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 unblindedand 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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low

Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Moderate	Large	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	Moderate	High	No included studies			High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies			High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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?

(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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

This table is based on the Grade Summary of Judgements Table as provided in the GradePRO software.

For all criteria: determine if it is to be included in your assessment, judge its outcome, and its impact on decision-making. Colour the cell with your judgement.

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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

This table is based on the Grade Summary of Judgements Table as provided in the GradePRO software.

For all criteria: determine if it is to be included in your assessment, judge its outcome, and its impact on decision-making. Colour the cell with your judgement.

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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

This table is based on the Grade Summary of Judgements Table as provided in the GradePRO software.

For all criteria: determine if it is to be included in your assessment, judge its outcome, and its impact on decision-making. Colour the cell with your judgement.

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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

This table is based on the Grade Summary of Judgements Table as provided in the GradePRO software.

For all criteria: determine if it is to be included in your assessment, judge its outcome, and its impact on decision-making. Colour the cell with your judgement

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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	Probably yes	Yes	Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes	Varies	Don't know	High/moderate/low

This table is based on the Grade Summary of Judgements Table as provided in the GradePRO software.

For all criteria: determine if it is to be included in your assessment, judge its outcome, and its impact on decision-making. Colour the cell with your judgement.

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	Small	Moderate	Large		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	Moderate	High		No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High		No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	Probably yes	Yes		Varies	Don't know	High/moderate/low

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

This table is based on the Grade Summary of Judgements Table as provided in the GradePRO software.

For all criteria: determine if it is to be included in your assessment, judge its outcome, and its impact on decision-making. Colour the cell with your judgement.

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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	JUDGEMENTS							IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies			High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies			High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	**JUDGEMENTS**						**IMPACT**
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	JUDGEMENTS						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low

			intervention or the comparison					
Equity	Reduced	Probably reduced	Probably no 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	Probably 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?

(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						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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						IMPACT
Desirable Effects	Trivial	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Small	Moderate	Large	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	Moderate	High	No included studies			High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies			High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Small	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Moderate	Large	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	Moderate	High	No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies / Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		High/moderate/low

Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	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 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	Small	Moderate	Large		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	Moderate	High		No included studies		High/moderate/low
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				High/moderate/low
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	High/moderate/low
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	High/moderate/low
Certainty of evidence of required resources	Very low	Low	Moderate	High		No included studies		High/moderate/low
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	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	Probably yes	Yes		Varies	Don't know	High/moderate/low
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	High/moderate/low