CLINICAL QUESTION 1: In people with diabetes-related foot ulcers, is enzymatic debridement, autolytic debridement, biosurgical debridement, ultrasonic debridement, hydrosurgical abrasion or chemical debridement more effective for achieving wound healing compared to best standard of care (including sharp debridement?)

(ENZYMATIC DEBRIDEMENT)

**Evidence statement**: We found five RCTS on clostridial collagenase ointment compared to standard of care (i.e. sharp debridement). All were exploratory RCTs that were designed to generate hypotheses and were not designed to provide a statistically significant outcome. All had significant methodological limitations, were mainly unblinded and at high risk of bias. Different time points, between 4 to 6 weeks, with limited follow up and different definitions of healing make comparisons between studies difficult.

Recommendation 2: Do not routinely use enzymatic debridement as opposed to standard of care (i.e. sharp debridement) to improve wound healing outcomes in people with diabetes and a foot ulcer. (Strength of recommendation: Strong; Certainty of evidence: Low)

Recommendation 2a: In specific situations where the availability of sharp debridement may be limited by access to resources and/ or availability of skilled personnel, consider using enzymatic debridement. (Conditional; Low).

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial	<mark>Small</mark>	Mo		te	Lar	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		Small		Triv	<mark>⁄ial</mark>	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	Hig	h	No includ	ed studies	High/moderate/low
Values	Important uncertainty or variability	Possibly impouncertainty of variability	ortant Probably		nt und nty or var		No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does no either th interven the com	ne Ition or	Probably favors the intervention		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligib and savi		Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	•	Modera	te	Hig	h	No includ	ed studies	High/moderate/low

Cost effectiveness	Favors the	<b>Probably favors</b>	Does not favor	Probably favor	s Favors	the Varie	s Don't know	High/moderate/low
	comparison	the comparison	either the	the intervention		ntion		
			intervention or					
			the comparison					
Equity	Reduced	Probably	Probably no	<b>Probably</b>	Increas	ed Varie	s Don't know	High/moderate/low
		reduced	impact	increased				
Acceptability	No	Probably no	Probably	<mark>/ yes</mark>	Yes	Varie	s Don't know	High/moderate/low
Feasibility	No	Probably no	Probably	<mark>/ yes</mark>	Yes	Varie	s Don't know	High/moderate/low

CLINICAL QUESTION 1: In people with diabetes-related foot ulcers, is enzymatic debridement, autolytic debridement, biosurgical debridement, ultrasonic debridement, hydrosurgical abrasion or chemical debridement more effective for achieving wound healing compared to best standard of care (including sharp debridement?)
(ULTRASONIC DEBRIDEMENT)

**Evidence statement**: We found three RCTS of low frequency ultrasonic debridement compared to standard of care (i.e. sharp debridement). All three studies were at high risk of bias with none being blinded. Only one suggested any differences between groups in time to healing, but this result should be treated with caution given the high risk of bias of the study. None showed any differences in absolute healing in the timescales of the follow-up of the studies. The other two studies presented either no difference between the two groups or did not present any between group analyses

Recommendation 3: Do not use any form of ultrasonic debridement over standard of care (i.e. sharp debridement). (Strong; Low)

CRITERIA				JUDGEMENTS				IMPACT
Desirable Effects	Trivial	<mark>Small</mark>	М	loderate	Large	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Sr	mall	Trivial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	М	loderate	High	No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly impouncertainty of variability	or <mark>im</mark> ur	robably no nportant ncertainty or ariability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not far either the intervention the compar	the intervent		Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible co		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	M	loderate	High	No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not far either the intervention the compar	the intervent		Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no	Pr	robably yes	Yes	Varies	Don't know	High/moderate/low

Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 1: In people with diabetes-related foot ulcers, is enzymatic debridement, autolytic debridement, biosurgical debridement, ultrasonic debridement, hydrosurgical abrasion or chemical debridement more effective for achieving wound healing compared to best standard of care (including sharp debridement?) (SURGICAL DEBRIDEMENT)

**Evidence statement**: We found one RCT of surgical debridement compared to standard of care (sharp debridement). No formal cost effectiveness data were found

Recommendation 4: Do not use surgical debridement in those for whom sharp debridement can be performed outside a sterile environment. (Strong; Low)

CRITERIA				JUDGEMENTS				IMPACT
Desirable Effects	Trivial	Small	Mod	erate	Large	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Smal		Trivial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Mode	erate	High	No includ	ded studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty variability	or <mark>impo</mark>	rtainty or	uncertainty or			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	the intervent		Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible cost and savings	s Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Mode	erate	High	No includ	ded studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	the intervent		Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no	Prob	ably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Prob	ably yes	Yes	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

(SURFACE ANTIMICROBIALS)

**Evidence statement**: There is very limited evidence to support the use of antimicrobial dressings or topical antiseptic applications for healing in diabetes-related foot ulcers

