Request for LCD Reconsideration
Local Coverage Determination (LCD): Oxygen and Oxygen Equipment (L33797)

Pursuant to the process described in Chapter 13 of the Medicare Program Integrity Manual, we the undersigned individuals write to formally request a revision of the Local Coverage Determination (LCD): Oxygen and Oxygen Equipment (L33797)[1]. We understand that the Durable Medical Equipment Medicare Administrative Contractors (DME MACs) have accepted as valid a requested update to LCD L33797 to include coverage of continuous topical oxygen therapy, including the NATROX Oxygen Wound Therapy System. This request reflects the commentary and questions posed by the DME MACs during our meeting on January 19, 2023, as well as the responses to questions we submitted to the DME MACs on February 23, 2023. We believe there is significant new clinical evidence that supports a reconsideration of the current noncoverage of the Topical Oxygen Treatment category consistent with previous reviews. Specifically, we believe the latest clinical evidence strongly supports coverage of intermittent topical oxygen therapy (ITOT or Intermittent TOT), HCPCS code A4575, in treating Diabetic Foot Ulcers (DFUs).

For your consideration, we are separately submitting the recent peer reviewed studies, including multiple systematic reviews and meta-analyses, and clinical practice guidance, upon which this reconsideration request and proposed coverage criteria are based. We look forward to working with the DME MACs to facilitate better care for the nation's Medicare beneficiaries, particularly those who would benefit significantly from coverage and access to Intermittent TOT.

Proposed Coverage Criteria

We believe that the far more extensive body of evidence demonstrating the effectiveness of Intermittent TOT in a broader range of DFU severities and patient comorbidities, when combined with its unique long-term healing efficacy and demonstrated reductions in amputations and hospitalizations, provides a clear differentiation over the Continuous TOT approach, which is delivered by Continuous Diffusion Oxygen (CDO) devices. Given the varying levels of clinical evidence across these modalities, we recommend separate consideration of coverage decisions and criteria for each, which can be accomplished utilizing the already assigned HCPCS codes (Intermittent A4575 and Continuous E0446).

Specifically, we propose that Intermittent TOT, HCPCS code A4575, be covered for beneficiaries with the following definitions, which are both consistent with existing LCD and NCD coverage policies for other adjunctive therapies for treating DFUs[2] [3] [4], as well as with existing A4575 coverage policy frameworks under state Medicaid programs. This coverage request, including the patient population and treatment regimen, is consistent with and supported by the extensive current body of clinical evidence specific to Intermittent TOT.

Proposed Coding Guidelines for Intermittent TOT

Intermittent TOT is the controlled application of oxygen under cyclical pressure of between 7.5 mmHg and 37.5 mmHg (10 mb and 50 mb) applied directly to a wound.

ITOT consists of a Food and Drug Administration (FDA) cleared and Randomized Controlled Trial (RCT) proven topical oxygen therapy controller device and extremity chamber (HCPCS code A4575), connected to an oxygen concentrator (HCPCS code E1390). The extremity chamber utilized should be single use (disposable), therefore reducing the risk of cross contamination.

Intermittent TOT should be provided for a minimum protocol of 90 minutes per day 5 days per week for an initial period of 30 days. Continued coverage should be assessed every 30 days.

A4575 is covered as a bundled payment for 4 weeks of services provided, which includes all necessary equipment, delivery, patient education, maintenance and repair costs, parts, supplies and services for equipment set-up and support as needed while a patient remains on therapy.

Indications and Limitations of Coverage

A. Covered Conditions

A4575 is considered an adjunctive therapy and will only be covered for Diabetic Foot Ulcers (DFU) that have not progressed sufficiently with 30 days of appropriate standard wound care, as defined below.

