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Continuous Diffused Oxygen Therapy for Wound Healing

Rapid Review

Key Messages

What Is the Issue?

- Wounds are prevalent across health care settings, costing Canada an estimated $12 billion per year in wound care. Chronic wounds (wounds that do not heal in the typical amount of time, which can depend on the size and type of wound) can have a significant impact on a patient's quality of life and health.
- Healing tissue has a high need for oxygen. Oxygen can be delivered in several ways, including topical oxygen therapy, which delivers oxygen directly to the wound. One type of topical oxygen therapy is continuously diffused oxygen (CDO) therapy, which uses a device that takes oxygen from the air and then delivers pure, humidified oxygen to the wound.
- We previously completed a Rapid Review on CDO therapy for wounds in 2020. This review aimed to determine if new evidence has since been published on this topic.

What Did We Do?

- To inform decisions about CDO therapy for wound healing, we sought to identify and summarize literature comparing the clinical effectiveness and cost-effectiveness of CDO therapy versus conventional wound care. We also attempted to identify evidence-based recommendations for the use of CDO therapy.
- We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence published since 2019. One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

What Did We Find?

- CDO therapy appears to be clinically effective for treating patients with diabetic foot ulcers, particularly chronic or hard-to-heal ulcers that have not responded to standard care. Rates of adverse events were comparable between patients receiving CDO and patients receiving standard care. Two cost-effectiveness studies reported that CDO is likely to be cost-effective compared to standard care for patients with chronic, hard-to-heal diabetic foot ulcers.
- We identified fewer studies for other types of wounds. Preliminary evidence suggests that CDO therapy may be helpful for patients with other types of wounds that are chronic or have not responded to standard care. Reporting on adverse events was limited.

Key Messages

- Limited evidence suggests that patients receiving CDO therapy had better outcomes if their wound was debrided more frequently as well as if they received CDO therapy for a longer time.
- The evidence-based guidelines recommend the use of topical oxygen therapy (of which CDO is a subtype) for treating diabetic foot ulcers that have failed to heal with standard care. One guideline suggested that topical oxygen therapy may be considered for other types of non-neoplastic, hard-to-heal wounds.
- We did not find cost-effectiveness evidence for wounds other than diabetic foot ulcers that met the inclusion criteria for our report. We also did not identify any clinical effectiveness or cost-effectiveness evidence, or any guidelines regarding the use of CDO to treat First Nations, Inuit, and Métis patients, that met the inclusion criteria for our report.

What Does This Mean?

- CDO therapy may be beneficial and more cost-effective than standard care for patients with hard-to-heal, chronic diabetic foot ulcers that have not responded to standard care. Evidence-based guidelines also recommend the use of CDO therapy for this patient population.
- The clinical effectiveness and cost-effectiveness of CDO therapy for other types of wounds is still unclear. It is also unclear if there is an optimal way to provide CDO (e.g., oxygen flow rate, debridement, length of treatment).
- We identified limited evidence that reported on patient ethnicity. Considering that some groups, including First Nations, Inuit, and Métis Peoples, have higher rates of diabetes than the overall population in Canada — which may lead to higher rates of diabetic foot ulcers — decision-makers involved in implementing CDO therapy should consider ways to ensure equitable access for all patients who may need this treatment.

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Abbreviations

CDO	continuously diffused oxygen
HTA	health technology assessment
NPWT	negative pressure wound therapy
NRS	nonrandomized study
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SR	systematic review
TPOT	topical pressurized oxygen therapy

Context and Policy Issues

The Impact and Cost of Wounds

Wounds are prevalent across health care settings, impacting patients, health care providers, and the health care system. A study based on Canadian Institute for Health Information data from 2011 to 2012 reported an estimated 28.2% of patients with continuing complex care had potentially preventable wounds, particularly chronic wounds (15.8%).[1] The prevalence across other settings included 9.6% in long-term care, 7.3% in home care, and 3.7% in acute care. However, the authors also noted this is an underestimate as the data did not capture all wounds.[1] In Ontario, 30% to 50% of service delivery includes acute and chronic wound care.[2] Recent reports estimate that the cost of wound care in Canada is approximately $12 billion per year.[3] However, this estimate is from the perspective of the health system and focuses on the direct costs of care and not the indirect costs (e.g., to patients and their carers and/or families). The report also notes the difficulty of accurately estimating the costs of chronic wounds.[3]

Chronic wounds are wounds that do not go through the typical sequence of repair or do not heal in the typical amount of time.[4,5] This may be because the wounds are closing very slowly, are reopening, or are not healing due to impaired physiological processes; this may be caused by conditions like poor blood flow or diabetes. A wound may be considered chronic if it does not heal within 4 to 12 weeks despite treatment[4,5] or if surface area of the wound does not reduce by approximately 15% weekly or 50% over a 1-month period.[6] Chronic wounds can impact a patient's quality of life (e.g., pain, poor sleep due to pain, depression), lead to infection, or require amputation.[4,5]

Caring for Wounds

Currently, standard wound care involves ensuring the wound is dressed, cleaned regularly, and debrided (removing materials like scabs, necrotic materials, infected tissues, pus, and other impurities that may delay wound healing) as needed.[7,8] Adjunct treatments may be also used to aid wound healing, such as delivering oxygen. Healing tissue has a high need for oxygen and nutrients for processes like forming new blood vessels (neovascularization), collagen deposition, and resisting infection.[9]

Oxygen can be delivered in several ways. Hyperbaric oxygen therapy involves having patients breathe in 100% oxygen, and it has been shown to be beneficial for some conditions; however, it also can cause adverse events such as oxygen toxicity and damage to surrounding tissue (i.e., around the wound).[9-11]

What Is CDO Therapy?

An alternative to hyperbaric oxygen is topical oxygen therapy, which provides localized oxygen directly to the wound.[6] There are several categories of topical oxygen therapy, including topical pressurized oxygen therapy (TPOT) and topical continuous oxygen therapy, which is also known as continuously diffused oxygen (CDO) therapy.[11] TPOT uses a chamber or bag that encloses the wound while enriched oxygen (87% to 93%) is administered into the chamber or bag using a respiratory oxygen concentrator. TPOT requires the patient to be immobile during treatment (typically 90 minutes). In CDO therapy, a device takes oxygen from room air and electrochemically converts it to pure, humidified oxygen, which is then continuously delivered

to the wound using an oxygen diffusion dressing to ensure even delivery of oxygen across the wound.[11] CDO devices are wearable, silent, and compact, allowing patients to engage in daily activities while being treated.[12,13]

Why Is It Important to Do This Review?

We previously published a Rapid Review on the use of CDO for wound healing in 2020, which identified 1 systematic review (SR), 3 randomized controlled trials (RCTs), and 1 guideline.[14] The identified evidence indicated that CDO is safe and most effective for patients with diabetic foot ulcers and limited comorbidities, with limited evidence (2 case series identified by the SR) indicating it is effective for patients with other chronic wounds. The guideline recommended against topical oxygen therapy as a primary or adjunctive intervention for diabetic foot ulcers; the strength of the recommendation was weak, and the evidence was graded as low-quality. The previous report also did not identify evidence related to the cost-effectiveness of CDO for wound healing. Overall, it concluded that further studies were needed, including on patients with chronic wounds other than diabetic foot ulcers.[14]

We prepared this report to identify new evidence that has been published since the previous report. Best practice-based wound care may help to improve patient outcomes as well as save health care costs.[15]

Objective

To support decision-making regarding the use of CDO therapy, we prepared this Rapid Review to summarize and critically appraise clinical studies, economic evaluations, and evidence-based guidelines on its use for wound healing.

Additional details of the methods used for this report are presented in Appendix 1.

Research Questions

1. What is the clinical effectiveness of CDO therapy compared with conventional wound care?
2. What is the cost-effectiveness of CDO therapy?
3. What are the evidence-based guidelines regarding the use of CDO therapy?

Methods

Literature Search Methods

An information specialist conducted a customized literature search, balancing comprehensiveness with relevancy, of multiple sources and grey literature on June 20, 2024. One reviewer screened citations, selected studies based on the inclusion criteria presented in Table 1, and critically appraised included publications using established critical appraisal tools.

Appendix 1 presents a detailed description of the methods.

Table 1: Selection Criteria

Criteria	Description
Population	Individuals with wounds. Subpopulations of interest: • First Nations, Inuit, and Métis people • Individuals with chronic wounds
Intervention	CDO therapy
Comparator	Conventional wound care
Outcomes	• Clinical effectiveness: time to wound healing, percentage of wound healing, need for surgical closure or debridement, infection rate, pain control, quality of life • Cost-effectiveness: cost per QALY • Guidance: recommendations regarding the use of CDO therapy for wound healing
Study designs	HTAs, SRs, RCTs, NRSs, economic evaluations, evidence-based guidelines
Publication date	Since January 1, 2019

CDO = continuously diffused oxygen; HTA = health technology assessment; NRS = nonrandomized study; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SR = systematic review.

Summary of Evidence

Quantity of Research Available

A total of 347 citations were identified in the literature search. Following screening of titles and abstracts, 308 citations were excluded and 39 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 31 publications were excluded for various reasons, and 12 publications met the inclusion criteria and were included in this report. These comprised 1 health technology assessment (HTA) which included 1 SR and 1 economic evaluation,[16] 1 scoping review,[17] 2 SRs,[7,18] 1 RCT,[19] 3 nonrandomized studies (NRSs),[20-22] and 4 evidence-based guidelines.[23-26]

Appendix 1 presents the PRISMA[27] flow chart of the study selection. Additional references of potential interest are provided in Appendix 7.

Summary of Study Characteristics

We identified 1 HTA (which included 1 SR and 1 economic evaluation),[16] 1 scoping review,[17] 2 SRs,[7,18] 1 RCT,[19] 3 NRSs,[20-22] and 4 evidence-based guidelines.[23-26] The scoping review[17] and 1 SR[18] had broader inclusion criteria than the current report: the scoping review[17] included topical oxygen therapy in general, while the SR[18] covered interventions to assist with healing of chronic diabetic foot ulcers. Only the characteristics and results of the subset of relevant studies will be described in this report.

Additional details regarding the characteristics of included publications are provided in Appendix 3.

Included Studies for Clinical Effectiveness

The HTA[16] and scoping review[17] were conducted in the UK, while the SRs were conducted in Australia[18] and the US.[7] The SR from the HTA[16] included studies from Canada, China, France, Germany, Israel, the UK, and the US as well as multinational studies; it included 2 SRs, 4 RCTs, and 2 NRSs. The scoping review[17] and 2 SRs[7,18] did not report where their included primary studies were conducted. The scoping review[17] identified 6 SRs and 12 primary clinical studies. One SR[7] was also focused on CDO and included 10 RCTs and 12 NRSs, while another SR[18] identified 7 RCTs relevant to this report. There was some overlap in the primary studies included in the reviews; the overlap table is available in Appendix 6. We also identified 1 RCT[19] and 3 NRSs[20-22] that were not covered by the reviews: the RCT[19] and 2 NRSs[21,22] were conducted in the US, while 1 NRS[20] was conducted in Singapore.

The intervention of interest was CDO, which was also referred to as continuous topical oxygen therapy; where reported, the duration of treatment ranged from 3 weeks to more than 25 weeks, using a flow rate from 3 mL/h to 15 mL/h. One study[19] had 2 CDO groups: 1 group had their wounds covered by a film, while the other group had their wounds covered by a silicone sheet. Comparators included standard care,[7,16-19] pre-post comparisons,[7,17,20,21] or placebo.[7,22] Some reviews did not clearly describe the control groups of the included studies.[7,17]

Across studies, populations included people with any type of wounds;[7,17] people with diabetic foot ulcers;[18,20,21] people with chronic, nonhealing, and complex wounds;[16] and people undergoing bilateral reduction mammoplasty (i.e., a surgical wound).[19] The scoping review[17] included patients with any wounds, but all articles relevant to this report were focused on patients with diabetic foot ulcers. Recognizing that gender is a spectrum, when the terms “men” or “women” were used in the included studies, we retained these terms in reporting on these studies. Reported mean ages ranged from 33 years to 76 years, with 0% to 82% of patients reported as male; articles did not report how sex or gender were defined or measured or report on sex or genders outside male and female. Three primary studies reported on ethnicity.[19-21]

Reported clinical effectiveness outcomes by the SRs and primary studies included:

- complete wound healing (e.g., proportion of wounds healed or proportion of patients whose wound healed)[7,16,20-22]
- change in wound size or partial healing (e.g., wounds less than 90% healed, change in wound size in cm^2)[7,16,20,21]
- score on the Pressure Ulcer Scale for Healing (PUSH) scale, a validated tool for monitoring foot ulcer healing that measures wound size, exudates, and tissue type[7,28]
- scar length[17]
- time to wound closure or healing[16,18,20]
- mortality[16,20]
- amputations[16]
- ulcer recurrence rates (e.g., wounds emerging in the same area as the previously treated wound) or proportion of wounds that stay closed[7,16,20]

- pain, measured by validated scales like the visual analogue scale (VAS)[28] or the Diabetic Foot Ulcer Scale-Short Form,[29] or general scales (e.g., on a scale of 1 to 10)[7,16,20]
- general or other adverse events (e.g., infection).[16,19,20]

Included Studies for Cost-Effectiveness

The SR from the HTA[16] included economic evaluations and identified 1 relevant study; the authors of the review also conducted their own economic evaluation. The identified study by Chan and Campbell was a microsimulation model with a time horizon of 5 years and the perspective of a public payer (Ontario Ministry of Health). The economic evaluation conducted by Health Technology Wales was a Markov model with a time horizon of 50 years from the perspective of the UK National Health Service and personal social services.[16]

Both models looked at patients with hard-to-heal or nonhealing diabetic foot ulcers; in the model by Health Technology Wales, the simulated patients had an average age of 58.20 years and 24% were female.[16] Both models used 6 health states (healed ulcer, diabetic foot ulcer, infected ulcer, minor lower leg amputation, major lower leg amputation, and death), though Chan and Campbell used a 1-year cycle and Health Technology Wales used a 1-month cycle.[16] Both models assessed 12 weeks of CDO compared to standard care; the model by Chan and Campbell also compared CDO to negative pressure wound therapy (NPWT), moist wound therapy, and offloading. Reported outcomes included quality-adjusted life-years (QALYs), life-years, and costs per person.[16]

Key assumptions in the model by Health Technology Wales included that patients had received treatment 12 weeks before model initiation and patients who had previously had an amputation also were at risk of reamputation.[16] Key assumptions in the model by Chan and Campbell included that clinical data from 2 primary studies had similar populations, that results from a US clinical trial were similar to what would occur in Canada, and that there are no additional benefits to CDO treatment after 12 weeks of treatment.[16]

Included Evidence-Based Guidelines

We identified 4 evidence-based guidelines that provided recommendations regarding the use of topical oxygen therapy for wounds; there were no guidelines or recommendations specific to CDO. All were developed by a working group or expert panel.

