 67 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath* or neuro path*)) or ((neuroisch?em* or neuro isch?em* or neuropath* or neuro path*) adj4 ulcer*)).tw,kw,kf. (98922)
- 68 leg ulcer/ (23730)
- 69 ((leg* or lower extremit*) adj2 ulcer*).tw,kw,kf. (21397)
- 70 varicosis/ (22876)
- 71 leg varicosis/ (1784)
- 72 (((venous or varicos*) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).tw,kw,kf. (23638)
- 73 vein insufficiency/ (6672)
- 74 (((venous or vein) adj2 insufficienc*) or CVI).tw,kw,kf. (24134)
- 75 or/64-74 (205258)
- 76 matrix metalloproteinase inhibitor/ (10306)
- 77 ((matrix metalloproteinas* or matrix metallo-proteinase* or matrix metalloproteas* or matrix metallo-proteas* or MMP*) adj4 (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*)).tw,kw,kf,dv. (50698)
- 78 matrix metalloproteinase/ and (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*).tw,kw,kf,dv. (23605)
- 79 (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligo* saccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*).tw,kw,kf,dv. (309)
- 80 (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS adj4 (impregnat* or dressing* or bandag*))).tw,kw,kf,dv. (336)
- 81 polyhydrat* ionogen*.tw,kw,kf,dv. (17)
- 82 (urgostart* or urgo start* or (urgo adj3 medical)).tw,kw,kf,dv. (116)
- 83 or/76-82 (66279)
- 84 75 and 83 (779)
- 85 limit 84 to yr="2019 -Current" (297)
- 86 "clinical trial (topic)"/ (129497)
- 87 "controlled clinical trial (topic)"/ (14079)
- 88 "randomized controlled trial (topic)"/ (265048)
- 89 randomization/ (210517)
- 90 Single Blind Procedure/ (54581)
- 91 Double Blind Procedure/ (216899)
- 92 placebo/ (390516)
- 93 trial.ti. (1091284)
- 94 (random* or sham or placebo* or RCT*1).tw,kw,kf. (5135823)

- 95 ((singl* or doubl*) adj (blind* or dumm* or mask*).tw,kw,kf. (820575)
- 96 ((tripl* or trebl*) adj (blind* or dumm* or mask*).tw,kw,kf. (6959)
- 97 or/86-96 (5823745)
- 98 85 and 97 (80)
- 99 98 use emez (46)
- 100 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (970868)
- 101 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (986017)
- 102 ((systematic* or methodologic*) adj3 (review* or overview*).tw,kw,kf. (748284)
- 103 (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,kf. (698420)
- 104 (evidence adj2 (review* or overview* or synthes#s)).tw,kw,kf. (105877)
- 105 (review of reviews or overview of reviews).tw,kw,kf. (2790)
- 106 umbrella review*.tw,kw,kf. (3151)
- 107 ((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,kf. (669681)
- 108 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebSCO* or scopus).ab. (769551)
- 109 cochrane.tw,kw,kf. (329547)
- 110 (meta regress* or metaregress*).tw,kw,kf. (34574)
- 111 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*).tw,kw,kf. (41231)
- 112 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (77784)
- 113 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*).tw,kw,kf. (104120)
- 114 or/100-113 (1942627)
- 115 85 and 114 (42)
- 116 115 use emez (24)
- 117 99 or 116 (60)
- 118 (exp animal/ or nonhuman/) not exp human/ (11918806)
- 119 117 not 118 (57)
- 120 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11253762)
- 121 119 not 120 (42)
- 122 limit 121 to english language [Limit not valid in CDSR; records were retained] (40)
- 123 63 or 122 (81)
- 124 123 use medall (22)
- 125 123 use emez (40)
- 126 123 use cctr (19)
- 127 23 use coch (0)
- 128 123 use cleed (0)
- 129 remove duplicates from 123 (53)