A4575 is covered when each of the following criteria are met:

1) A complete wound therapy program has been attempted for 30 days prior to the application of Intermittent TOT as documented in the patient's medical record, including the following management considerations:

   (a) Documentation of evaluation, care, and wound measurements, and
   (b) Application of dressings to maintain a moist wound environment, and
   (c) Debridement of non-viable tissue, if present, and
   (d) Evaluation of and provision for adequate nutritional status, and
   (e) Patient is on a comprehensive diabetic management program, and
   (f) Revascularization of ischemic wounds when necessary and possible, and
   (g) Reduction in pressure to a weight bearing foot ulcer has been accomplished with appropriate modalities, and
   (h) Management of infection if present

2) Documentation that an open wound has not shown measurable signs of healing after 30 days of standard wound care treatment.

Measurable signs of wound healing may be documented using validated objective wound assessment tools, such as the Bates-Jensen Wound Assessment Tool (BWAT)[5], or the Photographic Wound Assessment Tool (PWAT)[6].

Measurable signs of wound healing are defined as improvements in either criteria (a) or (b), or at least two of criteria (c) through (h) below:

   (a) Wound dimensions (surface measurements [L X W], and depth)
   (b) Tunneling or undermining
   (c) Drainage (color, amount, consistency)
   (d) Inflammation
   (e) Swelling
   (f) Pain and/or tenderness
   (g) Granulation tissue
   (h) Necrotic tissue/slough

B. Noncovered Conditions

All other indications not specified are not covered under the Medicare program. No program payment may be made for any conditions other than those listed in Section A.

C. Exclusions From Coverage

Intermittent TOT will be denied at any time as not reasonable and necessary if one or more of the following are present within the vicinity of the wound:

- Necrotic tissue with eschar, if debridement is not attempted
- Untreated osteomyelitis
- Cancer

Intermittent TOT devices not supported by Level 1 Randomized Controlled Trial (RCT) evidence demonstrating both 12-week and 12-month efficacy in complete wound healing will be denied as not reasonable and necessary.

D. Continued Coverage

Monthly evaluation of the wound by a licensed health care professional is required to determine whether the individualized treatment goals are being met for the patient and to document improvement in wound characteristics. A licensed health care professional may be a physician, physician's assistant (PA), registered nurse (RN), licensed practical nurse (LPN), or physical therapist (PT). The treating practitioner should be licensed to assess wounds and/or administer wound care within the state where the beneficiary is receiving ITOT.

Intermittent TOT may continue to be covered for up to 4 months, so long as measurable signs of wound healing continue to be demonstrated during the previous 4-week treatment period. The medical necessity of ITOT beyond 4 months will be given individual consideration and may require additional justification. Measurable signs of wound healing may be documented and assessed as described in Section A.

Intermittent TOT must be discontinued if any of the following conditions exist:

- Evaluation of the wound by a licensed health care professional is not completed monthly.
- In the judgment of the treating practitioner, adequate wound healing has occurred to the degree that Intermittent TOT may be discontinued.
- The wound is 100% epithelialized and durably closed.
- No measurable signs of wound healing, as described in Section A, have occurred over the prior month.
- Equipment or supplies are no longer being used for the beneficiary, regardless of the treating practitioner's prescribed order duration.

Appropriateness of the Proposed Coverage Criteria

Developing coverage criteria that reflects the clinical efficacy for the identified patient population as supported by the clinical evidence is the essential determination of whether a therapy is reasonable and

necessary. As detailed above, we strongly believe that our request meets this standard with respect to Intermittent TOT. In addition, we recognize that developing coverage criteria and corresponding requirements should meet the dual aim of being the least burdensome for prescribers and providers and the most straightforward to implement by payers (i.e., Medicare and the DME MACs).

With respect to the level of burden on prescribing and treating clinicians, the proposed coverage criteria align with those that exist across other payers, meaning practitioners have familiarity with and can more seamlessly advance clinically appropriate access to Intermittent TOT for Medicare beneficiaries. This reflects the high level of practicality of the proposed coverage criteria, such as the inclusion of quantifiable data points (e.g., measurable signs of wound healing using validated tools) as well as the requirement of documentation in the medical record, which is already current practice for these clinicians.

The minimum monthly assessment of wound healing requirement reflects other wound policies and is the medically appropriate cadence for assessing the effectiveness of this intervention. The documentation requirements can be further expanded upon via an accompanying policy article, with the primary goal of ensuring sufficient documentation that the elements of the coverage criteria have been met.