Two guidelines[23,25] were classified as international: the guideline from the International Working Group on the Diabetic Foot[23] had a working group with members from the US, the Caribbean, Europe, Asia, and Australia, while the other guideline[25] included an expert panel with members from the US and Europe. These guidelines thus may be intended to be used internationally. One guideline was from the Wound Healing Society[24] and another was from the American Diabetes Association;[26] as both associations are based in the US, they may be intended to apply to the US.

Three guidelines[23,24,26] were focused on people with diabetes and provided guidance for treating diabetic foot ulcers. One guideline[25] included patients with wounds in general, including diabetic foot ulcers and other types of hard-to-heal wounds.

Summary of Critical Appraisal

Additional details are provided in Appendix 4.

Scoping Reviews and SRs

All the reviews, including the SR from the HTA as well as the scoping review, stated their objective, the population, and the interventions of interest; all also provided their search strategy, searched multiple databases, and reported the funding source for the review.[7,16-18] All except the scoping review reported risk of bias of the included studies,[7,16,18] though 1[16] did not state what tool they used. Two SRs[7,18] stated that articles were assessed for inclusion by 2 reviewers and 1 reviewer conducted data extraction. In the scoping review,[17] 1 person reviewed the articles, but it was unclear how many reviewers were involved in data extraction. In the SR from the HTA, it was not reported how many reviewers were involved in screening or data extraction.[16] One SR[7] conducted meta-analyses and provided pooled estimates separately for double-arm and single-arm studies; however, they did not explain their choice of model and did not provide pooled results of RCTs only. One SR[18] reported registering the protocol in advance; it was unclear if this was done for the other 3 reviews.

None of the included reviews reported on sources of funding for included studies. It is unclear how many of these studies may have been funded by the device manufacturer and if that may have influenced the reporting. It is also unclear if any of the reviews searched grey literature, which may have resulted in some relevant literature being excluded.

Primary Clinical Studies

All primary clinical studies described their objective, main outcomes, patient characteristics, and intervention.[19-22] The staff and facilities may also have been representative of typical care for patients.[19-22]

The RCT[19] reported withdrawal rates with rationales. One NRS[20] reported that 5 patients discontinued the intervention and provided rationales; analyses appear to include all patients. It is unclear from the remaining 2 NRSs[21,22] if any patients were lost to follow-up or discontinued treatment. The RCT[19] did not blind patients or staff, but this may have had limited influence on the outcome of interest for this report (wound dehiscence or reopening of the surgical wound). None of the NRSs described confounders; thus, it is unclear if their findings may have been influenced by other noncontrolled factors. Although the RCT and 2 NRSs provided details about patient characteristics, no analyses were presented regarding associations between characteristics and outcomes, perhaps due to the relatively small sample sizes. Thus, it is unclear if certain patient characteristics may influence healing with CDO.

Adverse events are presented in 1 NRS[20]. The authors of the RCT[19] did not present adverse events in their analyses, but they noted that some patients discontinued the intervention due to allergies or noncompliance. Limited reporting of adverse events makes it unclear if the intervention may result in any unintended side effects, particularly for patients who are older and thus may be more susceptible to adverse events.

All primary clinical studies disclosed their funding source: the RCT[19] and 2 NRSs[21,22] were funded by a manufacturer of CDO devices, while 1 NRS[20] was funded by a local distributer of a CDO device and stated that the CDO devices were provided at a heavily subsidized price. The RCT[19] stated their report does not necessarily represent the official views of the funder, and 1 NRS[20] also confirmed the funding source did not

impact the study design or execution. Two NRSs[21,22] did not state if the funding source had any influence on study design or execution.

Economic Evaluations

For the economic evaluation conducted by Health Technology Wales as well as the cost-effectiveness study identified by that SR (Chan and Campbell), both reported their objective, the model's viewpoint, the time horizon, and the sources of data.[16] Both also conducted sensitivity analyses. The economic evaluation by Health Technology Wales did not provide a justification for the discount rate used and did not report quantities of events; only annual and per-event costs were reported. The authors based their clinical inputs on studies identified from a meta-analysis as well as a more recent primary study, but they did not describe how they chose the weights for each study. The study by Chan and Campbell used 2 trials for clinical inputs, with 1 comparing CDO to standard care and the other comparing NPWT to standard care; both studies assessed patients with diabetic foot ulcers, and it was assumed their cohorts were similar. The model inputs also used US clinical data when Canadian data were unavailable, but the US data may not be applicable to a Canadian context.

Evidence-Based Guidelines

All identified guidelines[23-26] were clear regarding their scope, purpose, and target users; in all, the guideline authors clearly presented their recommendations, described their methods of formulating recommendations, and appeared to be editorially independent. Three guidelines[23,24,26] were developed by a group of individuals from various professions, used systematic search methods to search for evidence, and clearly described the strengths and limitations of the evidence; it was unclear if 1 guideline[25] met these criteria. In 3 guidelines,[23,25,26] the authors indicated that they sought views of the target population. Two guidelines were externally reviewed before publication, and a procedure for updating them was provided.[23,26]

All guidelines[23-26] provided recommendations regarding the use of topical oxygen therapy. CDO is a subtype of topical oxygen therapy, and thus it is assumed these recommendations also apply to CDO. However, guidance was limited regarding details of how to provide treatment, such as the use of debridement or recommended oxygen flow rates.

Summary of Findings

There was some overlap in the primary studies that were included in the SRs; therefore, to avoid duplication of results, outcome data from an individual primary study are only reported once. Some SRs only presented meta-analyses results, which in some cases had overlapping primary studies. Appendix 5 presents the main study findings, with details regarding overlapping studies.

Clinical Effectiveness of CDO Therapy Versus Conventional Wound Care

Patients With Diabetic Foot Ulcers

Patients with diabetic foot ulcers who received CDO tended to show better results compared to standard care, including:

- higher rates of complete wound healing[16,22]

- greater reduction in wound size[16] — though the authors of the 1 identified RCT reported that their intention-to-treat analysis was not statistically significant, which may have been due to high levels of patient withdrawal.

Two noncomparative studies reported partial wound closure: in 1, 53% of wounds had healed by at least 50% after 3 weeks,[21] and in another, 70% of wounds had healed by at least 75% after 12 weeks.[20]

Patients with more severe diabetic foot ulcers may also be more likely to benefit from CDO — in 2 studies,[16,20] more patients with grade 2 and 3 ulcers (based on the University of Texas Classification scale) in the CDO group healed compared to patients in the standard care group.

Patients whose wounds are debrided more often may have better clinical outcomes. We identified 1 multicentre NRS[22] assessing the impact of CDO on patients with diabetic foot ulcers, and whereas most sites debrided at almost all visits, 1 site debrided at less than half of patient visits. The relative efficacy of CDO versus placebo was 240% when only sites with high debridement were included (i.e., when the 1 site with low debridement was excluded), which is higher than the overall rate with all sites included (204%).

Overall, adverse event rates were low for both the CDO and control groups. Reported adverse events included:

- Mortality: 2 RCTs from 1 SR[16] reported few deaths, with all stated as unrelated to the intervention; 1 NRS[20] reported no deaths.
- Amputation rates: 2 of 3 studies identified in 1 SR[16] had few amputations; 1 RCT (N = 120) reported that 12.5% (CDO plus standard care) and 15% (moist wound dressing therapy plus standard care) of patients had an amputation. However, none of the patients receiving CDO plus moist wound care plus standard care had an amputation. This effect was reported as statistically significant, though further research may be required to determine if other factors contributed to this high amputation rate.
- Wound recurrence (or reopening): No wound recurrence was reported in 2 trials,[16,20] while in 1 trial,[19] a few patients were reported to have experienced wound recurrence. The proportion of patients whose wound stayed closed was high for both the CDO and standard care groups in 2 studies identified by 1 SR[16] and the difference was not statistically significant.
- Self-reported pain: the CDO and control groups tended to both report reduced pain.[7,16] In a single-arm study, the change in pain for patients receiving CDO was reported to be statistically significant.[20] However, in studies that compared CDO to a control group, there was no statistically significant difference between groups on change in reported pain.[7,16]
- General and other adverse events (e.g., infection): Rates were low and tended to be similar between the CDO and control groups, with reported differences not being statistically significantly different across studies.[16,20] Rates of serious adverse events were low and reported as not related to the study.[16]

Patients With Other Types of Wounds — Clinical Benefits

One SR[16] identified 1 RCT and 1 NRS (Kaufman et al.) that included patients with venous leg ulcers:

- The RCT reported that, compared to the control group, the number of patients in the CDO group who had complete wound healing was statistically significantly higher, and their wound size was also statistically significantly smaller at follow-up.
- The NRS reported that 34% of venous ulcers had healed by at least 90%, and another 25% had healed by between 50% and 90%.

The NRS by Kaufman et al.[16] also reported on patients with arterial wounds, pressure ulcers, and other wounds (including burns, post-trauma, and postoperative wounds). The authors did not compare CDO with standard care, but they reported overall healing rates:

- For arterial wounds, 16% of arterial wounds had healed by at least 90%, and another 16% had healed by between 50% and 90%.
- For pressure ulcers, 31% of wounds had healed by at least 90%, and 23% had healed by between 50% and 90%.
- For other types of wounds, 20% of wounds had healed by at least 90%, and 36% of wounds had healed by between 50% and 90%.

The SR with meta-analysis[7] included patients with a mix of etiologies, including some studies also included in the SR[16] conducted by Health Technology Wales; details regarding which studies overlapped are available in Appendix 5. Overall, the meta-analyses of double-arm studies reported that CDO was:[7]

- statistically significantly more effective than control groups in terms of complete wound healing and wound reduction
- not statistically different from control groups in terms of ulcer healing as assessed by the PUSH scale.

They also conducted meta-analyses of single-arm studies, which reported that 48.0% of patients' ulcers completely healed after CDO treatment but wound reduction was not statistically significant.

Reporting on adverse events was limited for this patient population and was limited to wound recurrence or wounds staying closed:

- A meta-analysis of 2 studies[7] reported that the proportion of patients whose wound stayed closed was statistically significantly higher in the CDO group compared to the control group. This may be due to the inclusion of 1 NRS of patients with venous leg ulcers, where 14 of 30 patients had wound recurrence. It is unclear if this is due to patients with venous leg ulcers tending to have higher rates of wound recurrence compared to patients with diabetic foot ulcers or if it is due to other factors.
- An RCT[19] of patients who underwent a bilateral reduction mammoplasty found that the number of patients whose wounds reopened was low and not statistically significant between the CDO and standard care groups.

Cost-Effectiveness of CDO Therapy Versus Conventional Would Care

Health Technology Wales conducted an SR that included economic evaluations and identified 1 relevant study (Chan and Campbell, 2020); they also conducted their own cost-effectiveness study.[16] Overall, both studies reported that for patients with nonhealing or hard-to-heal diabetic foot ulcers, when compared to standard care, CDO was associated with higher total QALYs and lower costs, making the incremental cost-effectiveness ratio dominant (i.e., a greater benefit at a lower cost). Scenario analyses indicated that CDO remained dominant except under the following scenarios:

- Reported by Health Technology Wales:
  - Grade 1 ulcers (CDO and standard care were equally effective, but CDO costs more)
- Reported by Chan and Campbell; these scenarios reported lower costs for CDO, but worse outcomes:
  - Proportion of patients in the NPWT group whose ulcers healed was higher (57 out of 169 healed, or 33.7%; base case assumed 27.8%)[30]
  - Patients in the subgroup with a baseline ulcer size of 1.5 cm^2 to 2.15 cm^2 (the smallest size; the base case included ulcer sizes from 1.5 cm^2 to > 4.9 cm^2)

The economic evaluation by Health Technology Wales[16] also reported that CDO is likely to be cost-effective compared to standard care, with a probability of 95.36% at a willingness-to-pay threshold of £20,000 per QALY. They also reported that CDO was cost-effective if it could heal 32% of wounds, and was dominant if it could heal 40% of wounds.