CINAHL

#	Query	Results
S1	(MH "Diabetic Foot")	10,090
S2	(MH "Foot Ulcer")	1,605
S3	(MH "Diabetic Neuropathies+")	15,218
S4	TI ((diabet* N4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* N2 (foot or feet)) or (plantar N2 (ulcer* or neuropath* or neuro path*)) or ((neuroischem* or neuroischaem* or neuro ischem* or neuro ischaem* or neuropath* or neuro path* N4 ulcer*))	10,368
S5	AB ((diabet* N4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* N2 (foot or feet)) or (plantar N2 (ulcer* or neuropath* or neuro path*)) or ((neuroischem* or neuroischaem* or neuro ischem* or neuro ischaem* or neuropath* or neuro path* N4 ulcer*))	11,034
S6	(MH "Leg Ulcer")	4,033
S7	TI ((leg* or lower extremit*) N2 ulcer*)	2,814
S8	AB ((leg* or lower extremit*) N2 ulcer*)	3,208
S9	(MH "Venous Ulcer")	2,946
S10	TI (((venous or varicos*) N3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs)	2,057
S11	AB (((venous or varicos*) N3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs)	2,473
S12	(MH "Venous Insufficiency")	1,730
S13	TI (((venous or vein) N2 insufficienc*) or CVI)	532
S14	AB (((venous or vein) N2 insufficienc*) or CVI)	2,288
S15	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	30,423
S16	(MH "Matrix Metalloproteinases")	1,706
S17	TI (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*)	111,802
S18	AB (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*)	305,885
S19	S16 AND (S17 OR S18)	881

S20	TI ((matrix metalloproteinas* or matrix metallo-protein* or matrix metalloproteas* or matrix metallo-proteas* or MMP*) N4 (inhibit* or modul* or balanc* or dressing* or bandag* or impregnat*))	591
S21	AB ((matrix metalloproteinas* or matrix metallo-protein* or matrix metalloproteas* or matrix metallo-proteas* or MMP*) N4 (inhibit* or modul* or balanc* or dressing* or bandag* or impregnat*))	2,221
S22	TI (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligo* saccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*)	53
S23	AB (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligo* saccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*)	70
S24	TI (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS N4 (impregnat* or dressing* or bandag*)))	8
S25	AB (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS N4 (impregnat* or dressing* or bandag*)))	15
S26	TI polyhydrat* ionogen*	1
S27	AB polyhydrat* ionogen*	1
S28	TI (urgostart* or urgo start* or (urgo N3 medical))	6
S29	AB (urgostart* or urgo start* or (urgo N3 medical))	47
S30	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	3,067
S31	S15 AND S30	114
S32	(MH "Randomized Controlled Trials+")	137,477
S33	(PT "randomized controlled trial")	151,270
S34	(MH "Random Assignment")	79,255
S35	(MH "Single-Blind Studies")	15,943
S36	(MH "Double-Blind Studies")	54,197
S37	(MH "Placebos")	14,036
S38	TI trial	181,357
S39	(random* or sham or placebo* or RCT or RCTs)	542,596
S40	((singl* or doubl*) N1 (blind* or dumm* or mask*))	87,696
S41	((tripl* or trebl*) N1 (blind* or dumm* or mask*))	766

S42	S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41	605,029
S43	S31 AND S42	32
S44	(PT "Meta Analysis") or (PT "Systematic Review")	159,996
S45	(MH "Systematic Review") OR (MH "Meta Analysis")	153,512
S46	((systematic* or methodologic*) N3 (review* or overview*))	200,643
S47	(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*)))	127,020
S48	(evidence N2 (review* or overview* or synthes#s))	28,080
S49	((review or overview) N2 reviews)	9,121
S50	umbrella review*	694
S51	((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*)	127,675
S52	AB(medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebSCO* or scopus)	123,521
S53	cochrane	70,952
S54	(meta regress* or metaregress*)	5,151
S55	((integrative or collaborative or quantitative) N3 (review* or overview* or synthes*)) or (research N3 overview*)	13,489
S56	SO(cochrane or (health N2 technology assessment) or evidence report or systematic review*)	12,210
S57	((comparative N3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) N1 comparison*))	10,040
S58	S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57	356,632
S59	S31 AND S58	13
S60	S43 OR S59	41
S61	(MH "Animals+") not (MH "Animals+" and MH "Human")	95,577
S62	S60 NOT S61	41
S63	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,353,352

S64	S62 NOT S63	38
	S62 NOT S63	
S65	Limiters - English Language	36
	S62 NOT S63	
S66	Limiters - Published Date: 20190101-20241231; English Language	17

Economic Evidence Search

Search Date: July 5, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and NHS Economic Evaluation Database; and EBSCO CINAHL

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 27, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 26>, Ovid MEDLINE(R) ALL <1946 to July 03, 2023>

Search Strategy:

