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

Presentation to OntWIG | 6 April 2021

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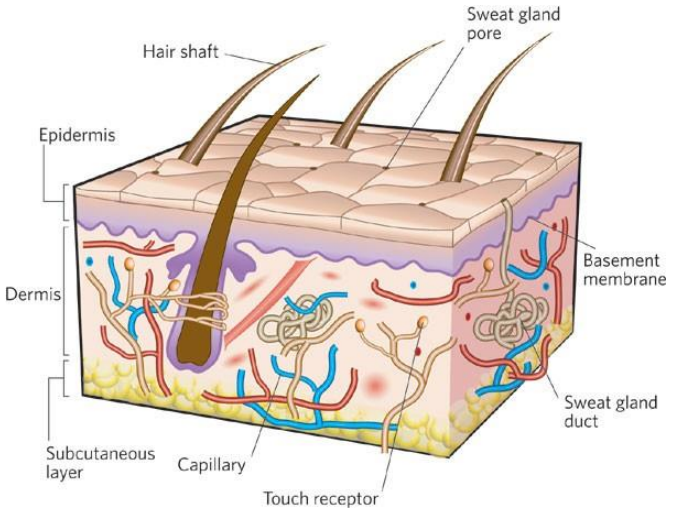
Background: Description of Technology

- Skin substitutes are a group of biologic, synthetic, or biosynthetic materials that provide temporary or permanent coverage of open skin wounds
  - The aim of skin substitutes is to replicate the properties of the normal skin
- There are several classifications
  - Cellular or acellular; autologous or allogeneic; single layer, bi-layer or tri-layer; natural or synthetic or a hybrid of both; temporary or permanent or semi-permanent
  - For ease of categorization we chose the layering classification

Background



Layering classification types

- Dermal substitutes
  - Bio-matrices that fulfil the functions of the cutaneous dermal layer. They act as matrices or scaffolds and promote new tissue growth and enhance wound healing, with enhanced pliability and a more favourable scar
- Epidermal substitutes
  - Made of cultured autologous keratinocytes, propagated to result in some layers representing epidermis
- Multi-layer substitutes
  - Bi-layer: comprised of two layers, including keratinocytes (or a removable silicone epidermal layer) on fibroblast-containing dermal substitutes
  - Tri-layer: Bi-layer plus a scaffold added to hypodermis

Regulatory Status

- At least eight brands have received Health Canada approval

Brand	Manufacturer	Class
Alloderm	LifeCell	Dermal
EpiFix	MiMedx	Dermal
Nanoderm	Axcelon	Dermal
OASIS	Healthpoint	Dermal
Biobrane	UDL Labs	Multilayer
Integra FM	Integra Life	Multilayer
Integra DRT	Integra Life	Multilayer
PriMatrix	Integra Life	Dermal

Use of Technology Nationally and Internationally

- Canada
  - Not publicly funded in Ontario. Patients must pay out of pocket.
  - Publicly funded in Manitoba (80% coverage for any skin substitute)
  - Funding status for other Canadian provinces and territories is unknown
- United Kingdom
  - NICE guidelines (2015) recommends to consider dermal or skin substitutes when treating difficult-to-heal DFU
- United States
  - Medicare covers several skin substitutes for DFU and VLU that fail to respond to standard care treatments

Clinical Evidence

Research Question

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

Methods

P Adults with DFUs or VLUs

I Skin substitutes as an adjunct to standard of care

C Any standard of care that includes conventional dressings

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

- We searched for studies published from database inception to Nov 26, 2019
- Types of studies included
  - English-language full-text publications
  - Systematic reviews, meta-analyses, health technology assessments, randomized controlled trials

Commonly Reported Exclusion Criteria In Eligible Studies

Diabetic Foot Ulcers	Venous Leg Ulcers
Non neuropathic DFU	VLU penetrating to muscle or bone
Ulcer infections	Ulcer infections
History of cancer	Poorly controlled diabetes
Pregnant or lactating women	Active Charcot's disease
Receiving oral or parenteral corticosteroids	Necrosis
Ulcer area ≤ 1 cm2	Arterial disease
Autoimmune diseases	Ulcer area > 25 cm^2
Coagulation disorders	Severe peripheral vascular disease
Poorly controlled diabetes	
Smokers	