#### Recommendation 6: Do not use topical antiseptic or antimicrobial dressings for wound healing of diabetes related foot ulcers (Strong, Moderate)

CRITERIA				JU	IDGEMENTS					IMPACT
Desirable Effects	Trivial	Small		Modera	ite	Lar	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderat	e	Small	Small T		rial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Low		ite	Hig	h	No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly uncertai variabilit	,	rtant Probably no important		uncertainty or				High/moderate/low
Balance of effects	Favors the comparison	Probably favo	on <mark>either t</mark> interver		Probably favours the intervention		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate cos		ole costs	Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low		Modera	ite	Hig	h	No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favo	on <mark>either t</mark> interver	<mark>he</mark>	Probably favor the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probabl impact		Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably	no	Probabl	y yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably	no	Probabl	y yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

(HONEY OR BEE PRODUCTS)

Evidence statement: There is very limited evidence to support the use of honey or bee-related products for wound healing in diabetes-related foot ulcers

Recommendation 7: Do not use honey (or bee related products) for the purpose of wound healing in diabetes-related foot ulcers (Strong, Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial	<mark>Small</mark>		Modera	te	Larg	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		Small		Trivial		Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Low		te	Higl	h	No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty of variability	or	rtant Probably no		uncertainty or ty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not to either the intervention the compa	<mark>on or</mark>	Probably favours the intervention		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible and saving		Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low		Modera	te	Higl	h	No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not feither the intervention the compa	<mark>on or</mark>	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably r	no	Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no		Probably	yes /	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probably	/ yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

(COLLAGEN/ALGINATES)

**Evidence statement:** The evidence to support the use of collagen or alginate dressings is of low certainty, with no studies at low risk of bias and limited evidence of benefit towards critical outcomes identified.

### Recommendation 8: Do not use collagen or alginate dressings for the purpose of wound healing of diabetes-related foot ulcers (Strong, Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial	Small		Modera	te	Larg	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		Small		Trivial		Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Low M		te	Higl	h	No includ	ed studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty variability				uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not either the intervent the comp	e cion or	Probably favours the intervention		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible and savin	e costs	Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low		Modera	te	Higl	h	No includ	ed studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not either the intervent the comp	e ion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact	no	Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

#### (SUCROSE OCTASULFATE)

**Evidence statement:** In non-infected, neuroischaemic ulcers that are hard to heal, the use of topical sucrose-octasulfate has been shown to benefit complete wound healing, percentage area reduction and the estimated time to healing.

Recommendation 9: Consider the use of the sucrose-octasulfate impregnated dressing as an adjunctive treatment, in addition to the best standard of care, in noninfected, neuro-ischaemic diabetes-related foot ulcers that are difficult to heal (Conditional; Moderate).

CRITERIA					JUI	OGEMENTS					IMPACT
Desirable Effects	Trivial	Sm	nall		Moderat	e	Larg	e	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Мо	oderate S		Small		Trivial		Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Lov	W	M		e	High	1	No includ	ed studies	High/moderate/low
Values	Important uncertainty or variability	und	ssibly impo certainty c riability		Probably importar uncertair variabilit	n <mark>t</mark> nty or	unce	mportant ertainty or ability			High/moderate/low
Balance of effects	Favors the comparison		ly favors nparison	Does not either th interven the com	e tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Modera	ate costs	Negligibl and savii		Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Lov	W		Moderat		High	1	No includ	ed studies	High/moderate/low
Cost effectiveness	Favors the comparison		ly favors nparison	Does not either th interven the com	ie tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	•	Probably impact	/ no	Probably increased		Increased	Varies	Don't know	High/moderate/low

Acceptability	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

(TOPICAL PHENYTOIN)

**Evidence statement:** The evidence to support the use of topical phenytoin is of low certainty. We identified 12 RCTs of which only 2 were double blind. Only one of these was designed as a definitive study, but failure to recruit meant it was underpowered to show any apparent benefit in wound healing.

#### Recommendation 10: Do not use topical phenytoin for the purpose of wound healing in diabetes-related foot ulcers (Strong; Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial Trivial	Small		Modera	te	Larg	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		Small		<b>Trivial</b>		Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	ow I		te	Higl	h	No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty of variability		rtant Probably no I		No important uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not either the intervent the comp	<mark>e</mark> tion or	Probably favours the intervention		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligibl and savir	<mark>e costs</mark>	Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low		Modera	te	Higl	h	No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not either the intervent	<mark>e</mark> tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact		Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

#### (TOPICAL HERBAL APPLICATIONS)

**Evidence statement:** The evidence to support the use of traditional medicinal preparations in wound healing of diabetes-related foot ulcers is of low certainty, with no studies at low risk of bias.