Recommendations Regarding the Use of CDO Therapy

Three guidelines recommended the use of topical oxygen therapy for diabetic foot ulcers.[23,24,26] The recommendation from the International Working Group on the Diabetic Foot (IWGDF) group[23] was a conditional recommendation due to low-certainty evidence, such as lack of reporting on adverse events and concerns around equity due to the costs of the device. The other 2 guidelines[24,26] noted that the evidence was of high quality but did not provide a strength of recommendation.

- Two guidelines[23,26] recommended using topical oxygen therapy as an adjunct therapy for diabetic foot ulcers that have failed to heal following standard care.
- The Wound Healing Society's guideline for diabetic foot ulcers states that topical oxygen increases healing and reduces time to heal, which may be an indirect recommendation for the use of topical oxygen therapy.[24]

The last guideline by Frykberg et al. (2023)[25] provided recommendations for topical oxygen therapy for hard-to-heal wounds in general, but noted the evidence for CDO was of high quality. They also did not provide strength of recommendations.

- They recommended using topical oxygen therapy for hard-to-heal wounds in general, including venous leg ulcers and pressure ulcers.
- They stated that there is currently insufficient evidence for patients with critical limb ischemia.

- They recommended against using topical oxygen therapy on wounds that are infected, undebrided or necrotic, or have a malignancy.

Recommendations regarding treatment duration were limited; this may be because treatment duration will depend on the patient's healing. Frykberg et al.[25] provided a treatment algorithm, stating that if topical oxygen therapy is provided, to reassess the patient at 1 to 2 weeks; if the wound is healing (defined as having reduced in size by at least 50%), the treatment could continue and be reassessed at 1 to 2 weeks.

First Nations, Inuit, and Métis Patients

We did not conduct any searches specific to First Nations, Inuit, and Métis patients. However, based on our general search of CDO and wound healing, we did not identify any studies on the clinical effectiveness or cost-effectiveness on CDO in these populations. We also did not identify any evidence-based guidelines regarding the use of CDO to treat First Nations, Inuit, and Métis patients. Three studies were identified that reported demographic information related to ethnicity, and these did not report analyses of First Nations, Inuit, and Métis patients.

Limitations

Study Quality

The included clinical effectiveness studies noted various limitations, including high withdrawal rates,[16] lack of blinding,[16,19] small sample sizes,[19-21] and short follow-up periods.[19,21] The meta-analysis[7] also tended to pool studies with different patient populations (i.e., different types of wounds). This may have resulted in biased or imprecise treatment effects.

Generalizability

Much of the clinical literature, as well as both economic evaluations and most guidelines identified by this report, were specific to patients with diabetic foot ulcers. We did not identify any cost-effectiveness studies for patients with nondiabetic foot ulcer wounds. Thus, the clinical- and cost-effectiveness of CDO compared to standard care for other types of wounds is unclear. It is also unclear if there are differences between different CDO devices.

There was limited information regarding patient ethnicity in most of the identified studies: we did not identify any relevant studies or recommendations related to the use of CDO for First Nations, Inuit, and Métis patients. In Canada, certain groups have higher prevalence rates for diabetes, including people who are South Asian, Black, First Nations, Inuit, or Métis; thus, they may also be disproportionately affected by diabetic foot ulcers.[31,32] Thus, it is unclear if the findings from the identified studies are generalizable to certain patient groups that may have high need for treatment for diabetic foot ulcers.

The identified publications included studies from various countries including Canada: 3 studies identified within 1 SR[16] were from Canada, including 1 RCT, 1 NRS, and 1 economic evaluation. All 3 of these studies focused on patients with diabetic foot ulcers. It is unclear if the findings for patients with other types of

wounds would be applicable to Canada, as clinical outcomes may vary due to differences between countries (e.g., how health care is delivered, population characteristics). We also did not identify any Canada-specific guidelines, though the international guidelines may be applicable for health care providers and patients within Canada.

Conclusions and Implications for Decision- or Policy-Making

In 2020, we published a review on CDO for wounds:[14] this report found limited clinical evidence related to CDO for wounds other than diabetic foot ulcers, no economic evaluations, and 1 weak recommendation for the use of topical oxygen therapy for diabetic foot ulcers based on low-quality evidence.

In this update, we identified 1 HTA that included 1 SR and 1 economic evaluation,[16] 1 scoping review,[17] 2 SRs,[7,18] 1 RCT,[19] 3 NRSs,[20-22] and 4 evidence-based guidelines[23-26] related to the use of CDO for patients with wounds. The reviews included 6 of the 7 primary studies previously identified in the 2020 report; the studies that were previously included are indicated in Appendix 6. However, we have also identified several new clinical studies in this report, adding evidence that suggests CDO is effective for diabetic foot ulcers (particularly those that are chronic and nonhealing), as well as a few studies related to other types of wounds. We also identified 2 economic evaluations[16] indicating that CDO has the potential to be cost-effective for hard-to-heal, chronic diabetic foot ulcers, including 1 from the perspective of the Ontario Ministry of Health. Several new evidence-based guidelines have been published that recommend topical oxygen therapy as an adjunctive therapy for nonhealing diabetic foot ulcers that have not healed with standard care alone,[26,33] with 1 also recommending the use of topical oxygen therapy for other types of hard-to-heal or chronic wounds.[25]

Thus, CDO appears to be clinically effective and cost-effective for hard-to-heal diabetic foot ulcers and has been recommended as an adjunct treatment for patients with diabetic foot ulcers that have not responded to standard care. Some studies suggest CDO may also be effective for treating other types of hard-to-heal wounds like venous leg ulcers and pressure ulcers, though we identified only a few studies related to patients with these types of wounds. Regarding implementation, it may be helpful to consider methods of ensuring equitable access to CDO so that all patients who need the treatment can receive it.

Considerations for Future Research

Overall, most of the identified evidence was focused on patients with diabetic foot ulcers, though a few studies also found positive outcomes for patients with other types of wounds. There was limited reporting on adverse events for other types of wounds (i.e., not diabetic foot ulcers), and we did not identify any cost-effectiveness studies on CDO for other types of wounds. In addition, most of the included studies did not report on patient ethnicity. Future research should consider investigating CDO for different types of wounds, including clinical effectiveness as well as adverse events, its cost-effectiveness compared to standard care, as well as its impact for different groups of patients. This would allow for a better understanding of whether CDO is effective for other types of wounds and across patient groups.

Additional research comparing CDO to other types of treatment may also be of interest. The guidelines by ElSayed et al.[26] and Chen et al. (IWGDF)[23] both suggest considering various treatments for nonhealing diabetic foot ulcers, including topical oxygen therapy, placental-derived products, and autologous fibrin and leukocyte platelet patches, but it is unclear if certain treatments are more effective and if they should be used for different situations (e.g., types of wounds). Additional studies comparing CDO to other active comparators may help to determine if certain treatments are more clinically effective overall or for specific types of wounds.

We identified limited evidence regarding the need for debridement with CDO as well as what oxygen flow rate is most effective. One NRS[22] indicates that patients who had follow-up visits at sites with higher rates of surgical debridement had greater benefits. One guideline[25] also recommends against using topical oxygen therapy on wounds that are undebrided. The authors of 1 SR[7] stated that studies of devices that deliver oxygen at a flow rate of 3 mL/h suggest they are as clinically effective as devices that deliver oxygen at 15 mL/h, but they did not report any formal analyses comparing devices with different flow rates. It is thus unclear if debridement is necessary and what types are best (e.g., autolytic, enzymatic, mechanical) as well as if certain flow rates are more clinically effective. Additional studies are required to better understand these factors, as they may help improve outcomes for patients receiving CDO therapy.

Advances in remote monitoring technology may also be applicable to CDO therapy. A case series reported on a pilot study in which patients with diabetic foot ulcers were treated with CDO alongside a remote assessment and monitoring tool that was able to capture wound measurement data remotely from patients and communicate it to a clinician via a noninvasive app.[34] The preliminary study reported positive outcomes, suggesting that this may be a useful tool for some patients (e.g., those who have difficulty travelling to a clinic regularly for appointments); however, in-clinic visits may still be required for patients who need wound debridement. Larger studies are required to better determine if CDO with remote monitoring technology should be adopted more widely and to assess the associated clinical outcomes, costs, and resource requirements.[34]

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Appendix 1: Methods

Note this appendix has not been copy-edited.

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were CDO therapy and wound healing. The search was completed on June 20, 2024 and limited to English-language documents published since January 1, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. As an update to a previous CADTH report, articles were included if they were made available since the previous search date and were not included in the 2020 CADTH report.[14] The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Figure 1 presents the PRISMA[27] flow chart of the study selection.

Exclusion Criteria

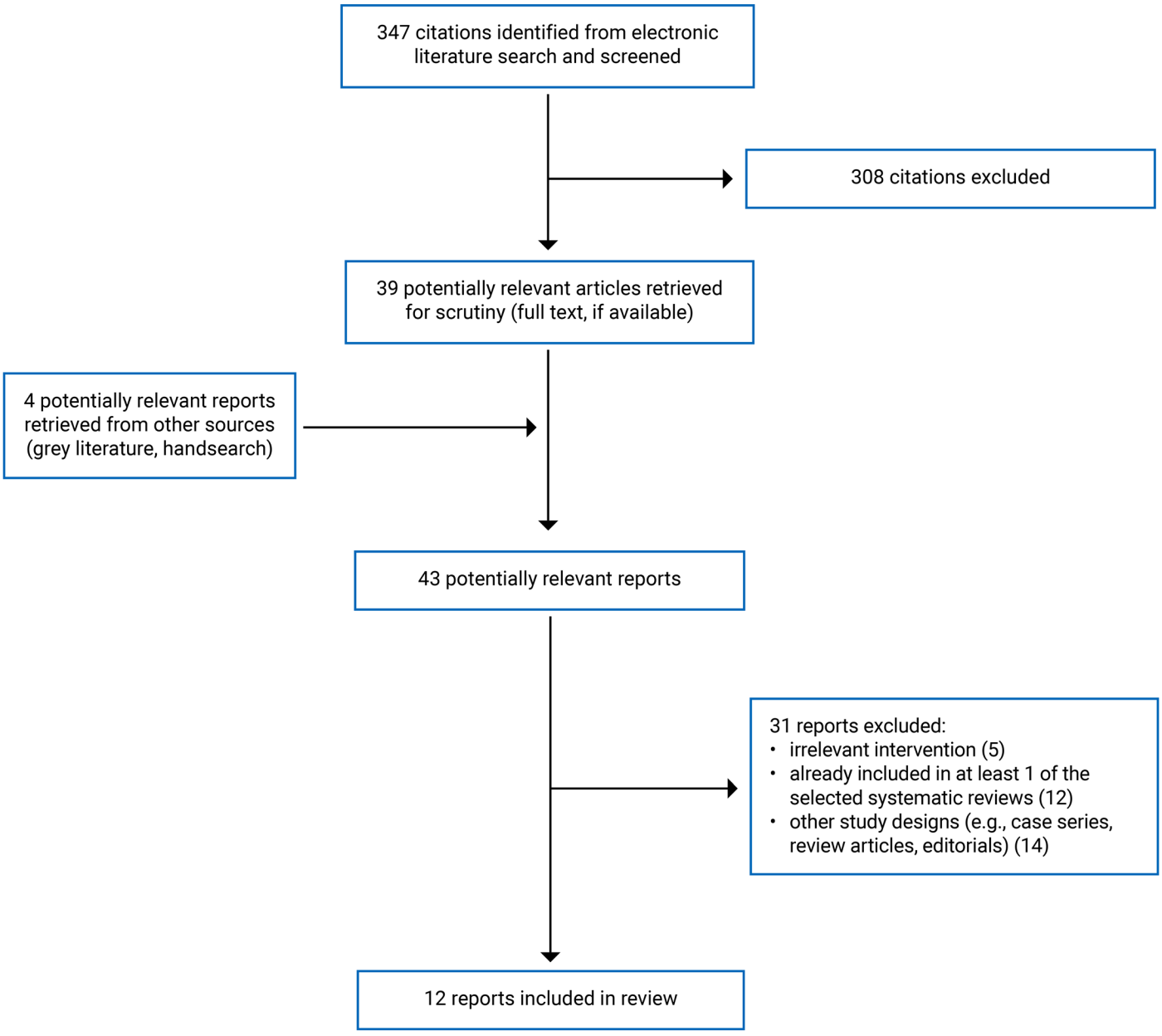
Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were duplicate publications. SRs in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[35] for SRs, the Downs and Black checklist[36] for RCTs and NRSs, the Drummond checklist[37] for economic evaluations, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[38] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Appendix 2: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 3: Characteristics of Included Publications

Note this appendix has not been copy-edited.