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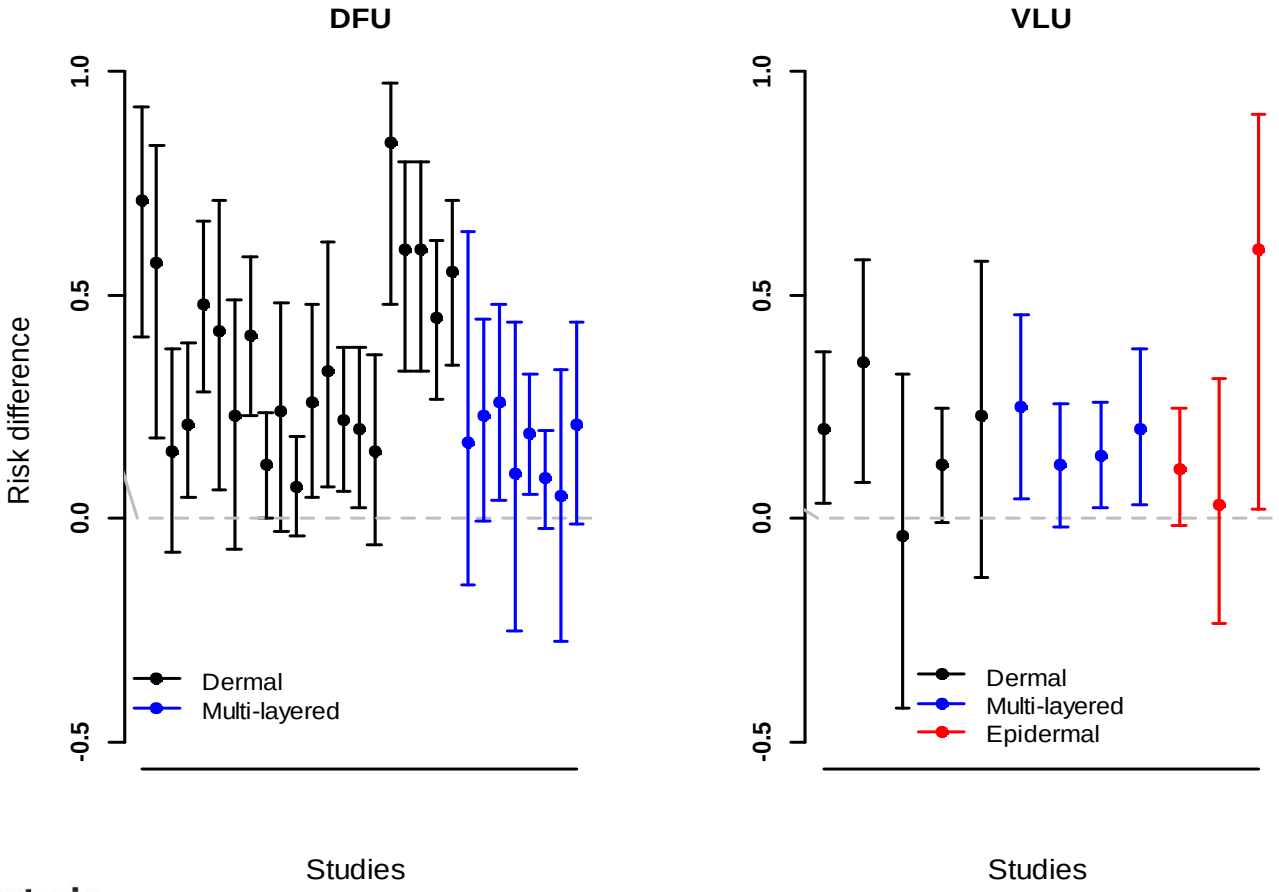
Results

- We identified 1,294 citations
- There was no suitable HTAs or SRs to use or build upon
- 41 RCTs met eligibility criteria
  - 26 evaluated dermal substitutes, 12 evaluated multi-layered substitutes, and three focused on epidermal substitutes
- We did not conduct a meta-analysis due to heterogeneity
  - Types of dressings in the standard care varied across studies
  - No consistency in the definition of “difficult-to-heal”
  - Duration of follow-up varied across studies

Results: Complete Wound Healing

By Class of Skin Substitutes



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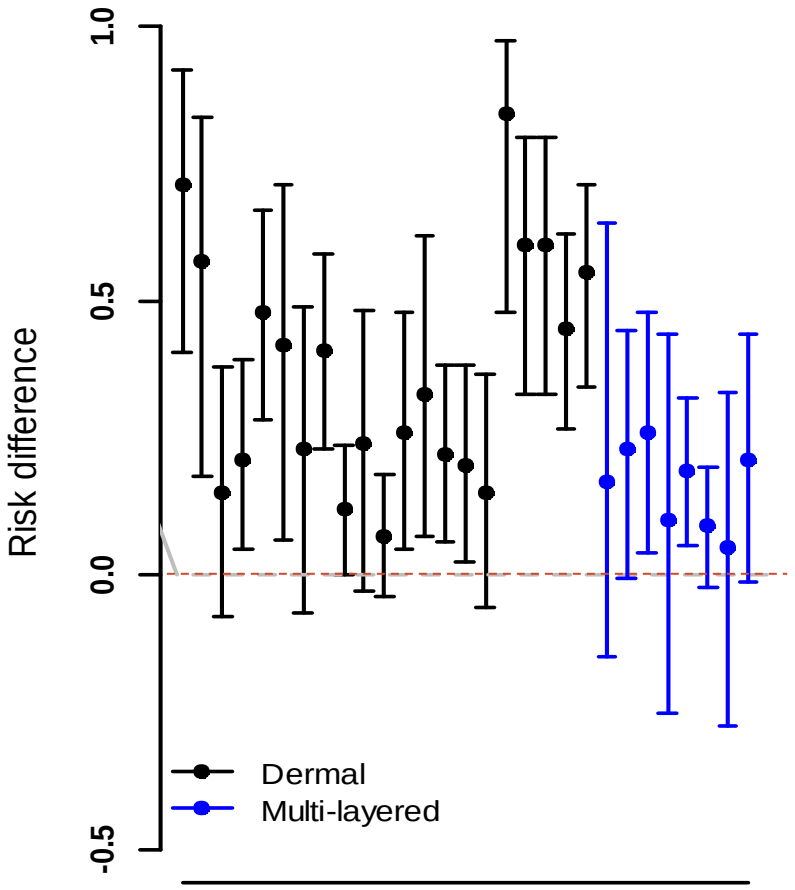
Results: Complete Wound Healing

By Class of Skin Substitutes

Diabetic Foot Ulcers



Dermal substitutes

- Most studies demonstrated complete healing for adults with diabetic foot ulcers.
- The GRADE rating of our certainty in the evidence for this outcome was **high**.