Recommendation 11: Do not use any dressing based or topical applications impregnated with herbal remedies for the sole purpose of wound healing in diabetes-related foot ulcers. (Strong; Low)

CRITERIA				JUDGEMENTS				IMPACT
Desirable Effects	Trivial	<mark>Small</mark>	Mo	derate	Large	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Sm	all	Trivial Trivial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Mo	derate	High	No includ	ded studies	High/moderate/low
Values	Important	Possibly impo	ortant Pro	bably no	No important			High/moderate/low
	uncertainty or	uncertainty o	or <mark>im</mark> i	oortant	uncertainty or			
	variability	variability	und	certainty or	variability			
			<mark>var</mark>	<mark>iability</mark>				
Balance of effects	Favors the	Probably favors	Does not fav	<mark>our</mark> Probably	Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	either the	favours the	intervention			
			intervention	or intervention				
			the comparis	<mark>on</mark>				
Resources required	Large costs	Moderate costs	Negligible co	sts Moderate	Large savings	Varies	Don't know	High/moderate/low
			and savings	savings				
Certainty of evidence	Very low	Low	Mc	derate	High	No includ	ded studies	High/moderate/low
of required resources								
Cost effectiveness	Favors the	Probably favors	Does not fav	or Probably fav	ors Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	either the	the interven	tion intervention			_
		·	intervention	<mark>or</mark>				
			the comparis	<mark>on</mark>				
Equity	Reduced	Probably	Probably no	Probably	Increased	Varies	Don't know	High/moderate/low
• •		reduced	impact .	increased				- '
Acceptability	No	Probably no		bably yes	Yes	Varies	Don't know	High/moderate/low

Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low
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CLINICAL QUESTION 3: In people with diabetes-related foot ulcers, is hyperbaric oxygen, topical oxygen or the use of other gases compared to standard of care more effective for achieving wound healing?

(HYPERBARIC OXYGEN)

**Evidence statement**: Of the 18 studies, only three were double blinded RCTs and thus considered at low risk of bias, on the evaluation of the use of hyperbaric oxygen as an adjunct therapy to improve DFU healing. Overall, the evidence is conflicting, but the studies with lowest risk of bias suggest that there may be some benefit for its use in improving absolute wound healing and reduction in ulcer area. Good evidence of benefit in preventing amputation is however lacking. Different time points (ranging between 30 days and 12 months), degree of ischaemia and definitions of healing make comparisons between studies difficult.

Recommendation 12: Consider the use of hyperbaric oxygen as an adjunct therapy in neuro-ischemic or ischemic diabetes related foot ulcers where standard of care alone has failed and where resources already exist to support this intervention. (Conditional; Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial	Small		Modera	te	Large		Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		Small	Tr			Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	High		No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty o variability	nportant Probably		nt uncerta nty or variabi		portant tainty or pility			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not either th interven the comp	ne tion or	Probably favo		avors the ntervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligibl and savir		Moderate savings	L	arge savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	•	Modera		High		No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not either the interventhe comp	ie tion or	Probably favo		avors the ntervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact	/ no	Probably increased	lı	ncreased	Varies	Don't know	High/moderate/low

Acceptability	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 3: In people with diabetes-related foot ulcers, is hyperbaric oxygen, topical oxygen or the use of other gases compared to standard of care more effective for achieving wound healing?

(TOPICAL OXYGEN)

**Evidence statement**: We found three double-blinded RCTs and seven non-blinded studies for the use of topical oxygen. Of the double-blinded studies, one was terminated early and had uneven baseline characteristics between control and intervention groups. Two double-blinded trials were at low risk of bias with ITT analysis, but only one had statistically significant results for complete wound healing in favour of topical oxygen at 12 weeks with the other showing no difference between topical oxygen and standard care. There was no benefit of topical oxygen on amputation, probably due to short duration of follow-up in most trials. We found no data on resource use, and few data on adverse events.

Recommendation 13: Consider the use of topical oxygen as an adjunct therapy to standard care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention. (Conditional; Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial	Small		Modera	<mark>te</mark>	Large	9	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	te Small		Small Tri		<mark>al</mark>	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	High		No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty o variability	portant Probably		nt uncertaii nty or variabilit		mportant ertainty or ability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does no either th interven the com	ne ntion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligib and savi		Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	1	Modera		High		No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does no either the interventhe com	ne ntion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact	y no	Probably increased		Increased	Varies	Don't know	High/moderate/low

Acceptability	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 3: In people with diabetes-related foot ulcers, is hyperbaric oxygen, topical oxygen or the use of other gases compared to standard of care more effective for achieving wound healing?

(OTHER GASES)

**Evidence statement**: The evidence to support the use of other gases such as nitric oxide, ozone, carbon dioxide and cold atmospheric plasma is poor, with no studies assessed to be at low risk of bias.