Further, payers have been able to meaningfully assess provider compliance with these types of requirements, and we anticipate the DME MACs would be able to assess compliance in a straightforward manner. In particular, the clinical evidence-supported coverage criteria rely on (1) documentation in the medical record and (2) a monthly assessment of wound healing reported via objective, validated tools. We believe that this is the most appropriate way to assess coverage and compliance with coverage requirements.

Description of Patient Population and the Need for Durable Treatment Options

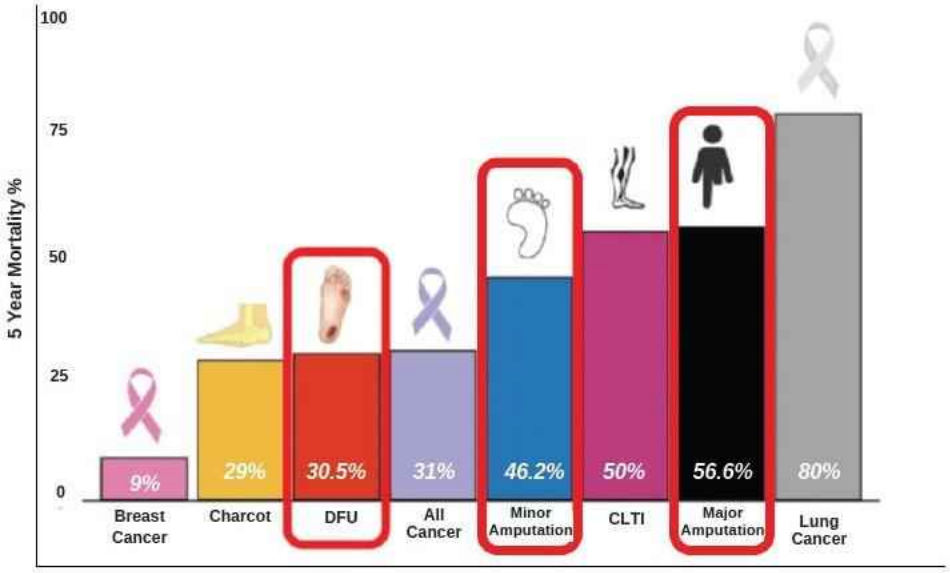
The American Diabetes Association's (ADA) launched in September 2022 a new Amputation Prevention and Health Equity Campaign entitled, "*Because Feet Matter"* that highlights the enormous life changing impact of non-healing DFUs on the Diabetic population.[7] Every 4 minutes in the USA a person with diabetes will have a limb amputated and approximately 15% of people with diabetes suffer with DFUs.[8] DFUs precede 80% of leg amputations in people with diabetes and account for over 20% of the total annual diabetes related costs in the US.[9]

In the USA, more than 37 million people have diabetes, representing approximately 11% of the USA population.[10] This means approximately 5.5 million people with diabetes will develop DFUs, without an effective, covered treatment to prevent exacerbation, amputations, or other avoidable adverse outcomes. The cost of treating diabetes is significant as $1 out of every $4 in US health care costs is spent on caring for people with diabetes. $237 billion is spent each year on direct medical costs alone and 61% of diabetes costs are for people 65 years or older, which is mainly paid by Medicare.[11] Furthermore, diabetes is more prevalent among ethnic minorities, as the non-Hispanic White population has the lowest prevalence of diagnosed diabetes.[12] Unfortunately, the COVID-19 pandemic has resulted in significant reductions in glucose level testing and routine monitoring of glycemic control, as well as regular clinic based wound maintenance. This means late complications of diabetes, including DFUs, are likely to be more prevalent in the coming years as many cases of diabetes have gone undiagnosed, and DFU patients will likely present themselves at a more severe stage.