Table 2: Characteristics of Included HTA, Scoping Review, and SRs

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Outcomes, length of follow-up
HTA				
Health Technology Wales (2022)[16] Wales **Funding source:** Health Technology Wales is funded by the Welsh Government	A rapid SR that prioritized SRs of RCTs, followed by RCTs, comparative NRSs, and then single-arm NRSs. Search was conducted on August 4, 2022, with no date limits. Included 9 studies: • 2 SRs on DFUs • 3 RCTs on DFUs • 1 RCT on multiple wound types • 2 NRSs on multiple wound types • 1 economic evaluation on DFUs	Population of interest was people with chronic, nonhealing and complex wounds (e.g., DFUs, venous leg ulcers, arterial ulcers). People with acute wounds were excluded.	**Intervention:** Continuous topical oxygen wound therapy (3 mL/h to 15 mL/h) in addition to standard care **Comparator**: Cleaning and dressing the wound, as well as standard care for the wound type: • DFUs: offloading, regular debridement, standard and advanced dressings • Venous leg ulcers: compression therapy, standard and advanced dressings • Arterial ulcers: revascularization, standard and advanced dressings	Outcomes: • Wound reduction (in size and time taken to reduce) • Wound recurrence or exacerbation • Need for further treatment • Length of hospital stay • Number of appointments needed to attend (general practitioner or home visits or outpatient) • Risk of amputation • Risk of infection • Mortality • Safety • Quality of life • Compliance • Cost Follow-up: preferred longer follow-up, but would include short-term if longer was not available
Scoping review				
Sýkorová et al. (2024)[17,a] UK **Funding source:** University of Nottingham; University of Nottingham; SOE Health Ltd.	A review of topical oxygen therapies, including CDO. Databases were searched for papers published until December 14, 2022. Included 49 studies in total, including 8 SRs (3 with MAs). Of the studies relevant to this report, there were • 6 SRs (2 with MAs)	Patients with any wounds. All relevant SRs and most primary studies were all related to patients with DFUs; other populations covered by the primary studies included surgical wounds and venous leg ulcers.	**Eligible interventions:** Topical oxygen therapies **Relevant intervention:** CDO (3 mL/h to 15 mL/h) **Comparator:** Any	Outcomes of interest: • Wound healing • Wound closure • Healing time • Wound area or size • Scar length • Tissue appearance • Ulcer recurrence • Adverse events (e.g., infection, amputation) Follow-up: relevant included

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Outcomes, length of follow-up
	• 12 primary clinical studies			studies follow-up ranged from 4 weeks to 1 year where reported
SRs				
Chen et al. (2024)[18] Australia Funding source: developed for the IWGDF guidelines,[33] which were sponsored by Mölnlycke, Urgo Medical, Reapplix, Advanced Oxygen Therapy Inc., and Essity	An SR of all RCTs up until October 2022. Included 262 RCTs in total. There were 10 studies for topical oxygen therapy, 7 of which were on CDO and thus relevant to this report.	Patients with DFUs	**Eligible interventions:** Interventions relevant to wound healing **Relevant intervention:** Topical oxygen therapy (flow rate NR) **Comparator:** Standard care unless otherwise stated	Outcomes: • Complete wound healing • Time to healing • Sustained healing • Reduction in ulcer area • Amputation (major or minor) • Quality of life • Maintenance of function and ability to perform activities of daily living • New infection • Resource utilization • Death/mortality Length of follow-up: NR
Nagarsheth et al. (2024)[7] US **Funding source:** NIH Awards and Veteran Affairs Awards	An SR with MA of literature on human patients published after 2012, as authors stated articles published before this were not relevant. Date of search not reported, but manuscript was submitted in 2023. Included 22 studies (10 RCTs and 12 NRSs; NRSs included prospective double-arm and single-arm studies, as well as case reports).	Patients with cutaneous wounds of any etiology. Identified papers included patients with: • DFUs • Pressure ulcers • Ulcers secondary to vascular etiology • Ulcers secondary to sickle cell wounds • Ulcers secondary to infected surgical wounds	**Intervention:** CDO (3 mL/h to 15 mL/h) **Comparator**: Standard of care, pre-post comparison, or undescribed control group	Outcomes: • Proportion of wounds completely healed • Wound reduction • PUSH score (to assess wound healing) • VAS (to assess pain rating) • Ulcer recurrence Follow-up: Ranged from 10 days to 9 years

CDO = continuous diffused oxygen; DFU = diabetic foot ulcer; HTA = health technology assessment; IWGDF = International Working Group on the Diabetic Foot; MA = meta-analysis; NR = not reported; NRS = nonrandomized study; RCT = randomized controlled trial; SR = systematic review; VAS = visual analogue scale.

Note: All outcomes reported by the reviews that were relevant to this report are listed. Due to overlap between reviews on included primary studies, some outcomes reported by a review may not be presented in the findings, as they have already been reported by a different review, to avoid double-reporting.

[a]Sýkorová et al. (2024)[17] labelled their study as a scoping review and used typical scoping review methodology. However, as they summarized clinical outcomes relevant to this report, it was included.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Relevant clinical outcomes, length of follow-up
RCT				
Zulbaran-Rojas et al. (2023)[19] US **Funding source:** EO_2 Concepts, Inc.	RCT (within person randomized trial, or split body trial: all patients received the intervention on 1 breast and the comparator on the other breast)	Adults (N = 16; does not include 3 participants who withdrew) undergoing a bilateral reduction mammoplasty: • Women: 100% • Age (years), mean (SD): 33 (8) • BMI (kg/m^2), mean (SD): 34.34 (5.85) • Ethnicity (%): African-American (93.8%), Hispanic (6.2%) • Comorbidities: former smoker (18.7%), diabetes (12.5%), asthma (31.2%), anemia (37.5%), medicated for depression (37.5%)	**Intervention:** CDO (15 mL/h) for 4 weeks; included • Direct CDO: wound was covered by a film • Silicon CDO: wound was covered by a silicon sheet **Comparator**: standard of care using an identical topical skin adhesive system	Outcomes of interest: • Exploratory outcomes: wound dehiscence (a total separation of previously approximated wound edges) Follow-up: 4 weeks
NRSs				
Tang et al. (2024)[20] Singapore **Funding source:** • Inotec AMD Ltd. provided the CDO devices at a heavily subsidized price • Somnotec Ltd., the local distributer, provided a small physician-initiated grant to conduct the study	NRS – before-after	Adults (aged 21 to 90 years) with diabetes and a DFU for more than 12 weeks but fewer than 18 weeks (between 0.5 cm^2 to 50 cm^2), minor amputation sites with < 50% healed in 4 weeks, 4 weeks of standard care at the hospital-based diabetic foot clinic (N = 20) • Age (years), mean (SD): 65.7 (11.6) • BMI (kg/m^2), mean (SD): 24.6 (4.3) • Sex or gender: 65.0% male • Ethnicity: Chinese (55.0%), Malay (25.0%), Indian (15.0%), Sikh (5.0%) • Smoking status: Nonsmoker (70.0%), Smoker (20.0%), Ex-smoker (10.0%) • HbA1c (mmol mol^{-1}), mean (SD): 6.9 (1.3) • Comorbidities: hypercholesterolemia (90%), hypertension (90%), ischemic cardiomyopathy (75%), end stage renal failure (60%) Wound types and characteristics:	**Intervention:** CDO (15 mL/h) at home for 12 weeks **Comparator**: Baseline measures	Outcomes: • Change in ulcer size • Absolute closure numbers • Number of infections • Quality of life improvement • Pain score (VAS) • Safety and adverse events Follow-up: • 16 weeks postbaseline or until ulcer has remained healed for 4 weeks • Mean days follow-up after 3 months of CDO therapy (SD): 70.9 (33.0)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Relevant clinical outcomes, length of follow-up
		• Chronic DFU: 40% • Surgical wounds (postamputation): 60% • Concomitant Angioplasties for CLTI: 90% • Transcutaneous oxygen measurement (mm Hg), mean (SD): 34.1 (19.6) • Toe pressure, (mm Hg), mean (SD): 50.8 (24.1) • Wound duration before CDO application (days), mean (SD): 114.4 (79.1) • Wound area at baseline (cm^2), mean (range): 12.6 (0.6 to 44.0)		
Lavery et al. (2020)[21] US **Funding source:** EO_2 Concepts, Inc.	NRS – Prospective cohort study with before-after comparison	Adults (aged 18 to 89) with a diagnosis of diabetes mellitus (based on American Diabetes Association criteria) with a full thickness ulcer below the ankle. Patient characteristics provided by patients who healed (healers; N = 12) and for those who did not heal (nonhealers, N = 11). Means of continuous variables are presented per group; dichotomous variables are presented as overall for both groups. Groups were not statistically significantly different on any characteristics. • Age (years), mean (SD): 58.2 (9.4) for healers, 54.1 (10.8) for nonhealers • BMI (kg/m^3), mean (SD): 34.80 (10.6) for healers, 36.49 (8.37) for nonhealers • Male, n/N: 15/23 • Race, n/N: Caucasian (11/23), African-American (5/23), Hispanic (7/23) • Substance use history: tobacco (7/23), alcohol (5/23) • Foot ulcer history, n/N: 13/23 • Amputation history: 15/23 • Type II diabetes: 22/23 • Diabetes duration (years), mean	**Intervention:** CDO (flow rate NR) for 3 weeks **Comparator**: baseline (pre-post comparison)	Outcome of interest: • Proportion of patients healed • Proportion of patients with at least 50% wound area reduction Follow-up: 3 weeks

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Relevant clinical outcomes, length of follow-up
		(SD): 13.5 (8.4) for healers, 14.8 (8.8) for nonhealers • Coronary artery disease, n/N: 3/23 • Congestive heart failure, n/N: 1/23 • Retinopathy, n/N: 3/23 • Chronic kidney disease, n/N: 7/23		
Lavery et al. (2019)[22] US **Funding source:** EO_2 Concepts, Inc.	Post hoc analysis of RCT (double-blind, placebo-controlled)	Adults with DFUs (N = 146) • Age (years), mean (SD): 56.3 (12.4) • Men: 77%	**Intervention:** CDO (3 mL/h) with debridement (frequency at discretion of physician) for 12 weeks **Comparator**: placebo	Outcomes: • Percentage of healed ulcers Follow-up: 12 weeks or wound closure

CDO = continuously diffused oxygen; DFU = diabetic foot ulcer; NR = not reported; NRS = nonrandomized study; RCT = randomized controlled trial; SD = standard deviation; VAS = visual analogue scale.

Table 4: Characteristics of Included Economic Evaluations

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Health Technology Wales (2022)[16] Wales **Funding source:** Health Technology Wales is funded by the Welsh Government	**Analysis:** Cost-utility analysis **Time horizon:** 50 years **Perspective:** UK NHS and personal social services	Patients with chronic, nonhealing DFUs; initiated with average age of 58.20 years, 24% female	**Intervention:** 12 weeks of CDO with standard care **Comparator:** 12 weeks of standard care	Markov structure with a 1-month cycle length, tracking patients over 6 health states over a lifetime: • healed ulcer • DFU • infected ulcer • minor lower leg amputation • major lower leg amputation • death	• Patient baseline characteristics: SR by Thanigaimani et al., 2024 (excluding 1 study that was not CDO) and Serena et al., 2021 • Efficacy data: SR by Thanigaimani et al., 2024 (excluding 1 study that was not CDO) • Transition probabilities: Chan and Campbell, 2020 • Mortality: Wales data (Office for National Statistics, 2021) • Resource use and costs: UK NHS, personal social services; diabetes costs from Stedman et al., 2020, NICE, NHS England • Treatment costs: manufacturer and NICE • Health-related quality of life: NICE	• Patients who had an amputation event had an annual risk of reamputation • Minor reamputation can include the amputation of another toe • Major reamputation would involve the amputation of the other limb • Patients assumed to receive treatment in 12 weeks before model initiation, which determined proportion of patients in “healed ulcer” or “DFU” state

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Chan and Campbell (2020) as reported by Health Technology Wales[16] Canada **Funding source:** EO_2 Concepts Inc.	**Analysis**: Cost-utility analysis **Time horizon**: 5 years **Perspective**: Public health care payer (Ontario Ministry of Health)	Individuals with hard-to-heal DFUs (Grade IA according to the University of Texas staging system for DFU); ulcer may be present for more than 1 month but less than 1 year	**Intervention:** 12 weeks of CDO **Comparator**: 12 weeks of NPWT, standard care, moist wound therapy, and offloading	Microsimulation model with 1-year cycle length; simulated individuals could move between 6 mutually exclusive states: • healed from ulcer • DFU • minor lower leg amputation • major lower leg amputation • infected ulcer • death	• Clinical data: Niederauer et al. (2018), Blume et al. (2008) • Cost of CDO: manufacturer's reported estimate • Treatment costs: Ontario Physician schedule of benefits, Wodchis et al. (2012) • Cost of NPWT: CADTH (2003) • Long-term cost of health care: Ontario diabetes population cohort • Utility data: Redekop et al. (2004) • Currency: Canadian dollars, but converted to US dollars for results	• No additional benefits of CDO treatment after 12-week treatment period • Assumed clinical data studies by Niederauer and Blume had similar patient populations, though they were different studies with different patient populations • Results of US clinical trials are similar in Canadian context

CDO = continuous diffusion oxygen; DFU = diabetic foot ulcer; NPWT = negative pressure wound therapy; OECD = Organisation for Economic Co-operation and Development.