Recommendation 14: Do not use other gases (e.g. cold atmospheric plasma, ozone, nitric oxide, CO2) in comparison to standard of care for wound healing in people with diabetes-related foot ulcers. (Strong; Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivia <mark>l</mark>	Small		Modera	te	Lar	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	e Small		all Tri		<mark>/ial</mark>	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	Hig	h	No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty of variability		ortant Probably no		uncertainty or				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does no either the interventhe com	ne Ition or	Probably favors the intervention		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligib and savi	le costs			Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	1	Modera			h	No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does no either th interven the com	ne ition or	Probably favo		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact	•	Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no		Probably yes		Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 4: In people with diabetes-related foot ulceration, is the use of interventions which physically alter the wound bed compared to standard of care more effective for wound healing?

**Evidence statement**: The evidence to support the use of heat application for DFU management is weak, depending on only one nonblinded RCT with poor outcome in the comparator group

Recommendation 15: Do not use any interventions reported in the field of physical therapies for wound healing in the management of diabetes-related foot ulcers. (Strong, Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial	Small		Modera	te	Lar	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	e Sma		Small		<mark>/ial</mark>	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	Hig	h	No includ	ed studies	High/moderate/low
Values	Important	Possibly imp	ortant	Probabl	y no	No	important			High/moderate/low
	uncertainty or	uncertainty		importa	nt	und	certainty or			
	variability	variability		uncertai	inty or	var	iability			
	•	,		variabili	ty		•			
Balance of effects	Favors the	Probably favors	Does no	t favor	Probably favo	ors	Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	either th	ie e	the intervent	ion	intervention			
			<mark>interven</mark>	<mark>tion or</mark>						
			the com	<mark>parison</mark>						
Resources required	Large costs	Moderate costs	Negligib	le costs	costs Moderate		Large savings	Varies	Don't know	High/moderate/low
			and savi	ngs	savings					
Certainty of evidence	Very low	Low		Modera	/loderate H		h	No includ	ed studies	High/moderate/low
of required resources										
Cost effectiveness	Favors the	<b>Probably favors</b>	Does no	t favor	Probably favo	ors	Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	either th	ie	the intervent	ion	intervention			
			interven	tion or						
			the com	parison						
Equity	Reduced	<b>Probably</b>	Probably	/ no	Probably		Increased	Varies	Don't know	High/moderate/low
		<mark>reduced</mark>	impact		increased					
Acceptability	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 5: In people with diabetes-related foot ulcers, are skin substitutes more effective for wound healing compared to best standard of care?

(CELLULAR SKIN SUBSTITUTES)

**Evidence statement**: Although evidence from 9 RCTs suggest Cellular Skin Substitutes may improve the incidence of healing and reduce the time to healing in patients with diabetes-related foot ulcers when provided in addition to standard of care, all studies were at moderate high risk of bias. There is insufficient evidence to establish which if any particular cellular skin substitutes are superior and there is also insufficient evidence on cost effectiveness of this modality. There is limited evidence to indicate that cellular skin substitutes are associated with a reduction in amputation rates, but this is of low certainty. No formal within-trial cost effectiveness data were found, but the products have a known barrier to utilization and equity due to their significant expense.

# Recommendation 16: We suggest not using cellular skin substitute products as a routine adjunct therapy to standard care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)

CRITERIA				JU	DGEMENTS					IMPACT		
Desirable Effects	Trivial	Small		Modera	te	Larg	ge	Varies	Don't know	High/moderate/low		
Undesirable Effects	Large	Moderate	derate S		Small		ial	Varies	Don't know	High/moderate/low		
Certainty of evidence	Very low	Low		Modera	te	Higl	า	No includ	ed studies	High/moderate/low		
Values	Important uncertainty or variability	Possibly im uncertainty variability				nt und i <mark>nty or</mark> var		No important uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not either the interven the com	ne ition or	Probably favors the intervention		Favors the intervention	Varies	Don't know	High/moderate/low		
Resources required	Large costs	Moderate costs	Negligibl and savi	le costs	Moderate savings		Large savings	Varies	Don't know	High/moderate/low		
Certainty of evidence of required resources	Very low	Low	•	Modera	te	Higl	า	No includ	ed studies	High/moderate/low		
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not either the interventhe com	ne Ition or	Probably favor the intervent		Favors the intervention	Varies	Don't know	High/moderate/low		

Equity	Reduced	Probably	Probably	Probably no			Increased	Varies	Don't know	High/moderate/low
		reduced	impact		increased					
Acceptability	No	Probably no		Probably	<mark>/ yes</mark>	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probably	yes yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 5: In people with diabetes-related foot ulcers, are skin substitutes more effective for wound healing compared to best standard of care?

(ACELLULAR SKIN SUBSTITUTES)

**Evidence statement**: There is insufficient evidence to establish which particular acellular skin substitutes are superior and there is also insufficient evidence on cost effectiveness of this modality. There is limited evidence to indicate that acellular skin substitutes are associated with a reduction in amputation rates, likely related to their increased healing rate and decreased time to healing. Limited resource utilization data were found, but the products have a known barrier to utilization and equity due to their significant expense.