-
- 1 Diabetic Foot/ (33956)
 - 2 Foot Ulcer/ (8777)
 - 3 Diabetic Neuropathies/ (37547)
 - 4 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath* or neuro path*)) or ((neuroisch?em* or neuro isch?em* or neuropath* or neuro path*) adj4 ulcer*).ti,ab,kf. (96663)
 - 5 Leg Ulcer/ (23736)
 - 6 ((leg* or lower extremit*) adj2 ulcer*).ti,ab,kf. (21129)
 - 7 Varicose Ulcer/ (17757)
 - 8 (((venous or varicos*) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).ti,ab,kf. (23493)
 - 9 Venous Insufficiency/ (12719)
 - 10 (((venous or vein) adj2 insufficienc*) or CVI).ti,ab,kf. (23969)
 - 11 or/1-10 (193588)
 - 12 Matrix Metalloproteinase Inhibitors/ (10306)
 - 13 ((matrix metalloproteinas* or matrix metallo-proteinase* or matrix metalloproteas* or matrix metallo-proteas* or MMP*) adj4 (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*).ti,ab,kf. (50602)
 - 14 exp Matrix Metalloproteinases/ and (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*).ti,ab,kf. (46738)
 - 15 (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligo* saccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*).ti,ab,kf. (306)

- 16 (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS adj4 (impregnat* or dressing* or bandag*))).ti,ab,kf. (335)
- 17 polyhydrat* ionogen*.ti,ab,kf. (15)
- 18 (urgostart* or urgo start* or (urgo adj3 medical)).ti,ab,kf. (92)
- 19 or/12-18 (78352)
- 20 11 and 19 (768)
- 21 limit 20 to english language [Limit not valid in CDSR; records were retained] (724)
- 22 21 use coch,cleed (1)
- 23 economics/ (264506)
- 24 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1055948)
- 25 economics.fs. (470127)
- 26 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1280980)
- 27 exp "costs and cost analysis"/ (688674)
- 28 (cost or costs or costing or costly).ti. (334722)
- 29 cost effective*.ti,ab,kf. (453080)
- 30 (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* or increment*)).ab,kf. (312640)
- 31 models, economic/ (16032)
- 32 markov chains/ or monte carlo method/ (108140)
- 33 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (67613)
- 34 (markov or markow or monte carlo).ti,ab,kf. (180300)
- 35 quality-adjusted life years/ (56436)
- 36 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (112910)
- 37 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (195696)
- 38 or/23-37 (3387778)
- 39 21 and 38 (76)
- 40 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6416997)
- 41 39 not 40 (76)
- 42 41 use medall,ctr (32)
- 43 22 or 42 (33)
- 44 diabetic foot/ (33956)
- 45 foot ulcer/ (8777)
- 46 diabetic neuropathy/ (44628)
- 47 ((diabet* adj4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* adj2 (foot or feet)) or (plantar adj2 (ulcer* or neuropath* or neuro path*)) or ((neuroisch?em* or neuro isch?em* or neuropath* or neuro path*) adj4 ulcer*)).tw,kw,kf. (98993)
- 48 leg ulcer/ (23736)
- 49 ((leg* or lower extremi*) adj2 ulcer*).tw,kw,kf. (21405)
- 50 varicosis/ (22887)
- 51 leg varicosis/ (1781)
- 52 (((venous or varicos*) adj3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs).tw,kw,kf. (23648)
- 53 vein insufficiency/ (6674)
- 54 (((venous or vein) adj2 insufficienc*) or CVI).tw,kw,kf. (24142)