Non-healing DFUs lead to worsening wound-related infections, resulting in increased Lower Extremity Amputations (LEA) and ultimately increased mortality. A recent meta-analysis of 21 published studies involving 6,505 participants showed that a history of a foot ulcers, osteomyelitis and gangrene were each

leading independent predictors of LEA.[13] The mortality rates at 1 and 4 years have been shown to be 33% and 65% for major LEA and 18% and 45% for minor LEA.[14] A recent meta-analysis published in the *New England Journal of Medicine* found that more than half of DFUs become infected and 20% of these infections lead to amputation. Additionally, 40% of patients have their DFU recur within 1 year after healing, which rises to 60% within 3 years.[15]

Armstrong, et al. in their 2020 systematic review, explored the 5-year mortality associated with DFUs and concluded that: "DFU are more than just a marker of poor health. They are independent risk factors associated with premature death... with 5 Year Mortality rates comparable to cancer." The following chart from the Armstrong publication illustrates how both minor and major amputations resulting from non-healing DFU increase mortality rates even further.[16]



Charcot = Charcot neuroarthropathy of the foot. DFU = diabetic foot ulcers. All Cancer = pooled 5 year survival of all reported cancer. CLTI = chronic limb threatening ischemia. Major Amputation = above foot amputation. Minor Amputation = foot level amputation.

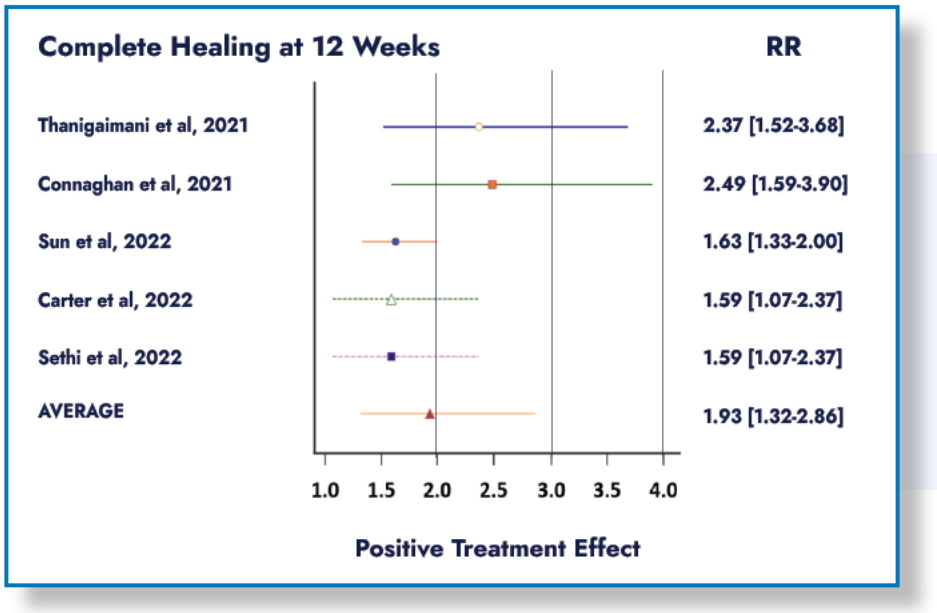
DFUs should first be treated with optimal standard of care (SOC), which is detailed within the joint clinical practice recommendations of the three leading professional societies associated with treating DFU patients. The recommendations for optimal SOC include: the debridement of bioburden and non-viable tissue, the management of the wound bed with appropriate dressings, the treatment of localized infections, and the application of offloading for weight bearing ulcers.[17] However, as discussed previously, even with optimal SOC, over 40% of DFUs either do not heal, or reoccur with 12 months, leading in many cases to limb amputation.

On July 7, 2022, within calendar year (CY) 2023 Physician Fee Schedule (PFS) Proposed Rule (CMS-1770-P), the Centers for Medicare & Medicaid Services (CMS) recognized the significance of this problem by citing these same statistics.[18] Further, CMS acknowledged that non-healing DFUs result in preventable LEAs and that high-quality care can reduce the risk of amputation. The agency has proposed the "*development of a process quality measure, as well as a composite measure, for inclusion in MIPS, designed to reduce the risk of LEA among patients with diabetes.*"[19] CMS stated that this initiative was based on a review of the literature, technical expert panel (TEP) feedback, and prioritization of health equity.