### Recommendation 17: We suggest not using acellular skin substitute products as a routine adjunct therapy to standard care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)

CRITERIA				JUDGEMENTS				IMPACT
Desirable Effects	Trivial	Small	Mod	erate	Large	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Smal		Trivial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Mod	erate	High	No includ	ded studies	High/moderate/low
Values	Important uncertainty or variability	Possibly impounded in the control of	or <mark>impo</mark>	ably no ortant rtainty or bility	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention of the compariso	the intervent		Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible cost and savings	s Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Mod	erate	High	No includ	ded studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention of the comparison	the interven		Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no	Prob	ably yes	Yes	Varies	Don't know	High/moderate/low

Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 5: In people with diabetes-related foot ulcers, are skin substitutes more effective for wound healing compared to best standard of care?

(AUTOLOGOUS SKIN GRAFTS)

**Evidence statement**: There is very limited and low level evidence on the topic of autologous skin graft substitutes for diabetes related foot ulcers. There is insufficient evidence to establish their utility and effectiveness.

Recommendation 18: Do not use autologous skin graft skin substitute products as an adjunct therapy for wound healing in patients with diabetes related foot ulcers. (Strong; Low)

CRITERIA				JU	DGEMENTS					IMPACT
Desirable Effects	Trivial	Small		Moderate		Lar	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	e <mark>Sm</mark>		Small T		<i>r</i> ial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	Hig	;h	No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty o variability			uncertainty or variability		certainty or			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison		the intervention ion or parison e costs Moderate		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings				Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	1	Modera	te	Hig	h	No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not either the interventhe com	ie tion or	Probably favo		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact		Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no		Probabl	y yes	Yes	;	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes	i	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 6: In people with diabetes-related foot ulcers, is the use of autologous products including growth factors and placenta-derived products more effective for wound healing compared to standard of care?

(AUTOLOGOUS PLATELETS)

**Evidence statement**: The evidence to support the use of autologous platelets is poor, with few studies graded at low risk of bias. The different timescales to the outcomes chosen make comparison of different interventions difficult to establish.

Recommendation 19: With the exception of the autologous leucocyte, platelet and fibrin patch we suggest not using autologous platelets therapy (including blood bank derived platelets) as an adjunct therapy to standard of care. (Conditional; Low)

CRITERIA		IMPACT							
Desirable Effects	Trivial	Small	Мо	Moderate La		Large		Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Sma	all	Trivial		Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Мо	derate	High		No includ	ed studies	High/moderate/low
Values	Important uncertainty or variability	Possibly impouncertainty of variability	or imp und	important und		No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favoreither the intervention of the comparis	the interventor		vors the tervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible cos	le costs Moderate		rge savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Mo	derate	High		No includ	ed studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention the comparis	the intervent		vors the tervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Ind	creased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no	Pro	bably yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		bably yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 6: In people with diabetes-related foot ulcers, is the use of autologous products including growth factors and placenta-derived products more effective for wound healing compared to standard of care?

(LEUCOPATCH)

**Evidence statement**: One definitive multicentre outcome blind RCT at low risk of bias has shown significant improvements in healing, time to healing and wound area reduction in patients with hard to heal ulcers when used in addition to best standard of care.

Recommendation 20: Consider the use of autologous leucocyte, platelet and fibrin patch for diabetes related foot ulcers as an adjunctive therapy to standard of care, where best standard of care alone has been ineffective, and where the resources and expertise exist for the regular venepuncture required. (Conditional; Moderate)

CRITERIA			IMPACT					
Desirable Effects	Trivial	<mark>Small</mark>	Mo	derate	Large	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Sma	all	Trivial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Mo	derate	High	No includ	ded studies	High/moderate/low
Values	Important uncertainty or variability	Possibly impu uncertainty o variability	or <mark>imp</mark> unc	bably no ortant ertainty or ability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention of the comparison	the intervent		Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible cos		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Mod	derate	High	No includ	ded studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favoreither the intervention of the comparison	the interventor		Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no	Pro	bably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Pro	bably yes	Yes	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 6: In people with diabetes-related foot ulcers, is the use of autologous products including growth factors and placenta-derived products more effective for wound healing compared to standard of care?

(OTHER CELLS)

**Evidence statement**: The evidence to support improved wound healing, wound area reduction or time to healing for the use of cultured keratinocytes, fibroblasts, adipocytes, either as fat grafting or following lipo-aspirates is currently poor, with most studies being at moderate to high risk of bias.