- 55 or/44-54 (205371)
- 56 matrix metalloproteinase inhibitor/ (10306)
- 57 ((matrix metalloproteinase* or matrix metallo-proteinase* or matrix metalloprotease* or matrix metallo-protease* or MMP*) adj4 (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*)).tw,kw,kf,dv. (50714)
- 58 matrix metalloproteinase/ and (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*).tw,kw,kf,dv. (23613)
- 59 (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligo* saccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*).tw,kw,kf,dv. (309)
- 60 (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS adj4 (impregnat* or dressing* or bandag*))).tw,kw,kf,dv. (336)
- 61 polyhydrat* ionogen*.tw,kw,kf,dv. (17)
- 62 (urgostart* or urgo start* or (urgo adj3 medical)).tw,kw,kf,dv. (116)
- 63 or/56-62 (66301)
- 64 55 and 63 (779)
- 65 limit 64 to english language [Limit not valid in CDSR; records were retained] (736)
- 66 Economics/ (264506)
- 67 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (147022)
- 68 Economic Aspect/ or exp Economic Evaluation/ (555100)
- 69 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1301280)
- 70 exp "Cost"/ (688674)
- 71 (cost or costs or costing or costly).ti. (334722)
- 72 cost effective*.tw,kw,kf. (461888)
- 73 (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* or increment*)).ab,kw,kf. (322262)
- 74 Monte Carlo Method/ (83969)
- 75 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (71009)
- 76 (markov or markow or monte carlo).tw,kw,kf. (183769)
- 77 Quality-Adjusted Life Years/ (56436)
- 78 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (116251)
- 79 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (216398)
- 80 or/66-79 (2907300)
- 81 65 and 80 (87)
- 82 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11259478)
- 83 81 not 82 (73)
- 84 83 use emez (33)
- 85 43 or 84 (66)
- 86 85 use medall (17)
- 87 85 use emez (33)
- 88 85 use cctr (15)
- 89 85 use coch (0)
- 90 85 use cleed (1)
- 91 remove duplicates from 85 (43)

CINAHL

#	Query	Results
S1	(MH "Diabetic Foot")	10,096
S2	(MH "Foot Ulcer")	1,608
S3	(MH "Diabetic Neuropathies+")	15,224
S4	TI ((diabet* N4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* N2 (foot or feet)) or (plantar N2 (ulcer* or neuropath* or neuro path*)) or ((neuroischem* or neuroischaem* or neuro ischem* or neuro ischaem* or neuropath* or neuro path*) N4 ulcer*))	10,371
S5	AB ((diabet* N4 (foot or feet or ulcer* or toe or toes or plantar* or neuropath* or neuro path* or neural* or wound*)) or DFU or DFUs or (ulcer* N2 (foot or feet)) or (plantar N2 (ulcer* or neuropath* or neuro path*)) or ((neuroischem* or neuroischaem* or neuro ischem* or neuro ischaem* or neuropath* or neuro path*) N4 ulcer*))	11,036
S6	(MH "Leg Ulcer")	4,039
S7	TI ((leg* or lower extremit*) N2 ulcer*)	2,814
S8	AB ((leg* or lower extremit*) N2 ulcer*)	3,208
S9	(MH "Venous Ulcer")	2,947
S10	TI (((venous or varicos*) N3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs)	2,057
S11	AB (((venous or varicos*) N3 ulcer*) or (venous adj disease*) or VLU or VLUs or CVLU or CVLUs or CVU or CVUs)	2,473
S12	(MH "Venous Insufficiency")	1,732
S13	TI (((venous or vein) N2 insufficienc*) or CVI)	534
S14	AB (((venous or vein) N2 insufficienc*) or CVI)	2,296
S15	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	30,444
S16	(MH "Matrix Metalloproteinases")	1,706
S17	TI (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*)	111,881
S18	AB (inhibit* or modulat* or balanc* or dressing* or bandag* or impregnat*)	306,071
S19	S16 AND (S17 OR S18)	881

S20	TI ((matrix metalloproteinases* or matrix metallo-proteinas* or matrix metalloproteases* or matrix metallo-proteases* or MMP*) N4 (inhibit* or modulate* or balance* or dressing* or bandage* or impregnate*))	591
S21	AB ((matrix metalloproteinases* or matrix metallo-proteinas* or matrix metalloproteases* or matrix metallo-proteases* or MMP*) N4 (inhibit* or modulate* or balance* or dressing* or bandage* or impregnate*))	2,223
S22	TI (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligosaccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*)	53
S23	AB (nano* oligosaccharide* factor* or nanooligosaccharide* factor* or nano* oligosaccharide* factor* or NOSF* or TLC NOSF* or TLCNOSF* or lipido colloid* or lipid colloid* or lipidocolloid*)	70
S24	TI (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS N4 (impregnate* or dressing* or bandage*)))	8
S25	AB (sucrose octasulfate* or sucrose octa sulfate* or sucrose octasulphate* or (SOS N4 (impregnate* or dressing* or bandage*)))	15
S26	TI polyhydrate* ionogen*	1
S27	AB polyhydrate* ionogen*	1
S28	TI (urgostart* or urgo start* or (urgo N3 medical))	6
S29	AB (urgostart* or urgo start* or (urgo N3 medical))	47
S30	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	3,069
S31	S15 AND S30	114
S32	(MH "Economics")	14,217
S33	(MH "Economic Aspects of Illness")	11,085
S34	(MH "Economic Value of Life")	667
S35	MH "Economics, Dental"	145
S36	MH "Economics, Pharmaceutical"	2,369
S37	MW "ec"	191,770
S38	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmaco-economic* or pharmaco-economic*)	343,147
S39	(MH "Costs and Cost Analysis+")	133,228
S40	TI cost*	62,423
S41	(cost effective*)	51,201

Draft – do not cite. Report is a work in progress and could change following public consultation.