Multi-layer substitutes

- Evidence was clear in two of seven studies.
- All point estimates from the other five studies favoured multi-layered substitutes, but the confidence intervals were too wide.
- As a result, we downgraded the GRADE rating of our certainty in the evidence for this outcome to **moderate** because of imprecision.

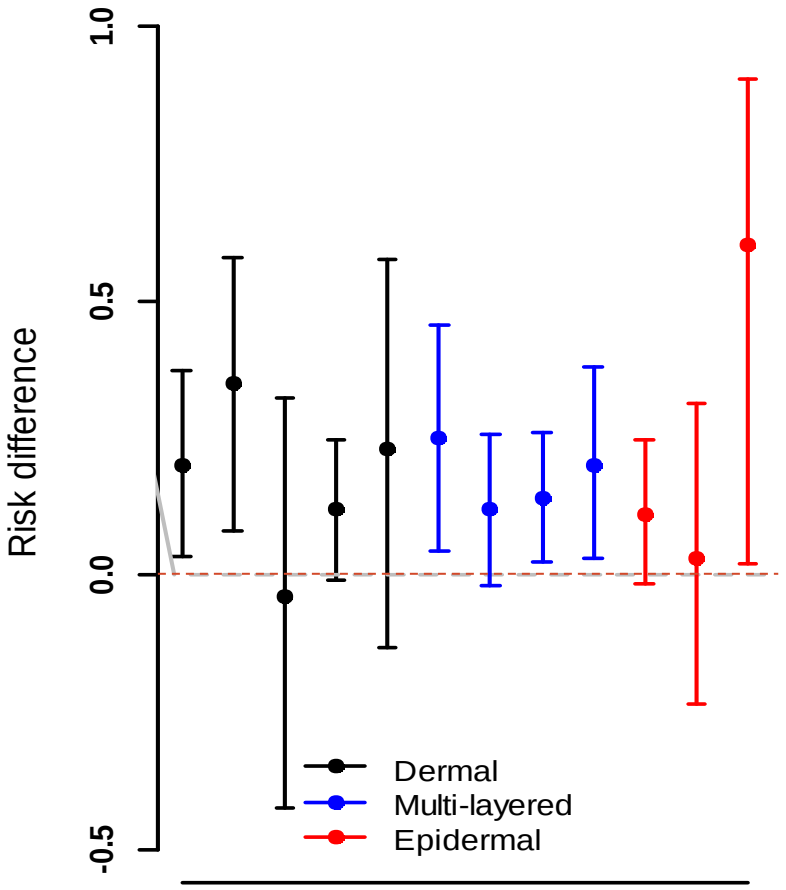
Epidermal substitutes

- No studies

Results: Complete Wound Healing

By Class of Skin Substitutes

Venous Leg Ulcers



Dermal substitutes

- Complete wound healing was clearly demonstrated in two of five studies.
- The remaining three studies reported point estimates that were imprecise
- We downgraded the GRADE rating for this outcome to **moderate** because of imprecision.

Multi-layer substitutes

- Complete wound healing was clearly demonstrated in three of four studies.
- The GRADE rating of our certainty in the evidence for this outcome was **high**.

Epidermal substitutes

- All three studies reported point estimates that were in favour of epidermal substitutes, the confidence intervals were too wide.
- We downgraded the GRADE rating for this outcome to **very low**.

Results: Adverse Effects

- 30 out of 41 studies assessed adverse effects
- Adverse effects occurred sporadically
  - Thus no formal assessment of comparisons was done
- For the few adverse effects that were reported, they included:
  - Dryness, inflammation, ischemia, injury, poisoning, and procedural complications (occurred in dermal substitutes)
  - Maceration* (occurred in multi-layered substitutes)
  - General disorders and reactions at the site the dressing was applied (occurred in epidermal substitutes)

**Maceration occurs when skin is in contact with moisture for too long. Macerated skin looks lighter in color and wrinkly.*

Discussion

- All eligible studies restricted the population to those with difficult-to-heal neuropathic DFUs or VLUs
  - Our conclusions only apply to difficult-to-heal ulcers
- Our review focused on tissue-based therapies
  - Therapies based on cells, such as stem cells or platelets, were out of the scope of this review
- We identified existing SRs/MAs on skin substitutes but they either asked a different research question or assessed a population which is different from ours
  - Findings from these reviews were mixed, some didn't reach a conclusion at all, others found evidence of effectiveness, whereas others didn't find evidence of effectiveness

Conclusions

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

Preferences and Values Evidence

Methods

Background

- Direct patient engagement through consultation - qualitative phone interviews
- Interviews sought to examine the lived-experience and treatment options of those diagnosed with DFU and VLU
- **Recruitment**
- 3 patients were engaged
  - 2 diabetic foot ulcers
  - 1 venous leg ulcer
- Incorporated previous HTA qualitative analysis to complement quality of life information

Methods

- Interview questions based on list developed by the HTA International (HTAi) Interest Group on Patient and Citizen Involvement:
  - Impact of DFU and VLU on daily activities and quality of life
  - Experience of DFU and VLU management using various health interventions
  - Experience with skin substitutes, including introduction of the technology, adjustments, barriers, benefits and limitations, impact on quality of life
- Qualitative analysis software (Nvivo) used to track responses. Results analysed through a modified version of a grounded theory, using iterative process of eliciting, documenting, and analysing responses.

Results

Symptoms

- Patients reported symptoms of painful and deep sores that were difficult to heal.