Table 5: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update)[23]						
Intended users: Health care professionals involved in care of people with diabetes **Target population**: People with diabetes	Intervention of interest: Topical oxygen therapy[a] Practice considered: NR	• Complete wound healing • Amputation • Resource use • Adverse events	GRADE and Cochrane methodology used to develop clinical questions and outcomes, conduct an SR (and a MA where appropriate).	• GRADE methods used to create a summary of findings table for each clinical question, then to create evidence statements for outcomes with certainty of evidence:[39] ◦ High: "We are very confident that the true effect lies close to that of the estimate of the effect" ◦ Moderate: "We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different" ◦ Low: "Our confidence in the effect estimate is limited: The true effect may	Multidisciplinary working group summarized findings, then drew conclusions for each intervention as evidence statements. Based on these and expert opinion, summary of judgment tables for each clinical question and the recommendation was drafted. The working group included members from podiatric surgery, podiatry, and endocrinology disciplines, with members from the US, Caribbean, Europe, Asia, and Australia. A voting procedure was used for each recommendation for the direction (for or against) and strength of the recommendation (strong or condition), with a majority vote needed for final recommendations.	Guidelines were sent to a panel of independent international experts and people with lived experience for their critical review; the guidelines were revised based on their comments.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
				be substantially different from the estimate of the effect" ◦ Very low: "We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect"		
WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines[24]						
Intended users: Clinicians **Target population:** People with diabetic foot ulcers	Intervention of interest: Topical oxygen therapy[a] Practice considered: NR	Unclear	Keyword search of multiple databases, focused on human and disease-specific data, limited to SRs, MAs, RCTs, retrospective series reviews, clinical case series, and expert recommendations published since January 2006.	Strength of evidence: • Level I: MA or at least 2 RCTs supporting intervention; or multiple laboratory or animal experiments with at least 2 clinical series supporting laboratory results • Level II: at least 1 RCT and at least 2 significant clinical series or expert opinion papers with literature reviews supporting intervention; convincing experimental evidence	Delphi consensus by panel members, which included academics, clinicians, and researchers.	NR

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
				but insufficient human experience • Level III: suggestive data of proof of principle, but lacking sufficient MA, RCTs, or multiple clinical series		
Use of topical oxygen therapy in wound healing[25]						
Intended users: Health care professionals **Target population:** People with wounds	Intervention of interest: CDO devices, disposable CDO devices Practice considered: NR	Outcomes from relevant studies included: • Healing time • Proportion of wounds healed • Number of patients who achieved complete wound closure • Reduction in wound area • Pain	NR	Quality of evidence and strength of recommendations were based on the American Diabetes Association GRADE system: • A: clear evidence from well-conducted, generalizable RCTs that are adequately powered • B: Supportive evidence from well-conducted cohort studies • C: Supportive evidence from poorly controlled or uncontrolled studies • E: Expert consensus or clinical experience	Expert panel of 9 key opinion leaders from US and Europe met to discuss clinical evidence in support of TOT in care of hard-to-heal wounds; meeting resulted in a consensus document.	NR
12. Retinopathy, neuropathy, and foot care: Standards of care in diabetes—2023[26]						
Intended users: Health care professionals	Intervention of interest: Topical oxygen therapy	Unclear	Systematic literature review conducted. Evidence summaries are	Quality of evidence and strength of recommendations were	Expert panel met for 2-day meeting to present evidence	Feedback obtained from external peer reviewers.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Target population: People with diabetes	Practice considered: NR		made by the Professional Practice Committee.	based on the American Diabetes Association GRADE system: • A: clear evidence from well-conducted, generalizable RCTs that are adequately powered • B: Supportive evidence from well-conducted cohort studies • C: Supportive evidence from poorly controlled or uncontrolled studies • E: Expert consensus or clinical experience	summaries and develop recommendations. A year-long public comment period requesting feedback was held.	

EWMA = European Wound Management Association; GRADE = Grading of Recommendations Assessment Development and Evaluation; IWGDF = International Working Group on the Diabetic Foot; MA = meta-analysis; NR = not reported; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Grouping Network; SR = systematic review.

[a]Recommendation is for topical oxygen therapy; it does not specify if this includes continuous diffused oxygen therapy.

Appendix 4: Critical Appraisal of Included Publications

Note this appendix has not been copy-edited.

Table 6: Strengths and Limitations of SRs Using AMSTAR 2[35]

Strengths	Limitations
HTA	
Health Technology Wales (2022)[16]	
• Stated objective. • Stated population, interventions, comparators, and outcomes of interest. • Literature search included multiple databases; search strategy used is provided. • Included studies were described in adequate detail, including study location (country). • Provides some critical appraisal of included SRs (e.g., potential double-counting of participants). • Reported risk of bias in SRs, as reported by original SR authors. • Reported heterogeneity in identified studies. • Funding information available on the website.	• Did not state if protocol was established before the conduct of the review, if it was registered, or if there were any significant deviations from the protocol. • Did not state if grey literature was searched. • Did not report how many reviewers were involved in screening or data extraction, so it is unclear if study selection and extraction were done in duplicate. • Did not provide lists of included or excluded studies. • Discussed risk of bias in primary studies but unclear what tool was used. • Did not state funding for included studies.
Scoping review	
Sýkorová et al. (2024)[17]	
• Stated objective. • Stated patients, concept, and context of interest. • Literature search included multiple databases; search strategy used is provided. • Included studies were described in adequate detail. • Reported funding and conflicts of interest of authors.	• Did not state if protocol was established before the conduct of the review, if it was registered, or if there were any significant deviations from the protocol. • Did not explain selection of study designs included, though nonrandomized studies were eligible; nonhuman studies were excluded. • Did not state if grey literature was searched. • Abstract and full-text reviewing was done by 1 reviewer. • Data were extracted using a tool developed by the project team; it is unclear if this was done by the tool or if a reviewer was involved. • Did not provide lists of included or excluded studies, possibly due to the volume of included literature (532 studies in total). • Risk of bias was not assessed. • Did not state funding for included studies. • Heterogeneity briefly mentioned, noting it does not allow for meaningful comparisons. • Did not assess overlap in primary studies between the included SRs.

Strengths	Limitations
SRs	
Chen et al. (2024)[18]	
• Stated objective. • Stated population, interventions, comparators, and outcomes of interest. • Provided justification in guideline for only including RCTs. • Protocol was registered in advance at PROSPERO. • Literature search included multiple databases, search strategy was provided. • Title-abstract screening was performed independently by 2 reviewers. Full texts were assessed by 1 of 6 pairs of reviewers independently. • Included studies were described in adequate detail. • Risk of bias was assessed using the Cochrane Risk of Bias 2 tool as well as 21-point criteria by Jeffcoate et al. The score was then translated to a level of evidence according to SIGN instructions. Risk of bias scoring was done in pairs, with 1 reviewer extracting data and 1 confirming accuracy; conflicts were resolved by consensus and, if necessary, a third reviewer. • Discussed bias when presenting and discussing results. • Discussed heterogeneity present in the results of the review. • Presented conflicts of statement. • Funding information is available on the guidelines website.	• Did not state if grey literature was searched. • One reviewer conducted data extraction. The second reviewer assessed the first reviewer's work. It was not reported if they checked agreement on a sample of studies. • Did not provide lists of included or excluded studies, possibly due to the volume of included literature (532 studies in total). • Did not report on sources of funding for included studies.
Nagarsheth et al. (2024)[7]	
• Stated objective. • Stated population and intervention of interest. • Described data extraction process, including extracted outcomes. • Literature search included multiple databases; authors stated MeSH terms used. • Two reviewers evaluated each included article. • Data extraction provided important patient characteristics data. • Risk of bias was assessed by 1 reviewer using the Cochrane Risk of Bias tool for randomized trials and the Cochrane Risk of Bias in Nonrandomized Studies of Interventions for nonrandomized studies. Domains assessed included confounding variables, participant selection, intervention classification, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. • Pooled estimates presented separately for double-arm and single-arm studies. • Presented authors' funding.	• Did not clearly present comparators of interest. • Did not state date of literature search. • Did not state if protocol was established before the conduct of the review, if it was registered, or if there were any significant deviations from the protocol. • Did not explain selection of study designs included, though nonrandomized studies were eligible; nonhuman studies were excluded. • Did not state if grey literature was searched. • One reviewer conducted data extraction. The second reviewer assessed the first reviewer's work. It was not reported if they checked agreement on a sample of studies. • Provided a list of included studies, but reporting is somewhat unclear; for example, a publication is listed as included, but risk of bias assessment is not presented. Another publication's (by the same author) risk of bias assessment is presented. • Did not provide a list of excluded studies. • Some details of the included studies were not described, such as what country the study was

Strengths	Limitations
	conducted in and funding. • Did not explain choice of meta-analysis model. • Unclear if studies pooled together for meta-analyses were sufficiently similar and thus appropriate for meta-analysis. • Pooled RCTs with double-arm NRSs and did not provide pooled results of RCTs only. • Did not appear to assess potential impact of risk of bias in individual studies on the results of the meta-analysis. • Did not appear to account for risk of bias in individual studies when interpreting or discussing results of the review. • Briefly discussed heterogeneity but did not explore further beyond indicating it was not statistically significant. • Did not discuss publication bias. • Did not present results by type of injury, making it unclear if outcomes vary by type of injury.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; HTA = health technology assessment; MeSH = Medical Subject Headings; NRS = nonrandomized study; RCT = randomized controlled trial; SR = systematic review.

Table 7: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[36]

Strengths	Limitations
RCT	
Zulbaran-Rojas et al. (2023)[19]	
• Objective presented. • Main outcomes described. • Characteristics of patients described. • Intervention described. • Main findings clearly described. • Exact P values reported. • Staff and facilities may be representative of typical treatment received by patients. • Presented flow chart of patients including the number of patients who were not included in the analysis with rationale for dropping out. • Statistical tests were appropriate. • Some outcomes were objective (e.g., wound dehiscence). • Stated funding source (industry) and that the content does not necessarily represent official views of sponsor.	• Confounders not described. • No blinding of patients or staff. This may have influenced some subjective outcomes. • Adverse events not reported. • Unclear if patients were representative of population from which they were recruited. • Effect of confounders not investigated. • Potential compliance issues, as some patients reported irritation to the intervention device. • Relatively small sample size; further studies needed to better understand effect of intervention. • Did not assess functional outcomes due to short follow-up period.

Strengths	Limitations
NRSs	
Tang et al. (2024)[20]	
• Objective presented. • Main outcomes described. • Characteristics of patients described. • Intervention described. • Main findings clearly described. • Exact P value reported for 1 outcome. • Adverse events reported. • Reported number of patients who discontinued treatment and rationales. • Staff and facilities may be representative of typical treatment received by patients. • Statistical tests were appropriate. • Compliance appears to have been reliable. • Some outcomes were objective (e.g., wound area). • Stated funding source (industry) and that funding source had no role in study design, execution, analysis, data interpretation, or decision to submit results for peer review.	• Confounders not described. • No blinding of patients or staff. • P values were not reported for all outcomes. • Unclear if patients were representative of population from which they were recruited. • As this was a before-after study, there was no randomization. • Effect of confounders not investigated. • Some outcomes were subjective and thus may be biased due to factors like lack of blinding.
Lavery et al. (2020)[21]	
• Objective clearly described. • Main outcomes described. • Characteristics of patients described. • Intervention described. • Actual P values reported. • Population was patients treated in clinics, therefore may be representative of this patient group. • Staff, locations, and facilities likely representative of treatment most patients receive. • Statistical tests were appropriate. • Compliance with intervention was likely reliable. • Stated funding source (industry).	• Confounders not described. • Outcomes of interest for this report (percentage of patients healed, percentage with wound reduction) not presented in simple form (e.g., numerators and denominators for percentage calculations; only percentages provided). This may be because this was not the main outcome. • Patients and staff were not blinded. • Adverse events not reported. • Unclear if any patients were lost to follow-up. • Unclear if findings are generalizable beyond the US. • There was no control arm, as this was a before-after comparison. • Duration of study was brief (3 weeks). • Did not state if funding source had any influence on study design, analysis, or data interpretation.
Lavery et al. (2019)[22]	
• Objective clearly described. • Main outcomes described. • Characteristics of patients briefly described, with reference to original study provided. • Intervention described. • Actual P values reported.	• Confounders not described. This is a post hoc analysis of a RCT, but it is unclear of potential confounding may have occurred. • Some outcomes were not presented in simple form (e.g., numerators and denominators for percentage calculations; only percentages provided). • Adverse events not reported.

Strengths	Limitations
• Patients were recruited from multiple sites across the US, and therefore may be representative of patients in the US. • Staff, locations, and facilities likely representative of treatment most patients receive. • Patients, physicians, and the observer assessing wound closure were blinded. • Statistical tests were appropriate. • Compliance with intervention was likely reliable. • Patients were randomized to intervention or control from the same population. • Stated funding source (industry).	• Unclear if any patients were lost to follow-up. • Unclear if findings are generalizable beyond the US. • This was a post hoc analysis and it is not clear if this analysis was planned for in advance. • Outcome was not objective and relied on self-reported rates of debridement. • Did not state if funding source had any influence on study design, analysis, or data interpretation.

NRS = nonrandomized studies; RCT = randomized controlled trial.