S42	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*))	40,276
S43	(decision N1 (tree* or analy* or model*))	11,674
S44	(markov or markow or monte carlo)	7,799
S45	(MH "Quality-Adjusted Life Years")	6,009
S46	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	15,264
S47	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analysis or sensitivity analyses)	25,404
S48	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	473,948
S49	S31 AND S48	21
S50	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,353,817
S51	S49 NOT S50	18
S52	S49 NOT S50 Limiters - English Language	17

Grey Literature Search

Performed on: July 5–13, 2023

Websites searched: Alberta Health Evidence Reviews, 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), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Université de Québec-Université Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services, Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used: sucrose octasulfate, urgostart, matrix metalloproteinases, matrix, MMP, technology lipido-colloid nano-oligosacchride factor, TLC-NOSF, nano oligosacchride, lipido colloid, modulating matrix, wound inhibitor, wound balancing, dressing, bandage, diabetic foot ulcer, venous leg ulcer, octasulfate de sucrose, lipido-colloïde, modulatrice matrice, pied diabétique, ulcère veineux

Clinical results (included in PRISMA): 2

Economic results (included in PRISMA): 3

Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 3

Ongoing clinical trials: 3

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias^a Among Randomized Controlled Trials for the Comparison of Sucrose Octasulfate–Impregnated Dressing and Lipido-Colloid Dressing in Patients With Diabetic Foot Ulcers (EXPLORER Trial)

Author, year	Bias due to randomization process	Bias due to deviation from intended intervention	Bias due to missing outcome data	Bias due to measurement of the outcome	Bias due to selection of the reported results	Overall risk of bias
Edmonds et al, 2018 ³⁶	No	No	No	No	No	Low

Note: Possible risk-of-bias levels: low, high, some concerns.

^aRisk of bias assessed using RoB 2.³⁴

Table A2: Risk of Bias^a Among Randomized Controlled Trials for the Comparison of Sucrose Octasulfate–Impregnated Dressing and Lipido-Colloid Dressing in Patients With Venous Leg Ulcers (CHALLENGE Trial)

Author, year	Bias due to randomization process	Bias due to deviation from intended intervention	Bias due to missing outcome data	Bias due to measurement of the outcome	Bias due to selection of the reported results	Overall risk of bias
Meaume et al, 2012 ³⁹	No	No	No	No	No	Low

Note: Possible risk-of-bias levels: low, high, some concerns.

^aRisk of bias assessed using RoB 2.³⁴

Table A3: Risk of Bias^a Among Randomized Controlled Trials for the Comparison of Sucrose Octasulfate–Impregnated Dressing and Oxidized Regenerated Cellulose and Collagen Dressing in Patients With Venous Leg Ulcers

Author, year	Bias due to randomization process	Bias due to deviation from intended intervention	Bias due to missing outcome data	Bias due to measurement of the outcome	Bias due to selection of the reported results	Overall risk of bias
Schmutz et al, 2008 ⁴⁰	Some concerns ^b	Some concerns ^c	No	No	No	Some concerns

Note: Possible risk-of-bias levels: low, high, some concerns.

^aRisk of bias assessed using RoB 2.³⁴

^bNo information about randomization process.

^cOpen randomized trial (patients and health care providers were not blinded to the allocated treatment).

Table A4: GRADE Evidence Profile for the Comparison of Sucrose Octasulfate–Impregnated Dressing and Lipido-Colloid Dressing in Patients With Diabetic Foot Ulcers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Complete wound closure							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Time to complete wound closure							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Absolute wound area reduction							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Relative wound area reduction							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Amputation due to diabetic foot ulcer							
1 (RCT)	No serious limitations	Serious limitation (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Health-related quality of life							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Adverse events							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

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

^aVariation in point estimates due to between-study differences cannot be determined when only 1 study is available.