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

“The symptom was a small open sore, a quarter of a centimeter depth.”

Mobility

- Reduced functionality of impacted leg

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

“I can stand in the shower and take a shower like a normal human being would do it. That is what I would like for myself.”

Results

Employment

- Leave of absences, modified work duties, scheduling treatment around work schedule.

"Up until it really got bad, I wasn't doing much too differently 'cause 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 the time off to just stay off the feet."

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

- Unable to hold employment.

"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, oh, gee, you're spiralling down into the abyss pretty quick."

Results

Social

- Negative impact on social and leisure activities..

“There is no social life like no like going out to watch a movie or going to a baseball or hokey game. We used to do all that stuff before.”

Emotional

- Toll on mental health.

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

- Impact on independence.

“Without my family, without my close friends, I don’t know where I would have been…I wouldn’t have been able to manage on my own those early months.”

- Pain and frustration due to slow healing times.

“It is frustrating at times; you think everything’s healed up, but they say the integrity of the skin takes two 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.”

Results

Treatment for DFU and VLU

- Patients reported familiarity with a wide variety of treatment options

"It started seven years ago….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 and then wrapped with gauze. That was changed every two days. The wounds were stable but they were not getting better."

Result

Treatment for DFU and VLU

- Burden of treatment

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

- Importance of ulcers to be fully heal

“Well, it was a little bit cumbersome and heavy and hot, but I knew the downside if it didn’t get healed up; I was kind of [would] probably face a further amputation.”

- Amputation

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

Results

Financial Barriers

- Patients burdened by the cost of treatment

"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."

- Other costs include transportation, parking and food.

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

- Gratitude for health insurance

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

Results

Skin Substitutes

- No direct experience with skin substitutes
- Opinion on skin substitutes

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

- Effectiveness, scaring, infection

"I guess it would depend on the effectiveness of the skin substitute. Whether it actually significantly accelerated the healing, does it significantly cut down the healing like 50% or more. The second thing would be reducing the risk of infection and then the third would be does it improve the scarring outcome significantly.

Results

Barriers to Skin Substitutes

- Limited clinics offering Skin Substitutes

"I didn't know was an available option, I knew that there have been research. I didn't think it was publicly accessible."

- Cost

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

Ethical Concerns

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

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

Discussion and Conclusion

- Patients discussed the impact on their quality of life living with DFU or VLU
- Long treatment journey with various treatment options
- Patients interested in skin substitutes but no direct experience with this treatment due to scarcity in Ontario

  -Barriers: cost and access
- Limitations
  - No direct experience with skin substitutes
  - Low recruitment rate

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Economic Evidence

Economic Evidence Review

Research Question

What is the cost-effectiveness of **skin substitute plus standard care** compared with **standard care alone** for the treatment of:

- Adults with DFUs?
- Adults with VLUs?

Ontario Health

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

Results

- 14 studies (5 in DFUs, 9 in VLUs)
- 4 skin substitute products evaluated:
  - Simple collagen-containing dressing
  - OASIS
  - Apligraf
  - Dermagraft
- Skin substitute plus standard care vs standard care alone resulted in:
  - Cost-savings (5 studies)
  - More costly and more effective (6 studies)
  - Dominated (3 studies)

Ontario Health

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

Results

- Overall, it was difficult to compare the results across studies, because of the wide range in key parameters used
- All included studies had limitations
  - 2 Canadian studies, informed by outdated clinical evidence
  - Several studies derived treatment effect and number of skin substitute applications from different sources
  - Most studies were sponsored or funded by manufacturers
- Therefore, we are unable to determine the cost-effectiveness of skin substitute from the results of the literature review
- Owing to these limitations, we conducted a primary economic evaluation

Abbreviations: QALY, quality adjusted life-year

Primary Economic Evaluation

Research Question

From the perspective of the Ontario Ministry of Health, what is the cost-effectiveness of **skin substitute plus standard care** compared with **standard care alone** for the treatment of:

- Adults with DFUs?
- Adults with VLUs?

Ontario Health

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

Methods

- **Analysis type**: Cost-utility analysis, cost-effectiveness analysis
- **Model type:** Markov model
- **Target population**: Difficult-to-heal DFUs and VLUs
- **Intervention**: Skin substitute plus standard care
- **Comparator**: Standard care alone
- **Perspective**: Ontario Ministry of Health
- **Time horizon**: 26 weeks
- **Outcomes**: $/QALY, $/ulcer-free weeks
- **Sensitivity analysis**: Scenario analysis, threshold analysis