Table 8: Strengths and Limitations of Economic Evaluations Using the Drummond Checklist[37]

Strengths	Limitations
Health Technology Wales (2022)[16]	
• Authors presented the economic importance of the research question, question being addressed, and viewpoint. • Described characteristics and rationale for choice of comparators. • Stated form of evaluation used. • Stated sources of data. • Briefly described clinical trials used as basis of model. • Clearly stated primary outcomes. • Reported currencies and how inflation was adjusted for. • Reported time horizon. • Reported discount rate used. • Described methods used for scenario and sensitivity analyses. • Reported incremental analysis and impact on major outcomes. • Answered original study question.	• Unclear how weighting of the clinical studies used as basis of inputs was calculated. • Reported annual and per-event costs but did not report quantities. • Did not provide justification for discount rate.
Chan and Campbell (2020) based on reporting by Health Technology Wales (2022)[16]	
• Authors presented the economic importance of the research question, question being addressed, and viewpoint. • Described characteristics and rationale for choice of comparators. • Stated form of evaluation used. • Stated sources of data. • Briefly described clinical trials used as basis of model. • Clearly stated primary outcomes.	• Used 2 clinical trials as basis of clinical outcomes data; assumed cohorts were similar, but did not indicate why this assumption was made. • There was no direct comparison of CDO to NPWT, so a clinical trial conducted in the US was used, which may impact the results due to differences between the studies (e.g., cohort characteristics). • Wounds healed associated with CDO was limited to 12-week follow-up due to lack of evidence regarding longer-term

Strengths	Limitations
• Reported cost and utility inputs with monetary values and quantities separately. • Reported currencies and how inflation was adjusted for. • Reported time horizon. • Reported and justified discount rate used. • Described methods used for sensitivity analysis. • Reported incremental analysis and impact on major outcomes. • Answered original study question.	follow-up. • Lack of long-term data regarding patients with chronic DFU meant the analysis was limited to 10 years. • Model inputs were heterogeneous, using Canadian data where available as well as US data when Canadian-specific data were not available; outcomes may differ in a Canadian context due to differences in health care delivery and population characteristics. • Based on publishing clinical trials that did not prospectively collect data for an economic evaluation. • NPWT is typically used for patients with larger and complex wounds, so these patients may have had more severe wounds compared to patients in the CDO trial. • CDO trial only included chronic wounds, unclear if this was also the case for the NPWT trial. • Quality of life estimates were based on other published literature instead of assessing within the trial.

CDO = continuous diffused oxygen; DFU = diabetic foot ulcer; NPWT = negative pressure wound therapy.

Table 9: Strengths and Limitations of Guidelines Using AGREE II[38]

Item	Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update) (2024)[23]	WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines (2024)[24]	Use of topical oxygen therapy in wound healing (2023)[25]	12. Retinopathy, neuropathy, and foot care: Standards of care in diabetes—2023 (2023)[26]
Domain 1: Scope and purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes
Domain 2: Stakeholder involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	NR	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	NR	Yes	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes
Domain 3: Rigour of development				
7. Systematic methods were used to search for evidence.	Yes	Yes[a]	NR	Yes

Item	Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update) (2024)[23]	WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines (2024)[24]	Use of topical oxygen therapy in wound healing (2023)[25]	12. Retinopathy, neuropathy, and foot care: Standards of care in diabetes—2023 (2023)[26]
8. The criteria for selecting the evidence are clearly described.	Yes	No	No	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	No	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Unclear	Unclear	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	No	Yes
13. The guideline has been externally reviewed by experts before its publication.	Yes	NR	NR	Yes
14. A procedure for updating the guideline is provided.	Yes	No	No	Yes
Domain 4: Clarity of presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes

Item	Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update) (2024)[23]	WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines (2024)[24]	Use of topical oxygen therapy in wound healing (2023)[25]	12. Retinopathy, neuropathy, and foot care: Standards of care in diabetes—2023 (2023)[26]
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	Yes	No	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	No	Yes	No
20. The potential resource implications of applying the recommendations have been considered.	Yes	No	Yes	No
21. The guideline presents monitoring and/or auditing criteria.	NR	NR	NR	Yes
Domain 6: Editorial independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes	Yes	Yes

Item	Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update) (2024)[23]	WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines (2024)[24]	Use of topical oxygen therapy in wound healing (2023)[25]	12. Retinopathy, neuropathy, and foot care: Standards of care in diabetes—2023 (2023)[26]
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; IWGDF = International Working Group on the Diabetic Foot; NR = not reported.

[a]Keyword search of databases.

Appendix 5: Main Study Findings

Note this appendix has not been copy-edited.

Table 10: Summary of Main Findings – Complete and Partial Wound Healing for Patients With Diabetic Foot Ulcers

Study citation and study design	For SRs: included study, first author, and study design	Method of measurement	Result	Notes
Health Technology Wales (2022)[16] HTA (SR)	Thanigaimani (2021) SR-MA including 6 RCTs: 530 participants from: Driver et al. (2017), Driver et al. (2013), Frykberg et al. (2020), Niederauer et al. (2017), Niederauer et al. (2018), Yu et al. (2016)	Main meta-analysis for complete wound healing, RR (95% CI)	1.94 (1.19 to 3.17)	Assumes patients lost to follow-up had full healing.
		Sensitivity meta-analysis for complete wound healing, RR (95% CI)	1.54 (1.07 to 2.30)	Assumes patients lost to follow-up did not achieve full healing.
		Meta-analysis for complete wound healing, including only 3 low risk of bias studies, RR (95% CI)	2.37 (1.52 to 3.68)	NA
		Leave-one-out analysis for complete wound healing, effect size (95% CI)	1.83 (1.03 to 3.25) • I^2: 0.57	Omits 1 study (Frykberg et al., 2020).
	Serena (2021)[a] RCT N = 145; for PP analysis, N = 128 Follow-up: 12 weeks	Number of wounds healed in ITT analysis:	• Continuous TOT: 36/81 (44.4%) • Control group: 18/64 (28.1%) • P = 0.044	Results from PP analysis are included in the MA by Nagarsheth et al. (2024).
		Number of wounds healed in PP analysis:	• Continuous TOT: 36/69 (52.2%) • Control group: 18/59 (30.5%) • P = 0.013	NA
		Difference in wound area between continuous TOT and control groups, mean (95% CI)	• ITT analysis: - 5.33 (−34.37 to 23.81) • P = 0.718 • PP analysis: - 29.74 (−50.54 to −8.96) • P = 0.005	PP analysis appears to have been included in the MA by Nagarsheth, 2024. This result has been included here to present both the ITT

Study citation and study design	For SRs: included study, first author, and study design	Method of measurement	Result	Notes
				and PP analyses. Study had high withdrawal.
		Reduction in wound area (%), mean (SD)	• Continuous TOT group: 70% (45.5) • Standard care group: 40% (72.1) • P = 0.005	NA
	Yu (2016) RCT	Healing rate of ulcers by UTC grade	Grade 1: • Continuous TOT: 100% • Standard care: 100% Grade 2: • Continuous TOT: 100% • Standard care: 0% Grade 3: • Continuous TOT: 50% • Standard care: 0%	Pooled results are included in the MA by Thanigaimani (2021); this result is presented here to show the differences by ulcer grade (i.e., severity).
	Connaghan, 2021 to 1 RCT N = 124 Follow-up: 4 weeks	Wound size reduction at week 4 (%), mean (range)	• Continuous TOT: 87% (55.7 to 100%) • Standard care: 46% (15 to 99%) • P < 0.05	RCT: Driver, 2017
	Kaufman, 2021 NRS Follow-up: NR	Percentage of wounds by healed state	• Healed (> 90% of wound closed): 26% • Healing (> 50% of wound closed) 32% • "Slow responders" (wound closed < 50% but > 10%): 19% • "Nonresponders" (wound closed < 10%): 23%	Refer to note in footnotes.
Tang et al. (2024)[20] NRS Follow-up: 12 weeks	NA	Complete healing by UTC grade ulcer, n of N (%)	• Grade 1: 1 of 2 (50%) • Grade 2: 5 of 5 (100%) • Grade 3: 8 of 13 (62%)	Pooled results are included in Nagarsheth et al. (2024); this result is presented here to show the difference between healing by ulcer grade.

Study citation and study design	For SRs: included study, first author, and study design	Method of measurement	Result	Notes
		Wounds with > 75% closure, n (%)	14 (70.0%)	
Lavery et al. (2020)[21] NRS Follow-up: 3 weeks	NA	Proportion of patients with healed ulcers	13%	NA
		Percentage of patients with at least 50% wound closure after 3 weeks	53%	NA
Lavery et al. (2019)[22] NRS Follow-up: 12 weeks	NA	Proportion of ulcers healed	At sites that debrided the wound at nearly every visit: • CDO: 51.2% • Placebo: 21.3% • P = 0.006	At sites with high debridement rates, the frequency was high for both CDO and placebo groups. Surgical debridement was used.
		Relative efficacy of active vs. placebo by frequency of ulcer debridement	• Overall: 204% • At sites with high debridement (excludes 1 site with low debridement): 240%	Mean debridement across all sites was 90.0% (of visits). Most sites had debridement at 92% to 100% of visits, except 1 site that conducted debridement at 41.3% of visits. When this 1 site was excluded, the average debridement rate 98.4%.
		Analysis of patients who were Hispanic: relative efficacy of active vs. placebo by frequency of ulcer debridement	• Overall: 220% • At sites with high debridement (excludes 1 site with low debridement): 382%	High debridement: average of 97.9% of visits had debridement. Included most sites except 1 (41.3% debridement).

CI = confidence interval; HTA = health technology assessment; ITT = intention-to-treat; NA = not applicable; NRS = nonrandomized study; OR = odds ratio; PP = per-protocol; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference; SR = systematic review; TOT = topical oxygen therapy; UTC = University of Texas Classification.

Note: The UTC ulcer grading system ranges from 0 to 4 (least to most severe respectively).[28] All patients in the study by Kaufman et al. (2021) had been previously treated with SoC but their wounds had failed to heal, with wounds being open for an average of 10.7 (SD = 15.7) months before study initiation.

[a]Patients in the study by Serena et al. (2021) included patients with diabetic foot ulcers and minor amputation wounds. Health Technology Wales included these findings alongside other studies focused on patients with diabetic foot ulcers only, so we have done the same here to match their reporting.

Table 11: Summary of Main Findings – Complete and Partial Wound Healing for Patients With Arterial Wounds, Leg Venous Ulcers, Pressure Ulcers, and Other Types of Wounds

Study citation and study design	For SRs: included study	Method of measurement	Result	Notes
Arterial wounds				
Health Technology Wales (2022)[16] HTA (SR)	Kaufman, 2021 NRS Follow-up: unclear	Percentage of wounds by healing state	• Healed (> 90% of wound closed): 16% • Healing (> 50% of wound closed): 16% • "Slow responders" (wound closed < 50% but > 10%): 25% • Nonresponders (wound closed < 10%): 44%	Refer to note in footnotes.
Leg venous ulcers				
Health Technology Wales (2022)[16] HTA (SR)	Altinbas and Şahsivar, 2022 RCT Follow-up: 45 days	Number of people with complete wound healing	• Continuous TOT: 28/64 (44%) • Control group: 1/64 (0.02%) • P < 0.001	NA
		Wound size (cm^2), mean (SD)	Baseline: • Continuous TOT: 30.82 (11.93) • Control: 27.73 (14.87) • P = 0.15 Day 15: • Continuous TOT group: 21.45 (4.24) • Control group: 27.75 (13.42) • P = 0.005 Day 30: • Continuous TOT: 13.21 (2.64) • Control: 26.84 (13.74) • P = 0.003 Day 45: • Continuous TOT: 4.41 (2.21)	Unclear if "mean" indicates total mean across the follow-up period or at a specific follow-up time.

Study citation and study design	For SRs: included study	Method of measurement	Result	Notes
			• Control: 27.41 (13.42) • P = 0.001 Mean: • Continuous TOT: 6.72 (3.35) • Control: 27.72 (14.66) • P = 0.001	
		Statistical significance of wound size change from baseline to day 45	• Continuous TOT: P = 0.001 • Control: P = 0.17	NA
	Kaufman, 2021 NRS Follow-up: varied; some followed for more than 25 days	Percentage of wounds by healing state	• Healed (> 90% of wound closed): 34% • Healing (> 50% of wound closed): 25% • "Slow responders" (wound closed < 50% but > 10%): 22% • Nonresponders (wound closed < 10%): 18%	Refer to note in footnotes.
		Reduction in wound area for patients treated with continuous TOT plus standard care by length of treatment (%), mean (SD)	• For patients treated for > 25 days: 67.9% (35.3%) • For patients treated for < 25 days: 36.6% (36.4%)	NA
Pressure ulcers				
Health Technology Wales (2022)[16] HTA (SR)	Kaufman, 2021 NRS N = 13 Follow-up: NR	Percentage of wounds by healing state	• Healed (> 90% of wound closed): 31% • Healing (> 50% of wound closed) 23% • "Slow responders" (wound closed < 50% but > 10%): 23% • Nonresponders (wound closed < 10%): 23%	Refer to note in footnotes.