Clinical Evidence Supporting TOT to Treat DFUs

We believe the DME MACs are aware of and have reviewed older publications, so this request instead builds on this historical body of evidence and focuses primarily on the newer evidence published since the DME MACs last considered coverage of TOT in 2019. Since this last review of TOT by the DME MACs, there has been a significant increase in the body of clinical evidence supporting improved healing outcomes for DFUs treated with TOT overall. In the last two years alone, there have been not only additional RCTs, but also five (5) Systematic Reviews and Meta Analyses (SRMA), published in peer reviewed journals by independent teams across four continents.[20] [21] [22] [23] [24] These SRMAs, as described in more detail below, universally demonstrate a consistent and significant positive effect in healing efficacy for DFUs treated with TOT (adjunctively to SOC). Although there is some variation in the calculated relative risk and margin of effect, based on the heterogeneity of the studies included in each analysis, they all consistently demonstrate a very significant complete healing benefit for TOT. These SRMAs help summate the magnitude of RCTs, retrospective studies, and other research that now exists in support of the clinical benefit of TOT in healing DFUs.

The chart below summarizes the outcomes from each of these SRMAs, with the average Relative Risk (RR), defined as increased likelihood of healing, being 1.93 (93%), with a range between 1.32 (32%) and 2.86 (186%) low and high confidence intervals respectively.



Universally, these SRMAs recommend the use of TOT in non-healing DFU, with the most recent USA-based review by Marisa Carter et al., which focused exclusively on RCTs with 12-week healing outcomes, rating the overall evidence level supporting TOT in more effectively healing DFUs to be at the second highest grade level (GRADE B, moderate), utilizing the universally accepted GRADE assessment technique.[25]

A summary of the design and the key findings from each of the above-referenced SRMAs follows:

S Thanigaimani, T Singh, J Golledge; Australia: *Diabetic Medicine*, April 2021[20]

- Six TOT RCTs involving 530 participants with a DFU were included.

- Meta-analysis suggested that TOT significantly increased the likelihood of ulcer healing compared to controls (Risk ratio [RR] 1.94; 95% CI 1.19, 3.17; I2 = 57%; NNT = 5.33) and the findings were robust in sensitivity analyses.
- A modified version of the Cochrane Collaboration's tool was used to assess the quality of the studies and risk of bias. The Frykberg study, included among the RCTs reviewed, was the only one awarded a perfect 100% score.
- Analysis of the three RCTs judged to be at low risk of bias suggested that TOT increased the likelihood of ulcer healing compared to controls by 137% (RR 2.37; 95% CI 1.52, 3.68; I2 = 0%)
- This meta-analysis concluded that TOT improves the likelihood of DFU healing.

F Connaghan, P Avsar, et al; Ireland: *Journal of Wound Care*, October 2021[21]

- Eight papers met the inclusion criteria, with five being RCTs, and formed the basis of this review.
- Meta-analysis suggested that TOT significantly increased the likelihood of ulcer healing compared to controls by 149% (Odds Ratio of healing of 2.49 (95% CI: 1.59 – 3.90; p=0.00001)).
- The findings suggest that TOT enhances healing for patients with hard-to-heal DFUs when used with standard care (SC).
- This review found evidence that the adjunct therapy of TOT may lead to faster healing rates and wound closure for some patients if used alongside standard diabetic foot care.

X-K Sun, R Li, X-L Yang, L Yuan; China: *International Wound Journal*, May 2022[22]

- Seven studies involving 614 participants were included in the review.
- Meta-analysis showed that TOT could improve the number of ulcers that completely healed compared with the control group by 63% (RR = 1.63, 95% CI [1.33, 2.00], P < .00001).
- TOT reduced the ulcer area and improved healing durability and quality of life and had no effect on the occurrence of adverse events.
- The Frykberg study was assessed with low risk of bias and showed that at one year, only 6.7% of DFUs in the TOT group recurred, compared with 40% of DFUs in the control group.