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

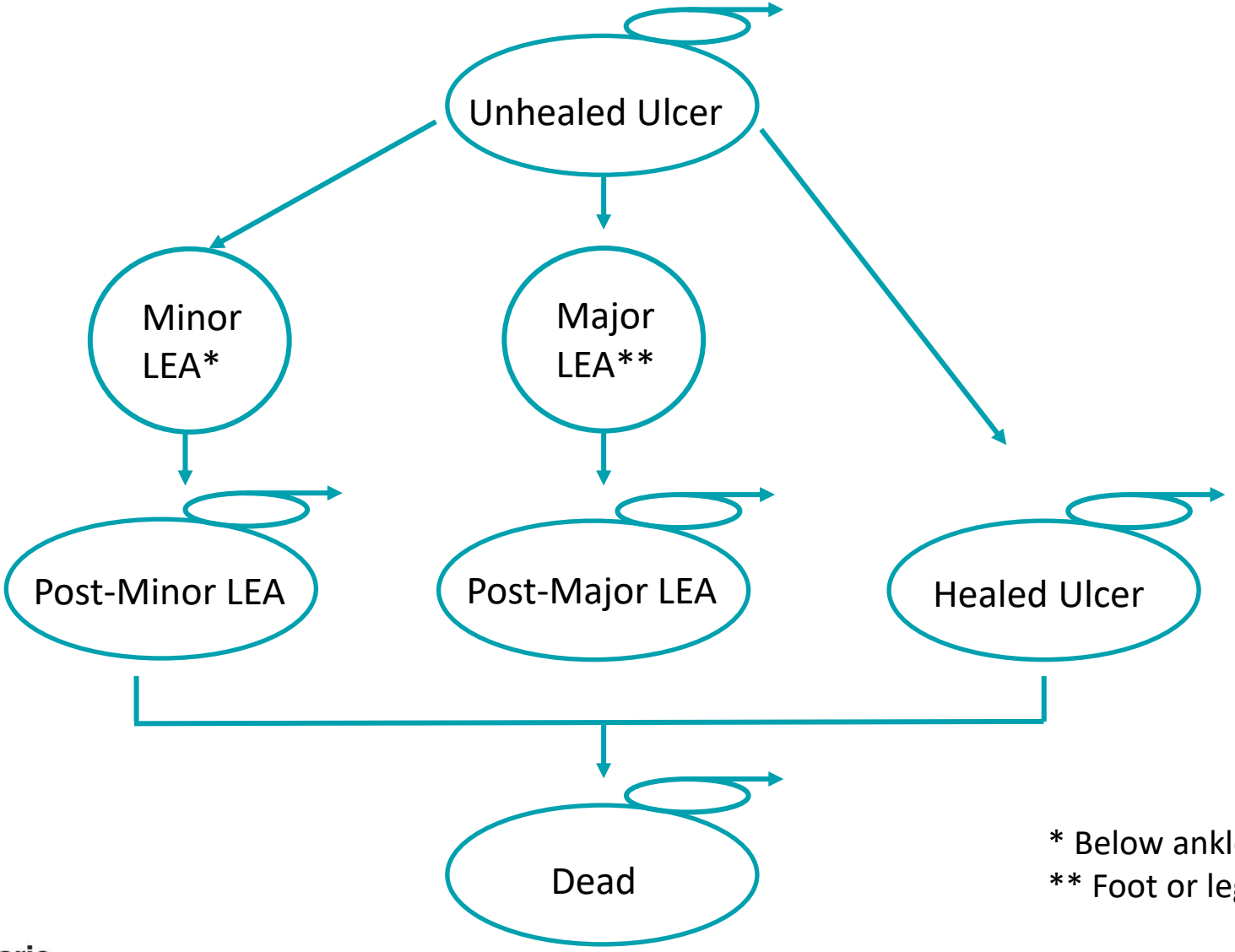
Model Assumptions

- All individuals with DFUs and VLUs enter the model presenting with a single ulcer
- We did not consider other adjunctive therapies (i.e., NPWT or HBOT), as they are not part of standard care
- We did not account for ulcer recurrence
  - Skin substitute products are not expected to have a treatment effect on the rate of ulcer recurrence over the longer-term period
- We did not consider costs associated with healthy lifestyle choices, pressure relieving, or compression therapy

Ontario Health

Abbreviations: DFU, diabetic foot ulcer; HBOT, hyperbolic oxygen therapy; NPWT, negative pressure wound therapy; VLU, venous leg ulcer

DFU Model Structure



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

DFU Key Model Inputs

Natural History

Model Parameter	Weekly Probabilities	Proportion and Length of Time in Primary Source		Reference
		%	Length of Time	
Unhealed DFU → Healed DFU	5.77%	51%	12 weeks	Pooled analysis of Zelen 2016 & Tettlebach 2018
Unhealed DFU → Minor LEA	0.11%	5.4%	1 year	Jeffcoate 2006
Unhealed DFU → Major LEA	0.10%	5.3%	1 year	Jeffcoate 2006

Treatment Effect

Model Parameter	Risk Difference and Length of Time		Reference
	%	Length of Time	
Unhealed DFU → Healed DFU	33%	12 weeks	Pooled analysis of Zelen 2016 & Tettlebach 2018

Abbreviations: CI, confidence interval; DFU, diabetic foot ulcer; LEA, lower-extremity amputation

DFU Key Model Inputs

Resource Use and Cost Parameters

Health State	Costs		Reference
	Skin Substitute + Standard Care	Standard of Care	
Unhealed Ulcer (weekly cost) – for 5.97 weeks	$629 + $374.59	$374.59	Woo 2015, MiMedx, CMS ASP Drug Pricing
Unhealed Ulcer (weekly cost) – beyond 5.97 weeks	$374.59	$374.59	Woo 2015
Healed Ulcer (weekly cost)	$0		
Minor LEA (cost per event)	$2,910.75		SoB, Hopkins 2015
Major LEA (cost per event)	$36,180.03		SoB, OCC
Post-minor/major LEA (weekly cost)	$114.44		O'Rielly 2007