# Recommendation 21: We suggest not using other cell therapy as an adjunct therapy to standard of care for wound healing in people with diabetes related foot ulcers (Conditional; Low)

CRITERIA	JUDGEMENTS									IMPACT
Desirable Effects	Trivial	Small		Modera	Moderate L		ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Moderate Si			Triv	<sub>r</sub> ial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	Hig	h	No includ	ed studies	High/moderate/low
Values	Important uncertainty or variability		uncertainty or imvariability un		<mark>important</mark> un		important certainty or iability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not either the interventhe com	ie tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings				Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low		Modera	te	Hig	h	No includ	ed studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does no either the interventhe com	ie tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact	/ no	Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 6: In people with diabetes-related foot ulcers, is the use of autologous products including growth factors and placenta-derived products more effective for wound healing compared to standard of care?

(GROWTH FACTORS)

**Evidence statement:** With the evidence of high quality RCT (Park 2018) of EGF the quality of the data to support the use of other GFs is poor. The single RCT at low risk of bias of EGF, suggests that EGF may be associated with improved absolute healing, and time to healing, however we found no evidence for this intervention in reduction of amputation, quality of life or resource use, and as such the data to support this intervention in clinical practice is limited.

Recommendation 22: We suggest not using growth factor therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers (Conditional; Low)

CRITERIA		JUDGEMENTS								IMPACT
Desirable Effects	Trivial	<mark>Small</mark>		Modera	te	Lar	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		<u>Small</u>		Trivial		Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	<mark>te</mark>	Hig	;h	No includ	ed studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty variability		Probably importa uncertai variabili	nt inty or	unc	important certainty or iability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not either th interven the com	e tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligibl and savi	e costs	Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low		Modera	te	Hig	h	No includ	ed studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not either the interventhe com	<mark>e</mark> tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact	no	Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no		Probably	y yes	Yes	5	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes	3	Varies	Don't know	High/moderate/low

CLINICAL QUESTION 6: In people with diabetes-related foot ulcers, is the use of autologous products including growth factors and placenta-derived products more effective for wound healing compared to standard of care?

(PLACENTAL DERIVED PRODUCTS)

**Evidence statement**: Although a few of the studies were considered at high risk of bias, and none of the definitive studies were patient or care giver blind, those at low risk of bias suggest that the use of placental derived products particularly amniotic membrane are associated with improved absolute healing at times up to 20 weeks, and reduced time to healing. We found no evidence to suggest that there was an influence on new infections, and the short term nature of the majority of studies and the lack of inclusion of patients with significant PAD means that we have no evidence of improvement in amputation rates. No formal cost effectiveness data were found, but the resource use data suggest the interventions may be less expensive for some providers compared to other skin substitutes. Overall, however it appears that these agents do have a significant effect on wound healing, although the choice of agent and cost effectiveness remains to be established

Recommendation 23: Consider the use of placental derived products as an adjunct therapy to standard care for wound healing in people with diabetes related foot ulcers where standard of care alone has failed. (Conditional; Low)

CRITERIA				JUI	DGEMENTS					IMPACT
Desirable Effects	Trivial	Small		Moderat	:e	Larg	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		Small		Triv	ial	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Moderat	:e	Higl	h	No includ	ed studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty of variability		Probably importal uncertai variabilit	nt nty or	unc	important ertainty or ability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not either the intervent	e tion or	Probably favo the intervent	_	Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible and savin	e costs	Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low		Moderat	ce	Higl	h	No includ	ed studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not either the		Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low

			interver the com							
Equity	Reduced	Probably reduced	Probabl impact	y no	Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably n	)	Probable	/ yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably n	)	Probable	<mark>/ yes</mark>	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 7: In people with diabetes-related foot ulcers, is the use of pharmacological interventions more effective for wound healing compared to best standard of care?

(AGENTS PROMOTING PERFUSION AND ANGIOGENESIS)

**Evidence statement**: We found eight studies of agents promoting perfusion and angiogenesis. All were considered at moderate or high risk of bias.

Recommendation 24: Do not use pharmacological agents promoting perfusion and angiogenesis to improve wound healing outcomes over standard of care. (Strong; Low).

CRITERIA		JUDGEMENTS								
Desirable Effects	Trivial	Small	Mod	erate	Lar	ge	Varies	Don't know	High/moderate/low	
Undesirable Effects	Large	Moderate	oderate Small		Triv	<mark>⁄ial</mark>	Varies	Don't know	High/moderate/low	
Certainty of evidence	Very low	Low	Mod	erate	Hig	h	No includ	ed studies	High/moderate/low	
Values	Important uncertainty or variability	Possibly imp uncertainty o variability	or <mark>impo</mark> unce	ably no ortant ortainty or bility	unc	important certainty or iability			High/moderate/low	
Balance of effects	Favors the	Probably favors	Does not favor		ors	Favors the	Varies	Don't know	High/moderate/low	
	comparison	the comparison	either the intervention o	the intervent	ion	intervention				
			the compariso	<u>_</u>						
Resources required	Large costs	Moderate costs	Negligible cost and savings	s Moderate savings		Large savings	Varies	Don't know	High/moderate/low	
Certainty of evidence of required resources	Very low	Low	·	erate	Hig	h	No includ	ed studies	High/moderate/low	
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention o the compariso	the intervent		Favors the intervention	Varies	Don't know	High/moderate/low	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased		Increased	Varies	Don't know	High/moderate/low	
Acceptability	No	Probably no		ably yes	Yes	<u> </u>	Varies	Don't know	High/moderate/low	
Feasibility	No	Probably no		ably yes	Yes		Varies	Don't know	High/moderate/low	