Study citation and study design	For SRs: included study	Method of measurement	Result	Notes
Mixed or unclear etiologies				
Nagarsheth et al. (2024)[7] SR with MA	MA of double-arm studies: includes 7 studies. N = 725 (treatment: n = 369; control: n = 356)	Complete healing, OR (95% CI)	4.48 (2.05 to 9.77) P < 0.001 I^2 = 76.34%	Includes results from Serena (2021) reported above (from Health Technology Wales, 2022), as well as 3 studies presented by Thanigaimani's SR (also from Health Technology Wales, 2022): Driver (2017), Frykberg (2020), Niederauer (2017). The remaining 3 studies included in this meta-analysis (Azimian (2015), Tawfick (2013; NRS), Altinbas (2022)) have not been reported elsewhere in this report.
	Single-arm studies; includes 9 studies N = 4,273	Participants who completely healed after continuous TOT, n/N	1195/4273	Studies included: Includes results from Tang (2021) which are also reported above (by UTC grade). Other studies included: Hunter (2020), Kaufman (2018), Segey (2019), Copeland (2017), Hayes (2017), Igwegbe (2015), Cole (2020), Massenburg (2016). Removal of case series did not change results regarding proportion of wound healed.

Study citation and study design	For SRs: included study	Method of measurement	Result	Notes
		Pooled prevalence, % (95% CI)	48.0% (0.34 to 0.62) • P < 0.001 • I^2 = 84.11%	NA
	MA of 6 double-arm studies N: • Treatment: n = 226) • Control: n = 236	Difference in wound reduction between treatment and control, SMD (95% CI)	−0.85 (−1.88 to 0.18) • P = 0.12 • I^2 = 95.93%	Includes Serena (2021) described above in the report by Health Technology Wales. This MA appears to based on their PP analysis.
	MA of 2 single-arm studies N = 29	Wound reduction after continuous TOT, treatment mean (95% CI)	1.54 (0.71 to 2.38) • P = 0.33	Heterogeneity was < 25% (I^2 = 0).
	MA of 2 RCTs N: • Treatment: n = 79 • Control: n = 74	Difference in change on PUSH score between intervention and control, SMD (95% CI)	0.65 (−0.56 to 1.86) • P = 0.29 • I^2 = 92.38%	Includes children with pressure ulcers and patients infected chronic surgical wounds.
Health Technology Wales (2022)[16] HTA (SR)	Kaufman, 2021 NRS Follow-up: unclear	Percentage of wounds by healing state	• Healed (> 90% of wound closed): 20% • Healing (> 50% of wound closed): 36% • "Slow responders" (wound closed < 50% but > 10%): 8% • Nonresponders (wound closed < 10%): 36%	• Other wounds: burns, post-trauma and postoperative wounds. • Refer to note in footnotes.

CI = confidence interval; HTA = health technology assessment; ITT = intention-to-treat; MA = meta-analysis; NA = not applicable; NRS = nonrandomized study; PP = per-protocol; PUSH = pressure ulcer scale for healing; RCT = randomized controlled trial; SMD = standardized mean difference; SR = systematic review; TOT = topical oxygen therapy.

Note: All patients in the study by Kaufman et al. (2021) had been previously treated with SoC but their wounds had failed to heal, with wounds being open for an average of 10.7 (SD = 15.7) months before study initiation.

Table 12: Summary of Main Findings — Mortality in Patients With Diabetic Foot Ulcers

Variable	Health Technology Wales (2022)[16] – HTA (SR)		Tang (2024)[20] – NRS
	Thanigaimani, 2022 – SR (1 RCT)	Serena et al., 2021 – RCT	
Total number of patients	NR	145	20
Follow-up	12 weeks	12 weeks	12 weeks
Number of deaths			
Continuous TOT plus standard care	0	1[a]	0
Standard care	2[a]	0	0

HTA = health technology assessment; ITT = intention-to-treat; NR = not reported; PP = per-protocol; NRS = nonrandomized study; SR = systematic review; TOT = topical oxygen therapy.

[a]Deaths reported as not related to the intervention.

Table 13: Summary of Main Findings — Amputations in Patients With Diabetic Foot Ulcers

Variable	Health Technology Wales (2022)[16] – HTA (SR)		
	Thanigaimani, 2022 – SR (1 RCT)	Al-Jalodi, 2022 – Post hoc analysis of RCT	He, 2021 – RCT
Total number of patients	124	22	120
Follow-up	12 weeks	1 year	1 year
Number of amputations (n)			
Continuous TOT plus standard care	0	0	NR
Standard care	1	1	NR
Proportion of patients who had amputations (%)			
Continuous TOT plus standard care	NR	NR	12.5%
Moist wound dressing therapy plus standard care	NR	NR	15%
Continuous TOT plus moist wound care dressing plus standard care	NR	NR	0%
P value	NR	NR	0.045

HTA = health technology assessment; NR = not reported; RCT = randomized controlled trial; SR = systematic review; TOT = topical oxygen therapy.

Table 14: Summary of Main Findings — Wound Recurrence or Wounds Staying Closed in Patients

Variable	Health Technology Wales (2022)[16] – HTA (SR)			Nagarsheth et al. (2024)[7] – SR	Tang et al. (2024)[20] – NRS	Zulbaran-Rojas et al. (2023)[19] – RCT
	Connaghan, 2021 (SR – 1 RCT)	Connaghan, 2021 (SR – 1 NRS)	Al-Jalodi, 2022 (Post hoc analysis of RCT)	MA of 2 double-arm studies (1 RCT, 1 NRS)	NA	NA
Total number of patients	100	10	22[a]	101	20	32
Follow-up	12 weeks	8 weeks	1 year	12 or 50 weeks	12 weeks	4 weeks
Type of wound(s) included	DFUs	DFUs	DFUs	DFUs, venous ulcers	DFUs	Postsurgery
Number of patients who had recurrence or reopening of wound						
CDO plus standard care	NR	0	NR	4/66	0	1
Silicon CDO	NR	NR	NR	NR	NR	0
Standard care	NR	0	NR	16/35[b]	0	2
Pooled odds ratio (95% CI)	NR	NR	NR	0.08 (0.02 to 0.26)	NR	NR
P value	NR	NR	NR	0.001	NR	NR
I^2	NR	NR	NR	45.99%	NR	NR
Proportion of patients whose wound stays closed						
Continuous TOT plus standard care	90%	NR	85%	NR	NR	NR
Standard care	87.5%	NR	60%	NR	NR	NR
Statistical significance	Not significantly different	NR	Too small to reach statistical significance	NR	NR	NR

DFU = diabetic foot ulcer; HTA = health technology assessment; ITT = intention-to-treat; NA = not applicable; NR = not reported; NRS = nonrandomized study; PP = per-protocol; RCT = randomized controlled trial; SR = systematic review; TOT = topical oxygen therapy.

Note: Recurrence typically defined as a wound emerging in the same area as the previously treated wound.

[a]29 participants consented to participants; 7 were lost to follow-up.

[b]Most of these events (14/30) occurred in the study of patients with venous ulcers.

Table 15: Summary of Findings by Outcome — Pain for Patients With Diabetic Foot Ulcers

Study citation and study design	For SRs: included studies (study design), follow-up	Method of measurement	Result	Notes
Nagarsheth et al. (2024)[7] SR-MA	3 RCTs Follow-up: NR N = • Treatment: n = 163 • Control: n = 151	SMD of VAS between treatment and control arms (95% CI)	−0.17 (−0.92 to 0.59): • P = 0.67 • I^2 = 90.88%	NR
Health Technology Wales (2022)[16] SR	Connaghan, 2021 – includes 1 NRS Follow-up: 8 weeks N = 10	Number of patients who rated their pain as 5 or higher on a scale of 1 to 10 (analogue scale)	• Start of study: 39% • End of study: 7%	NR
	Serena (2021) RCT Follow-up: 12 weeks N = 145; for PP analysis, N = 128	VAS score, mean (SD)	**ITT analysis** • Continuous TOT: ◦ Baseline: 1.8 (2.53) ◦ Final visit: 0.95 (1.9) • Control: ◦ Baseline: 2.02 (2.57) ◦ Final visit: 0.68 (1.43) • P = 0.278 **PP analysis** • Continuous TOT: ◦ Baseline: 1.85 (2.51) ◦ Final visit: 0.62 (1.27) • Control: ◦ Baseline: 1.98 (2.51) ◦ Final visit: 0.71 (1.47) • P = 0.956	Nagarsheth et al. (2024)'s MA includes the results from this study; however, it is unclear if they used the ITT or PP analysis results.
Tang et al. (2024)[20] N = 33 Follow-up (days), mean (SD): 70.9 (33.0) after finishing 3 months of treatment	NA	Mean pain score based on the Diabetic Foot Ulcer Scale-Short Form (DFU-SF)	• Baseline: 2.4 (1.8) • 3 months: 0.5 (1.0) • P = 0.008	NR

ITT = intention-to-treat; MA = meta-analysis; NA = not applicable; NR = not reported; PP = per-protocol; RCT = randomized controlled trial; SD = standard deviation; SMD = standardized mean difference; SR = systematic review; TOT = topical oxygen therapy; VAS = visual analogue scale.

Table 16: Summary of Findings by Outcome — General and Miscellaneous Adverse Events

Study citation and study design	For SRs: included studies (study design), follow-up	Method of measurement	Result	Notes
Diabetic Foot Ulcers				
Health Technology Wales (2022)[16] HTA (SR)	Thanigaimani, 2021 (SR – includes 2 RCTs) Follow-up: 12 weeks N = 163	Number of adverse events	• Continuous TOT group: 23 • Control group: 26	None of the adverse events reported as related to the intervention.
		Number of serious adverse events	• Continuous TOT group: 0 • Control group: 2 (gangrene)	None of the adverse events reported as related to the intervention.
	Connaghan, 2021 (SR – includes 1 RCT) Follow-up: 12 weeks N = 124	Proportion of patients who had infections	• Continuous TOT group: 3.6% • Control group: 10.15%	Not statistically significantly different.
		Proportion of patients who had cellulitis incidents	• Continuous TOT group: 1.2% • Control group: 6.9%	Not statistically significantly different.
	Serena, 2021 – RCT Follow-up: 12 weeks N = 145	Number of adverse events, n/N	Continuous TOT group: • Mild: 22/41 • Moderate: 12/41 • Severe: 6/41 • Life-threatening:1/42 Standard care group: • Mild: 15/32 • Moderate: 9/32 • Severe: 8/32 • Life-threatening: 0/32	Life-threatening adverse event reported as not related to the study. Unclear if any severe adverse events were due to the device; 2 events (1 intervention, 1 control) were deemed as possibly related to the intervention used.
Tang et al. (2024)[20] NRS N = 33 Follow-up (days), mean (SD): 70.9 (33.0) after finishing 3 months of treatment	NA	Number of adverse events	4 (all due to secondary infection)	NR

CDO = continuous diffused oxygen; HTA = health technology assessment; NA = not applicable; NR = not reported; NRS = nonrandomized study; RCT = randomized controlled trial; SR = systematic review; TOT = topical oxygen therapy.

Table 17: Summary of Main Findings of Included Economic Evaluations

Outcome	Result
Health Technology Wales (2022)[16]	
Total QALYs	
Continuous TOT + standard of care	7.89
Standard of care	7.72
Incremental	0.17
Total life-years	
Continuous TOT + standard of care	10.75
Standard of care	10.59
Incremental	0.17
Total costs per patient	
Continuous TOT + standard of care	£35,786
Standard of care	£35,997
Incremental	-£211
ICER	Dominant (greater benefit at lower cost)
Sensitivity analyses	• Results were robust in probabilistic and deterministic sensitivity analyses, and scenario analyses. • From deterministic analysis, continuous TOT is only likely to be nondominant if the comparative efficacy of continuous TOT to SoC is altered, if the proportion of patients whose wound remains healed following treatment is decreased, or if patient baseline age increases. However, it is still cost-effective. • Likely to be cost-effective compared to standard of care alone at a probability of 95.36% and a willingness-to-pay threshold of £20,000 per QALY. • From scenario analyses, continuous TOT was not cost-effective only if the efficacy of continuous TOT and standard of care were assumed equivalent, due to higher costs of continuous TOT.
Author conclusions	"There appeared to be improvements across outcomes for DFUs, usually over a period of up to 12- weeks of continuous TOT-use, but up to one-year for some outcomes. However, the evidence we identified varied according to DFU aetiology, DFU grade, duration of continuous TOT treatment and follow-up times, duration of SoC prior to study, and type of SoC."[16]
Chan and Campbell (2020) as reported in Health Technology Wales (2022)[16]	
Base-case, 5-year cost per person	
CDO (US$), mean (95% CI)	$78,500 ($77,700 to $79,300)
NPWT (US$), mean (95% CI)	$83,300 ($82,500 to $84,100)
Mean difference (CDO – NPWT)	-$4,800

Outcome	Result
5-year QALYs per person	
CDO, mean (95% CI)	3.650 (3.639, 3.661)
NPWT, mean (95% CI)	3.625 (3.6137, 3.637)
Mean difference (CDO – NPWT)	0.025
ICER	Dominant (greater benefit at lower cost)

For other scenario analyses (e.g., different time frames, comparators, costs, outcome variables, discount rates)	• All resulted in lower cost for CDO
	• Most resulted in increase in QALYs
	• Scenarios where CDO had lower cost, but worse outcomes:
	  ○ Alternative NPWT healing outcomes
	  ○ Healing outcomes for subgroup with baseline ulcer size 1.5 to 2.15 cm^2.