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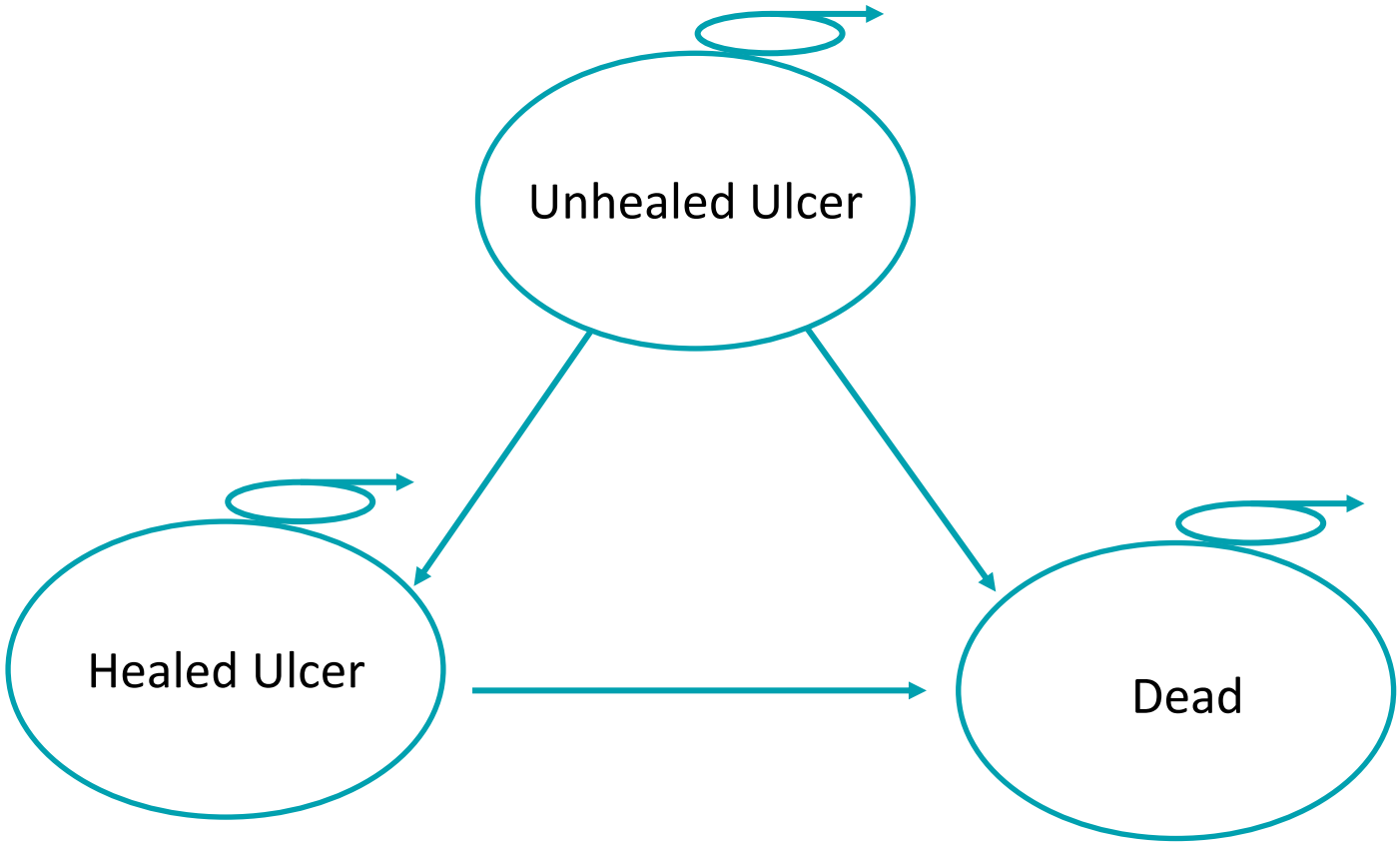
Abbreviations: ASP, average sales price; CMS, US Centres for Medicare and Medicaid Services; DFU, diabetic foot ulcer; LEA, lower-extremity amputation; OCC, Ontario Case Costing; SoB, Schedule of Benefits

VLU Model Structure



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Abbreviations: VLU, venous leg ulcer

VLU Key Model Inputs

Natural History

Model Parameter	Weekly Probabilities	Proportion and Length of Time in Primary Source		Reference
	Weekly Probabilities	%	Length of Time	
Unhealed VLU → Healed VLU	3.04%	39%	16 weeks	Bianchi 2018

Treatment Effect

Model Parameter	Risk Difference and Length of Time		Reference
	%	Length of Time	
Unhealed VLU → Healed VLU	20%	16 weeks	Bianchi 2018

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Abbreviations: ASP, average sales price; CMS, US Centres for Medicare and Medicaid Services; OCC, Ontario Case Costing; SoB, Schedule of Benefits; VLU, venous leg ulcer

VLU Key Model Inputs

Resource Use and Cost Parameters

Health State	Costs		Reference
	Skin Substitute + Standard Care	Standard of Care	
Unhealed Ulcer (weekly cost) – for 7.2 weeks	$1,901.04 + $374.59	$374.59	Woo 2015, MiMedx, CMS ASP Drug Pricing
Unhealed Ulcer (weekly cost) – beyond 7.2 weeks	$374.59	$374.59	Woo 2015
Healed Ulcer (weekly cost)	$0		

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Abbreviations: ASP, average sales price; CMS, US Centres for Medicare and Medicaid Services; OCC, Ontario Case Costing; SoB, Schedule of Benefits; VLU, venous leg ulcer