CLINICAL QUESTION 7: In people with diabetes-related foot ulcers, is the use of pharmacological interventions more effective for wound healing compared to best standard of care?

(VITAMINS AND TRACE ELEMENTS)

**Evidence statement**: We identified four studies using supplementation of vitamins and trace elements that reported on the outcome on reduction of ulcer area, all at moderate or high risk of bias

Recommendation 25: Do not use pharmacological agents that supplement vitamins and trace elements to improve wound healing outcomes over standard of care. (Strong; Low)

CRITERIA		JUDGEMENTS								
Desirable Effects	Trivial	Small	Mo	oderate	Larg	ge	Varies	Don't know	High/moderate/low	
Undesirable Effects	Large	Moderate	rate Small		Triv	<mark>rial</mark>	Varies	Don't know	High/moderate/low	
Certainty of evidence	Very low	Low	Mo	oderate	Higl	h	No includ	led studies	High/moderate/low	
Values	Important uncertainty or variability	Possibly imp uncertainty o variability	ly important Probably no No important und		unc	important ertainty or ability			High/moderate/low	
Balance of effects	Favors the comparison	Probably favors the comparison	Does not faveither the intervention the comparis	the interven		Favors the intervention	Varies	Don't know	High/moderate/low	
Resources required	Large costs	Moderate costs	Negligible co			Large savings	Varies	Don't know	High/moderate/low	
Certainty of evidence of required resources	Very low	Low	Mo	oderate	Higl	h	No includ	led studies	High/moderate/low	
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not faveither the intervention the comparis	the interven		Favors the intervention	Varies	Don't know	High/moderate/low	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased		Increased	Varies	Don't know	High/moderate/low	
Acceptability	No	Probably no	Pro	bably yes	Yes		Varies	Don't know	High/moderate/low	
Feasibility	No	Probably no		bably yes	Yes		Varies	Don't know	High/moderate/low	

CLINICAL QUESTION 7: In people with diabetes-related foot ulcers, is the use of pharmacological interventions more effective for wound healing compared to best standard of care?

(RED CELL PRODUCTION)

**Evidence statement**: We identified one study of agents that stimulate red cell production or protein supplementation, which was at moderate risk of bias.

Recommendation 26: Do not use pharmacological agents that stimulate red cell production or protein supplementation to improve wound healing outcomes over standard of care. (Strong; Low)

CRITERIA				JUDGEMENTS					IMPACT
Desirable Effects	Trivial	<mark>Small</mark>	Mo	derate	Large	9	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Small		Trivial		Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Mo	derate	High		No includ	led studies	High/moderate/low
Values	Important uncertainty or variability	Possibly imp uncertainty o variability	or <mark>imp</mark> und	bably no portant certainty or iability	No in	nportant rtainty or bility			High/moderate/low
Balance of effects	Favors the	Probably favors	Does not favo		ors	Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	either the	the interven	tion	intervention			
	·		intervention the comparis						
Resources required	Large costs	Moderate costs	Negligible co	sts Moderate savings		Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Mo	derate	High		No includ	led studies	High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favoreither the intervention the comparis	the interven		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably no impact	Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	Probably no	Pro	bably yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		bably yes	Yes		Varies	Don't know	High/moderate/low

CLINICAL QUESTION 7: In people with diabetes-related foot ulcers, is the use of pharmacological interventions more effective for wound healing compared to best standard of care?

(OTHER PHARMACOLOGICAL)

Evidence statement: We identified 3 studies of other pharmacological agents, and all were at moderate or high risk of bias

Recommendation 27: Do not use other pharmacological agents to improve wound healing outcomes over standard of care. (Strong; Low)