Table A5: GRADE Evidence Profile for the Comparison of Sucrose Octasulfate–Impregnated Dressing and Lipido-Colloid Dressing in Patients With Venous Leg Ulcers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Complete wound closure							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	Serious limitations (-1) ^b	No serious limitations	Undetected	None	⊕⊕ Low
Time to reach wound surface area reduction >40%							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	Serious limitations (-1) ^c	No serious limitations	Undetected	None	⊕⊕ Low
Absolute wound area reduction							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Relative wound area reduction							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Health-related quality of life							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Adverse events							
1 (RCT)	No serious limitations	Serious limitations (-1) ^a	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

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

^aVariation in point estimates due to between-study differences cannot be determined when only 1 study is available.

^bDue to short duration of studies that is not sufficient to show a difference between groups for complete wound closure.

^cDue to selection of an arbitrary cut-off threshold.

Table A6: GRADE Evidence Profile for the Comparison of Sucrose Octasulfate–Impregnated Dressing and Oxidized Regenerated Cellulose and Collagen Dressing in Patients With Venous Leg Ulcers

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Complete wound closure							
1 (RCT)	Serious limitations (-1) ^a	Serious limitations (-1) ^b	Serious limitations (-1) ^c	No serious limitations	Undetected	None	⊕ Very low
Time to reach wound surface area reduction >40%							
1 (RCT)	Serious limitations (-1) ^a	Serious limitations (-1) ^b	Serious limitations (-1) ^d	No serious limitations	Undetected	None	⊕ Very low
Absolute wound area reduction							
1 (RCT)	Serious limitations (-1) ^a	Serious limitations (-1) ^b	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Relative wound area reduction							
1 (RCT)	Serious limitations (-1) ^a	Serious limitations (-1) ^b	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Adverse events							
1 (RCT)	Serious limitations (-1) ^a	No serious limitations (-1) ^b	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Note: Time to complete wound closure and health-related quality of life were not reported.

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

^aDue to some concerns in risk of bias.

^bVariation in point estimates due to between-study differences cannot be determined when only 1 study is available.

^cDue to short duration of study that is not sufficient to show a difference between groups in complete wound closure.

^dDue to selection of an arbitrary cut-off threshold.

Appendix 3: 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
Ramachandran V, Mohanasundaram T, Karunakaran D, Gunasekaran M, Tiwari R. Physiological and pathophysiological aspects of diabetic foot ulcer and its treatment strategies. <i>Curr Diabetes Rev.</i> 2023;19(8):e031122210617.	Not a systematic review
Dissemond J, Augustin M, Dietlein M, Faust U, Keuthage W, Lobmann R, et al. Efficacy of MMP-inhibiting wound dressings in the treatment of chronic wounds: a systematic review. <i>J Wound Care.</i> 2020;29(2):102-18.	Systematic review of MMP-inhibiting wound dressings
Lobmann R, Grunerbel A, Lawall H, Ludemann C, Morbach S, Tigges W, et al. Impact of wound duration on diabetic foot ulcer healing: evaluation of a new sucrose octasulfate wound dressing. <i>J Wound Care.</i> 2020;29(10):543-51.	Economic analysis
Nair H, Venkateshwaran N, Seetharaman SS, Deng W, Uthapaisanwong A, Galea E. Benefits of sucrose octasulfate (TLC-NOSF) dressings in the treatment of chronic wounds: a systematic review. <i>J Wound Care.</i> 2021;30(Suppl 4):S42-S52.	Included all study designs
Meaume S, Edmonds M, Lobman R, Lázaro-Martínez JL, Martini J, Piaggese A, et al. Sucrose octasulfate dressing versus neutral dressing in patients with diabetic foot ulcer: results of a prospective, European, randomised, double-blind, controlled trial ('Explorer'). <i>Journal of the Dermatology Nurses' Association.</i> 2019;12(2):6.	Conference abstract
Rayman G, Edmonds M, Lobmann R, Lázaro-Martínez JL, Martini J, Petit J-M, et al. The efficacy of sucrose-octasulphate dressing in neuro-ischaemic DFU considering factors influencing wound closure rate: a post-hoc analysis of the Explorer RCT. <i>Diabetologia.</i> 2018;61:S480-S1.	Conference abstract
Alberto P. Sucrose octasulfate dressing* versus neutral dressing in patients with diabetic foot ulcer: results of a prospective, European, randomised, double-blind, controlled trial ('Explorer'). <i>J Wound Care.</i> 2020;29(Suppl 7B):157.	Conference abstract