Results: DFU Reference Case

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

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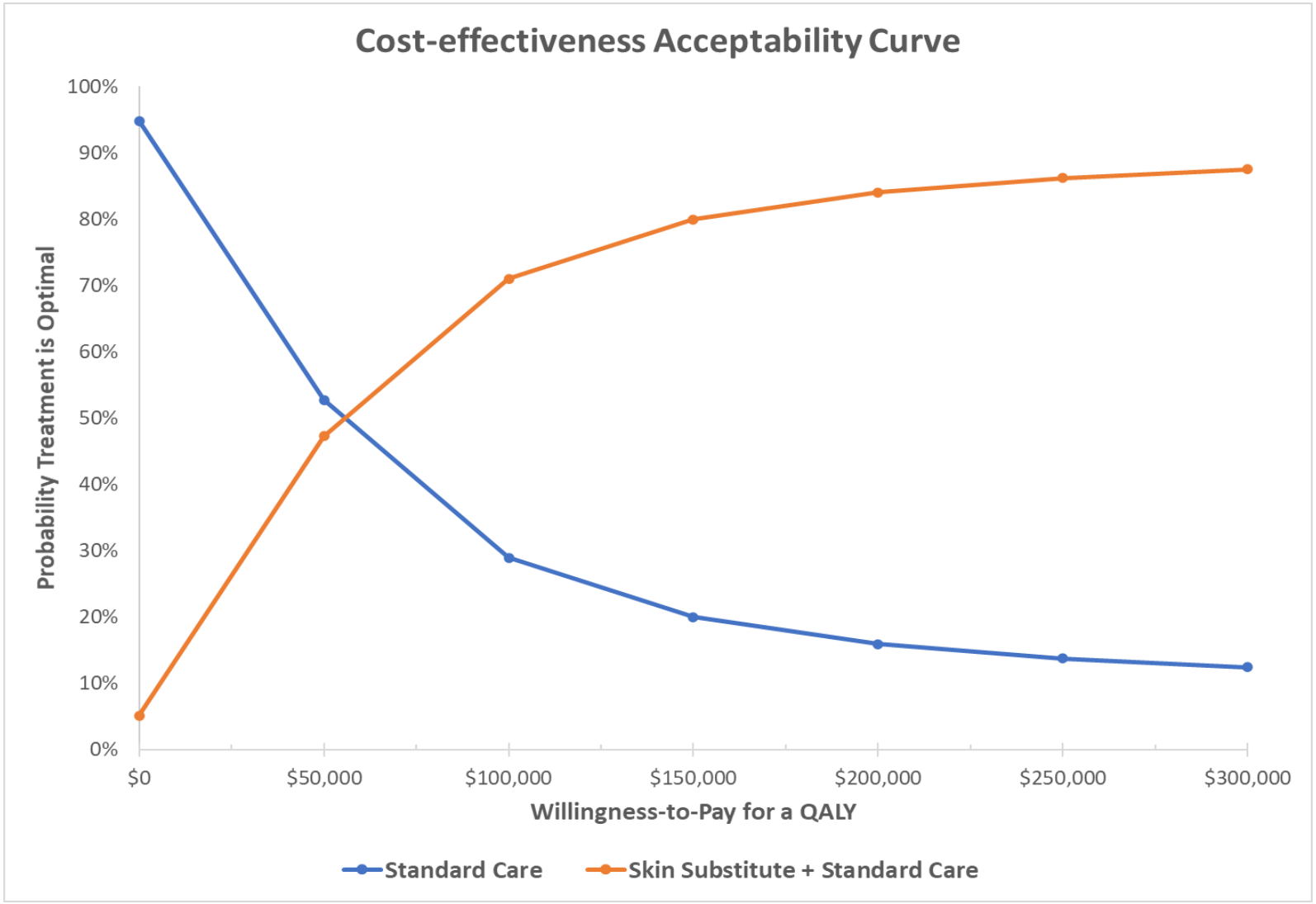
Abbreviations: DFU, diabetic foot ulcer; Crl, credible interval; ICER, incremental cost-effectiveness ratio; LEA, lower-extremity amputation; QALY, quality adjusted life-years

Results: Probabilistic Analysis



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Abbreviations: DFU, diabetic foot ulcer

Results: DFU Scenario Analysis

- Reference case results were significantly impacted by cost parameters
  - 20% price reduction of skin substitutes decreased the ICER to $13,315/QALY and $43/ulcer-free week
  - Larger skin substitute dimensions increased the ICER to $194,423/QALYs and $617/ulcer-free week
  - Increase to 12 weekly applications per person resulted in the ICER increase significantly to $222,441/QALY and $709/ulcer-free week
- Parameter variations that affect overall cost of skin substitutes (e.g., unit cost, number of applications) have the largest impact on cost-effectiveness results

Abbreviations: DFU, diabetic foot ulcer; ICER, incremental cost-effectiveness ratio, QALY, quality adjusted-life years

Results: VLU Reference Case

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

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Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; VLU, venous leg ulcer

Results: VLU Scenario Analysis

- Reference case results were sensitive to skin substitute costs
  - When parameters from the multilayered skin substitute (Mostow 2005) were used, the skin substitute strategy became dominant
  - An increase of the time horizon to 1 year saw the ICER drop to $777,952/QALY and $1,346/ulcer-free week
  - An increase to 12 weekly applications raised the ICER to $3,190,954/QALY and $5,523/ulcer-free week
- A significant price reduction is required to achieve:
  - $100,000/QALY (84% discount)
  - $50,000/QALY (86% discount)

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Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted-life years; VLU, venous leg ulcer

Budget Impact Analysis

Research Question

What is the 5-year budget impact for the Ontario Ministry of Health of publicly funding **skin substitute plus standard care** in:

- Adults with DFUs?
- Adults with VLUs?