Probabilistic sensitivity analysis results for 5,000 repetitions of the model simulation	• 87% had a negative mean incremental cost for CDO • 90% had positive incremental QALY • 79% resulted in dominance for CDO (negative mean incremental cost and positive incremental QALY)

CDO = continuous diffusion oxygen; CI = confidence interval; DFU = diabetic foot ulcer; ICER = incremental cost-effectiveness ratio; NA = not applicable; NPWT = negative pressure wound therapy; NR = not reported; QALY = quality-adjusted life-year; TOT = topical oxygen therapy.

Table 18: Summary of Recommendations in Included Guidelines

Recommendations	Strength of recommendations, supporting evidence, and quality of evidence
Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update) (2023)[23]	
Recommendation: For DFUs where standard of care alone has failed and resources exist: consider using TOT as an adjunct therapy.	Strength of recommendation: Conditional; low. Supporting evidence: 3 double-blinded RCTs and 7 nonblinded studies, overall found moderate benefits on wound healing and reduced ulcer area but no evidence for reduced amputation up to 12 weeks; few reported adverse events. Quality of evidence: Evidence was of low certainty across different devices, and concerns were raised regarding the costs of single-use devices potentially reducing equity. Thus, although there was evidence favouring the intervention, a conditional recommendation was made.
WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines[24]	
Guideline: "Topical oxygen has been shown to increase the incidence of healing and decrease the time to heal."[24] (p. 44)	Strength of recommendation: NR Supporting evidence: Cites 1 SR-MA, 1 SR, 3 double-blinded RCTs. Quality of evidence: Level I (high)
Use of topical oxygen therapy in wound healing (2023)[25]	
Recommendation: TOT as an adjunctive therapy is endorsed for hard-to-heal wounds or wounds that have failed to reduce in size by at least 50% after 4 weeks of optimal standard of care.	Strength of recommendation: NR Supporting evidence: Several RCTs and NRSs indicated improved outcomes with CDO, including higher proportion of healed wounds, faster healing rates, greater reduction in wound area, and pain relief. Studies were primarily for patients with DFU, though review panels

Recommendations	Strength of recommendations, supporting evidence, and quality of evidence
	have suggested that venous leg ulcers and ischemic ulcers may be responsive to TOT as well. Quality of evidence for CDO: Grade A (high)
Recommendation: TOT is generalizable to most nonneoplastic, hard-to-heal wounds (not just DFUs). Considering the use of TOT earlier for these wounds is appropriate.	Strength of recommendation: NR Supporting evidence: Cited 4 studies supporting use of TOT in venous leg ulcers and pressure ulcers. Quality of evidence: NR
Recommendation: For patients with critical limb ischemia, there is insufficient evidence to support use of TOT.	Strength of recommendation: NR Supporting evidence: Limited evidence, insufficient to support use of TOT; anecdotal reports indicate it has been used in patients with no option for revascularization and only partial revascularization was achieved Quality of evidence: NR
Recommendation: TOT can be considered for early treatment of ischemic DFUs.	Strength of recommendation: NR Supporting evidence: Unclear; may be based on RCTs and NRSs, but did not report if any of these studies were focused on ischemic DFUs. Quality of evidence: NR
Recommendation: TOT should not be used: • On wounds with an untreated infection or osteomyelitis • If a malignancy is present • On wounds that are un-debrided or necrotic.	Strength of recommendation: NR Supporting evidence: NR Quality of evidence: NR
Treatment algorithm: 1. If healing of the hard-to-heal wound has stalled (less than 50% size reduction after 4 weeks of standard care), consider topical oxygen therapy and reassess at 1 to 2 weeks. 2. If the wound is healing (more than 50% size reduction), continue topical oxygen therapy and reassess at 1 to 2 weeks. If healing is stalled, stop therapy and re-evaluate the wounds. 3. Continue to reassess every 1 to 2 weeks of topical oxygen therapy; continue to use if wound is healing and stop if healing has stalled.	Strength of recommendation: NR Supporting evidence: NR Quality of evidence: NR
12. Retinopathy, neuropathy, and foot care: Standards of care in diabetes—2023[26]	
Recommendation: For chronic DFUs that have failed to heal with optimal standard care alone, adjunctive treatment with RCT-proven agents should be considered, such as TOT.	Strength of recommendation: NR Supporting evidence: Several high-quality RCTs, at least 5 SR and meta-analyses. Quality of evidence: A (high)

DFU = diabetic foot ulcer; CDO = continuous diffusion oxygen; IWGDF = International Working Group on the Diabetic Foot; MA = meta-analysis; NR = not reported; NRS = nonrandomized study; RCT = randomized controlled trial; SR = systematic review; TOT = topical oxygen therapy.

Appendix 6: Overlap Between Included SRs

Note this appendix has not been copy-edited.

Table 19: Overlap in Relevant Primary Studies Between Included SRs

Primary study citation	Chen et al. (2024)[18]	Nagarsheth et al. (2024)[7]	Sýkorová et al. (2024)[17]	Health Technology Wales (2022)[16]
Ahmadinejad M et al. Int J Pharm Phytopharm Res. 2020;10(1):61 to 9.	—	Yes	—	—
Al-Jalodi O et al. Int Wound J. 2022;19(7):1838 to 1842	—	—	Yes	Yes
Altinbas O and Şahsıvar MO. Ann Clin Anal Med. 2022;13(1):50 to 3.	—	Yes	Yes	Yes
Azimian J et al. Iran Red Crescent Med J. 2015;17:e20211.	—	Yes	—	—
Cole W et al. Wounds. 2020;32:294e298.	—	Yes	—	—
Copeland K and Purvis AR. Adv Wound Care. 2017;6:143e152.	—	Yes	—	—
Driver VR et al. Ostomy/Wound Manag. 2013;59:19e26.[d]	—	Yes	Yes	Yes[a]
Driver VR et al. Ostomy/Wound Manag. 2017;63:12e28.[d]	Yes	Yes	Yes[a]	Yes[a]
Frykberg RG et al. Diabetes Care. 2020;43:616e624.	Yes	Yes	Yes[a]	Yes[a]
Hayes PD et al. J Wound Care. 2017;26:652e660.	—	Yes	—	Yes[a]
He S et al. Diabetes Res Clin Pract. 2021;174:108743.	Yes	—	Yes	Yes
Hunter P et al. Wounds. 2020;32:81e85.	—	Yes	—	—
Igwegbe I et al. Adv Skin Wound Care. 2015;28: 206e210.	—	Yes	—	—
Kaufman H et al. J Wound Care. 2018;27: 426e433.	—	Yes	—	Yes
Kaufman H et al. Wounds Int. 2021;12:63 to 8.	—	—	—	Yes
Massenburg BB and Himel HN. J Wound Care. 2016;25:S23eS27.	—	Yes	—	—
Niederauer MQ et al. Wound Med. 2015 Apr 1;8:19 to 23.[c,d]	—	—	Yes[c]	—
Niederauer MQ et al. J Diabetes Sci Technol. 2017;11(5):883 to 891.[d]	—	Yes	Yes	Yes [a]
Niederauer MQ et al. J Wound Care. 2018;27: S30eS45.	Yes	—	Yes[a]	Yes[a]
Otaviano MH et al. Braz J Infect Dis. 2021;25:1e9.	—	Yes	—	—
Segev R. Nephrol Nurs J. 2019;46:330e336.	—	Yes	—	—

Primary study citation	Chen et al. (2024)[18]	Nagarsheth et al. (2024)[7]	Sýkorová et al. (2024)[17]	Health Technology Wales (2022)[16]
Serena TE et al. J Wound Care. 2021;30:S7eS14	Yes	Yes	Yes[a]	Yes
Song Z et al. Am J Transl Res. 2021;13:7294e7299.	—	Yes	—	—
Tang TY et al. Int J Low Extrem Wounds. 2021:15347346211053694.	—	Yes	Yes	—
Tawfick WA and Sultan S. Vasc Endovascular Surg. 2013;47:30e37.	—	Yes	—	—
Varetto G et al. Ann Vasc Surg. 2020;64: 246e252.	—	Yes	—	—
Wang S et al. Ann Palliat Med. 2021;10(2):973-983.	Yes	—	—	—
Woo KY et al. Adv Skin Wound Care. 2012;25:543e547.[d]	—	Yes	—	—
Yu J et al. Wound Repair Regen. 2016;24(6):1066-1072.[d]	Yes	—	Yes	Yes[b]
Zulbaran-Rojas A et al. J Surg Res. 2021;268:585 to 594.	—	—	Yes	—

— = not included in the systematic review; SR = systematic review.

Notes: Sýkorová et al. (2024) and Health Technology Wales (2022) included and reported findings from previous systematic reviews (SRs). These have been indicated with letters as described below. For example, Health Technology Wales (2022) included an SR by Connaghan et al. (2021), which included 2 randomized controlled trials and 2 nonrandomized studies; these 4 primary studies are indicated in the table as "Yes" with a footnote "a"; Sýkorová et al. (2024) included several relevant SRs. The primary studies included in these SRs have all been included in other SRs that are included in this report.

[a]Indicates a primary study that was included as part of an SR; the author of the report presented findings from the SR.

[b]Indicates a primary study that was included as part of an SR; the author of the report presented findings from the SR as well as results from the original primary study that were not presented in the SR.

[c]While the results from Niederauer (2015) were reported, the review authors noted that these are interim findings, with the final results published in Niederauer (2017). To avoid double-counting, the findings from Niederauer (2015) have not been included in this report.

[d]Indicates studies that were identified by and described in our previous report published in 2020[14] reviewing continuously diffused oxygen for wound healing.

Appendix 7: References of Potential Interest

Note this appendix has not been copy-edited.

Previous CADTH Reports

Continuously diffused oxygen therapy for wound healing: a review of the clinical effectiveness, cost-effectiveness, and guidelines. (*CADTH Rapid response report: summary with critical appraisal*). Ottawa (ON): CADTH; 2020. PubMed: PM33289990

Nonrandomized Studies

Unclear Methods

Su S, Ding X, Zou H, et al. Wound management of multi-site pressure ulcer at different stages in elderly patients. *Clin Cosmet Investig Dermatol*. 2021;14:747-751. PubMed: PM34234500

Alternative Outcome

Hunter P, Greco E, Cross K, Perry J. Topical oxygen therapy shifts microbiome dynamics in chronic diabetic foot ulcers. *Wounds*. 2020 Mar;32(3):81-85. PubMed: PM32163040

Case Series

Cole W, Woodmansey E. Monitoring the effect of continuous topical oxygen therapy with near-infrared spectroscopy: a pilot case series in wound healing. *Wounds*. 2024 05;36(5):154-159. PubMed: PM38861210

Lee A, Woodmansey E, Klopfenstein B, O'Leary JL, Cole W. Remote assessment and monitoring with advanced wound therapy to optimise clinical outcomes, access and resources. *J Wound Care*. 2024 Feb 02;33(2):90-101. PubMed: PM38329827

Cole W, Woodmansey E, LoDico III LR. Management of late radiation tissue injury ulcers with continuous topical oxygen therapy supports wound healing in patients of advanced age following Mohs surgery: a case series. *Wounds*. 2023 12;35(12):E420-E424. PubMed: PM38277630

Jebril W, Nowak M, Palin L, Nordgren M, Bachar-Wikstrom E, Wikstrom JD. Topical oxygen treatment relieves pain from hard-to-heal leg ulcers and improves healing: a case series. *J Wound Care*. 2022 Jan 02;31(1):4-11. PubMed: PM35077209

Tabanjeh SF, Al-Malki T, Alhazzani AR, Robert AA. Management of Diabetic Foot Ulcers Using Topical oxygen Therapy: a case series. *Curr Diabetes Rev*. 2022;18(6):e051021196984. PubMed: PM34636303

Guidelines and Recommendations

Consensus-Based Methodology

Bem R, Chadwick P, Cvjetko I, Koliba M, Kokeny Z, Lipinski P, Mrozikiewicz-Rakowska B, Rozsos I, Wegrzynowski A. A new algorithm for the management of diabetic foot ulcer: recommendations from Central and Eastern Europe. *J Wound Care*. 2023 May 2;32(5):264-72. https://www.magonlinelibrary.com/doi/full/10.12968/jowc.2023.32.5.264 Accessed 2024 Jul 2. PubMed

Wounds International: International consensus document on diabetic foot ulcer care in the Asia-Pacific region (2022) https://woundsinternational.com/wp-content/uploads/sites/8/2023/02/065579205d506991f8070505779d5ba3.pdf Accessed 2024 Jun 26.

Serena T, Andersen C, Cole W, Garoufalis M, Frykberg R. Guidelines for the use of topical oxygen therapy in the treatment of hard-to-heal wounds based on a Delphi consensus. *J Wound Care*. 2021 Sep 1;30(Sup9):S30-4. https://www.magonlinelibrary.com/doi/abs/10.12968/jowc.2021.30.Sup9.S30 Accessed 2024 Jul 3.

Review Articles

Oyebode OA, Jere SW, Houreld NN. Current therapeutic modalities for the management of chronic diabetic wounds of the foot. *J Diabetes Res*. 2023;2023:1359537. PubMed: PM36818748

Ngeow WC, Tan CC, Goh YC, Deliberador TM, Cheah CW. A narrative review on means to promote oxygenation and angiogenesis in oral wound healing. *Bioengineering (Basel)*. 2022 Nov 02;9(11):02. PubMed: PM36354548

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