CRITERIA		JUDGEMENTS								IMPACT
Desirable Effects	Trivial	<mark>Small</mark>		Modera	te	Lar	ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate		Small	Small Triv		<mark>/ial</mark>	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low		Modera	te	Hig	h	No includ	ed studies	High/moderate/low
Values	Important	Possibly impo	ortant	Probabl	y no	No	important			High/moderate/low
	uncertainty or	uncertainty o	or	importa	<mark>nt</mark>	und	ertainty or			
	variability	variability		uncerta	i <mark>nty or</mark>	var	iability			
				variabili	ty					
Balance of effects	Favors the	Probably favors	Does not	<mark>t favor</mark>	Probably favo	ors	Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	<mark>either th</mark>	<mark>ie</mark>	the intervent	ion	intervention			
			<mark>interven</mark>	<mark>tion or</mark>						
			the com	<mark>parison</mark>						
Resources required	Large costs	<b>Moderate costs</b>	Negligib	le costs	Moderate		Large savings	Varies	Don't know	High/moderate/low
			and savi	ngs	savings					
Certainty of evidence	Very low	Low		Modera	te	Hig	h	No includ	ed studies	High/moderate/low
of required resources					1		1			
Cost effectiveness	Favors the	Probably favors	Does not		Probably favo		Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	either th		the intervent	ion	intervention			
			interven							
			the com							
Equity	Reduced	Probably	Probably	/ no	Probably		Increased	Varies	Don't know	High/moderate/low
		reduced	impact		increased					
Acceptability	No	Probably no		Probabl		Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no		Probabl	y yes	Yes	i	Varies	Don't know	High/moderate/low

Clinical question 8: In people with diabetes-related foot ulcers, is the use of negative pressure wound therapy more effective for wound healing when compared to standard of care?

**Evidence statement**: The evidence suggests an apparent benefit of NPWT in achieving complete wound closure and faster time to healing versus standard of care in post-operative diabetes-related foot wounds. One study noted no difference in complete wound healing and healing time between traditional NPWT delivered at 125 mmHg continuous pressure and NPWT with simultaneous 0.1% polyhexanide-betaine irrigation in patients with diabetes-related foot infections needing incision and drainage. For chronic ulcers, there is insufficient evidence to establish whether NPWT reduces time to healing when provided in addition to standard of care. The evidence suggests no difference in sustained healing, rate of amputation, rates of infection between NPWT and standard most wound care. Data from post hoc secondary analyses suggest greater cost effectiveness and lower resource utilization with NPWT when compared to moist wound therapy.

Recommendation 28: Consider the use of NPWT as an adjunct therapy to standard of care for the healing of postsurgical diabetes-related foot wounds. (Conditional; Low).

Recommendation 28a. Do not use NPWT as an adjunct therapy to standard of care for the healing of non-surgically related diabetes foot ulcers (Strong; Low)

CRITERIA	JUDGEMENTS								IMPACT	
Desirable Effects	Trivial	Small	Small		Moderate		e	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Mode	Moderate		<mark>Small</mark>		al	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Low		Moderate			No included studies		High/moderate/low
Values	Important uncertainty or variability		oly important tainty or vility	Probabl importa uncerta variabili	i <mark>nt</mark> inty or	unce	mportant ertainty or ability			High/moderate/low
Balance of effects	Favors the comparison	Probably fa the compa	rison either interve	not favor the ention or mparison	Probably favor the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate o	oderate costs Negligib and sav				Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	•	Modera	te	High		No includ	ed studies	High/moderate/low

Cost effectiveness	Favors the	Probably favors	Does not favor	Probably favor	s Favors the	Varies	Don't know	High/moderate/low
	comparison	the comparison	either the	the intervention	n intervention			
			intervention or					
			the comparison					
Equity	Reduced	Probably	Probably no	Probably	Increased	Varies	Don't know	High/moderate/low
		reduced	impact	increased				
Acceptability	No Probably no		Probabl	y yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probabl	y yes	Yes	Varies	Don't know	High/moderate/low

Clinical question 9: In people with diabetes-related foot ulcers, are education and lifestyle programmes compared to standard of care more effective for wound healing?

**Evidence statement**: We found one RCT of educational and lifestyle support programmes which was of low quality and high risk of bias

Recommendation 29: We do not recommend any specific educational and lifestyle support programmes over standard of care to improve healing of diabetes related foot ulcers (Strong; Low)

CRITERIA	JUDGEMENTS								IMPACT	
Desirable Effects	Trivial	<mark>Small</mark>	Small		Moderate		ge	Varies	Don't know	High/moderate/low
Undesirable Effects	Large	Moderate	Moderate		Small		<mark>⁄ial</mark>	Varies	Don't know	High/moderate/low
Certainty of evidence	Very low	Low	Low		Moderate		h	No included studies		High/moderate/low
Values	Important uncertainty or variability		Possibly important uncertainty or variability uncertainty or variability		nt inty or	uncertainty or				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does no either the interventhe com	ie tion or	Probably favo the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligib	Negligible costs Moderate and savings savings			Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	/ery low Low		Moderate		Hig	h	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	e comparison either to interve		the intervent		Favors the intervention	Varies	Don't know	High/moderate/low
Equity	Reduced	Probably reduced	Probably impact		Probably increased		Increased	Varies	Don't know	High/moderate/low
Acceptability	No	No Probably no		Probably yes		Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably no Probab		y yes	Yes		Varies	Don't know	High/moderate/low