Appendix 4: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A7: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Sucrose Octasulfate–Impregnated Dressings

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 judgement ^a
Wen et al, 2021, ⁴⁷ Canada	Yes	Yes	Yes	Yes; Canadian public payer	Yes	Yes; 1.5%	Yes	Partially; costs of minor/major amputations were not differentiated	Directly applicable
Maunoury et al, 2021, ⁴⁸ France	Yes	Yes	Partially; French public health care system	Yes; French societal perspective	Yes	Yes; 2.5%	Yes	Partially; disaggregated costs are not shown; minor/major amputations were not differentiated	Partially applicable
Lobmann et al, 2019, ⁴⁹ Germany	Yes	Yes	Partially; German public health system	Yes; German public payer	No; QALYs were not included	Unclear; discount rate was not reported	No	Partially; disaggregated costs are not shown; minor/major amputations were not differentiated	Partially applicable
NICE, 2019, ¹⁹ UK, DFU model	Yes	Yes	Partially; UK public health system	Yes; UK public payer	No; QALYs were not included	No; time horizon was within 1 y	No	Yes	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 judgement ^a
NICE, 2019, ¹⁹ UK, VLU model	Partially; study population was patients with leg ulcers, which includes both venous and mixed etiology	Yes	Partially; UK public health system	Yes; UK public payer	No; QALYs were not included	No; time horizon was within 1 y	No	Yes	Partially applicable
Augustin et al, 2016, ⁵⁰ Germany	Partially; study population was patients with vascular leg ulcers, which includes both venous and mixed etiology	Yes	Partially; German public health system	Yes; German public payer	No; QALYs were not included	NA	No	Partially; inpatient and adverse event costs were not fully disaggregated	Partially applicable

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

Abbreviations: DFU, diabetic foot ulcer; QALY, quality-adjusted life-year; VLU, venous leg ulcer.

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

Table A8: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Sucrose Octasulfate–Impregnated Dressings

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 judgement ^b
Wen et al, 2022, ⁴⁷ Canada	Yes	Yes	Yes	Yes	Yes	No; cost of conventional dressings was not included in analysis; did not differentiate between minor and major amputations	Yes	Yes	Yes	Yes	No	Minor limitations
Maunoury et al, 2021, ⁴⁸ France	Yes	Yes	Yes	Yes	Yes	No; did not differentiate between minor and major amputation costs	Yes	Yes	Yes	Yes	Yes; this study was funded by Urgo Medical and provided salaries to authors	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 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 judgement ^b
Lobmann et al, 2019, ⁴⁹ Germany	Yes	Yes	No; QALYs were not included	Unclear; transition probabilities were extrapolated from outcomes in the 20-wk timeframe in the EXPLORER trial ³⁶ to 100 wk, but method of extrapolation not described in detail	Yes	No; did not differentiate between minor and major amputation costs	Yes	Yes	Yes	Partially; only one-way DSA was conducted; PSA was not conducted	Yes; this study was supported by Urgo GmbH, and some authors received consultation fees for this work	Potentially serious limitations
NICE, 2019, ¹⁹ UK, DFU model	Yes	Yes	No; QALYs were not included	Yes	Yes	Yes	Yes	Yes	No; incremental effects are not reported; final calibration of model results not sufficiently described	Yes	No	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 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 judgement ^b
NICE, 2019, ¹⁹ UK, VLU model	Yes	Yes	No; QALYs were not included	Yes	Yes	Yes	Yes	Yes	No; incremental effects are not reported; final calibration of model results not sufficiently described	Yes	No	Minor limitations
Augustin et al, 2016, ⁵⁰ Germany	Yes	No; this study considered only an 8-wk time horizon, which may not be long enough to assess long-term prognosis of healing	No; QALYs were not included	Yes	Yes	Yes	Yes	Yes	Yes	Partially; only one-way DSA was conducted; PSA was not conducted	Yes; this study was supported by Urgo GmbH, and some authors received consultation fees for this work	Potentially serious limitations

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

Abbreviations: DFU, diabetic foot ulcer; DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; VLU, venous leg ulcer.

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

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

References

- (1) Monteiro-Soares M, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, et al. Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). *Diabetes Metab Res Rev.* 2020;36 Suppl 1:e3273.
- (2) Hinchliffe RJ, Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, et al. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev.* 2020;36 Suppl 1:e3276.
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We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province’s health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

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Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

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ISSN 1915-7398 (online)
ISBN TBD (PDF)

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