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

Methods

- **Analysis type**: Budget impact analysis
- **Target population**: Difficult-to-heal DFUs and VLUs
- **Intervention**: Skin substitute plus standard care
- **Comparator**: Standard care alone
- **Perspective**: Ontario Ministry of Health
- **Time horizon**: 5 years
- **Outcomes**: Cost (2020 CAD)
- **Sensitivity analysis**: Scenario analysis (e.g., price reduction, uptake rate increase)

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

Model Assumptions

- 50% and 60% of difficult-to-heal DFUs and VLUs respectively are eligible for skin substitutes
- Uptake rate of skin substitute in eligible populations are assumed to be gradual in the first two years before increasing more steadily
  - 3% in year 1, 5% in year 2, 10% in year 3, 15% in year 4, 20% in year 5
- The average individual with DFUs and VLUs present with a single ulcer

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

Target Population – DFU

ON population → Annual prevalence of diabetes → Annual prevalence of DFUs → % of DFUs that are difficult-to-heal → % of difficult-to-heal DFUs eligible for skin substitutes

Volume of Intervention in DFUs

	Volume of Intervention				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Eligible difficult-to-heal DFUs	5,288	5,369	5,451	5,534	5,619
Uptake rate	3%	5%	10%	15%	20%
Annual volume of difficult-to-heal DFUs receiving skin substitutes	159	268	545	830	1,124

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Abbreviations: DFU, diabetic foot ulcer

Target Population – VLU

ON population ≥25 years → Annual prevalence VLU → % of VLUs that are difficult-to-heal → % of difficult-to-heal VLUs eligible for skin substitutes

Volume of Intervention in VLUs

	Volume of Intervention				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Eligible difficult-to-heal VLUs	2,917	2,968	3,020	3,072	3,125
Uptake rate	3%	5%	10%	15%	20%
Annual volume of difficult-to-heal VLUs receiving skin substitutes	88	148	302	461	625

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Abbreviations: VLU, venous leg ulcer

Results: DFU Reference Case

DFU Budget Impact Analysis Results

Scenario	Budget Impact, $, Millions					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario	28.1	28.5	29.0	29.4	29.9	144.8
New scenario	28.3	28.8	29.5	30.3	31.0	148.0
Skin substitute + standard care	1.0	1.7	3.5	5.3	7.2	18.6
Standard care alone	27.3	27.1	26.1	25.0	23.9	129.3
Budget impact	0.2	0.3	0.6	0.9	1.2	3.1

DFU Skin Substitute Cost Only

	Budget Impact (Skin Substitute Cost Only)					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Annual volume of DFUs receiving skin substitutes, n	159	268	545	830	1,124	2,926
Skin substitute cost, $ (Millions)	0.6	1.0	2.0	3.1	4.2	11.0

Ontario Health

Abbreviations: DFU, diabetic foot ulcer

Results: VLU Reference Case

VLU Budget Impact Analysis Results

Scenario	Budget Impact, $, Millions					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario	20.8	21.2	21.6	21.9	22.3	107.9
New scenario	21.9	23.0	25.3	27.6	30.0	127.8
Skin substitute + standard care	1.7	2.8	5.9	8.9	12.1	31.5
Standard care alone	20.2	20.1	19.4	18.7	17.9	96.3
Budget impact	1.1	1.8	3.7	5.7	7.7	20.0

VLU Skin Substitute Cost Only

	Budget Impact (Skin Substitute Cost Only)					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Annual volume of VLUs receiving skin substitutes, n	88	148	302	461	625	1624
Skin substitute cost, $ (Millions)	1.2	2.0	4.1	6.3	8.6	22.2

Ontario Health

Abbreviations: VLU, venous leg ulcer

Results: DFU Sensitivity Analysis

DFU Sensitivity Analysis

Scenario	Budget Impact, $, Millions					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Reference case	0.2	0.3	0.6	0.9	1.2	3.1
20% price reduction	0.05	0.08	0.16	0.24	0.33	0.85
Multilayered skin substitute (Cazzell 2015)	-0.2	-0.3	-0.5	-0.8	-1.1	-2.8
Double uptake rate	0.3	0.6	1.1	1.7	2.3	6.1

VLU Sensitivity Analysis

Scenario	Budget Impact, $, Millions					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Reference case	1.1	1.8	3.7	5.7	7.7	20.0
50% price reduction	0.5	0.8	1.6	2.5	3.4	8.8
Multilayered skin substitute (Mostow 2005)	-0.05	-0.08	-0.16	-0.25	-0.34	-0.87
Multiple ulcers (1.5 ulcers)	1.6	2.7	5.4	8.2	11.2	29.0

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

Strengths and Limitations (PEE and BIA)

- Strengths:
  - We focused on studies of skin substitutes that had a HC license, and evaluated all in our analysis either as our reference case or a scenario
  - Unit cost of skin substitutes was determined based on the cost of the size of sheets supplied at the international market closest to the estimated wound surface area for DFUs and VLUs
- Limitations:
  - Both models assume that all individuals receive the level of standard care that is considered best practice, which may not be reflective of the current state in Ontario
  - Our models are based on the average difficult-to-heal DFUs and VLUs, and does not reflect the diverse care needs of these chronic wounds
  - Unit costs of skin substitutes were derived from US-based pricing, which may differ from the Canadian pricing of these products

Abbreviations: BIA, budget impact analysis; DFU, diabetic foot ulcer; HC, Health Canada; PEE, primary economic evaluation; VLU, venous leg ulcer

Thank you.