Marissa J Carter, Robert G Frykberg, Alisha Oropallo, Chandan K. Sen, David G. Armstrong, Harikrishna K.R. Nair, and Thomas E. Serena, USA: *Advances in Wound Healing*; May 2022[23]

- 4 RCTs only with 12-week complete wound healing outcomes were included in the review and analysis.
- A random-effects meta-analysis showed that TOT improved wound healing at 12 weeks over SOC alone by 59% (RR: 1.59; 95% CI: 1.07–2.37; p = 0.021).).
- Sensitivity analysis, based on imputed values for missing outcomes, demonstrated that both the RR and 95% CIs changed little.
- The overall GRADE level of evidence for TOT was assessed as Moderate with the Frykberg study being the only study assessed with a low risk of bias across all domains.
- Conclusion of this systemic review and meta-analysis supports the use of TOT as an adjunctive therapy in the treatment of Wagner 1 and 2 DFUs that have not responded to preliminary treatment with optimal SOC alone.

Amar Sethi, Yashvini Khambhayta, Prashanth Vas; United Kingdom: *Health Sciences Review*, June 2022[24]

- Seven studies totaling 627 participants met eligibility criteria, of which four studies totaling 492 participants were used in the final qualitative synthesis.
- TOT significantly improved complete wound healing in comparison to SC (RR 1.59 95% confidence interval 1.07, 2.37 p = 0.02; NNT 6.3), with no difference in adverse events between the groups.
- TOT is associated with a higher rate of complete wound healing in DFU when added to SC, with a 60% higher likelihood of healing at 12 weeks.

The extensive body of clinical evidence cited above consistently shows the complete healing benefit in DFUs of TOT in general. This is both demonstrated in and summarized by the five SRMAs. As would be expected, there are some variations between these reviews based on which studies they included in their analysis, but all show a consistent positive TOT treatment effect.

The most recent such study, the Sethi SRMA of 2022, had some shortcomings in its commentary due to the authors' lack of understanding of all the study designs. However, because this SRMA only included RCTs in its analysis, the authors calculated the exact same likelihood of complete healing at 12-weeks Risk Ratio of 1.59 (1.07 – 2.37) as the Carter SRMA of 2022, which we believe to be the most complete and balanced of the analyses.

The Carter SRMA was conducted by USA-based subject matter experts and was published in the high impact factor journal of the Wound Healing Society (WHS) and concluded that "*this systemic review and meta-analysis supports the use of TOT as an adjunctive therapy in the treatment of Wagner 1 and 2 DFUs that have not responded to preliminary treatment with optimal SOC alone.*"

It is important to point out that as the same standardized 12-week complete wound healing outcome was the primary endpoint of all the RCTs, and reductions in amputations was not an endpoint in any of the RCTs analyzed, the SRMAs were therefore unable to offer any valid commentary on such outcomes, which were only explored separately in the real world evidence (RWE) retrospective study by Yellin published in late 2022 and discussed in the following analysis.

This peer reviewed clinical evidence, in the form of a gold standard RCT (included in the SRMAs detailed above), and RWE study that specifically demonstrates the clinical benefit, durability, and generalizability of Intermittent TOT in healing patients suffering from DFUs are described in detail in the following section.

Description of Intermittent TOT (A4575) and its Unique Clinical Benefit

The Carter SRMA provides a clear comparison of the RCTs, and outcomes demonstrated by the two distinctly different approaches to delivering TOT, via either Continuous Diffusion Oxygen (CDO) devices, sometimes referred to as CTO or Continuous TOT, or the Intermittent TOT delivered by the TWO2 device. Such differentiations within the TOT category had already been discussed and established by CMS in its 2017 NCA - Hyperbaric Oxygen (HBO) Therapy (Section C, Topical Oxygen) (CAG-00060R) - Decision Memo,[26] where separate HCPCS codes were delineated for each approach (Intermittent A4575 and Continuous E0446). In this decision memorandum, CMS also decided that topical oxygen for the treatment of chronic wounds would be determined by local contractors. A Noridian coverage article from April 2017 indicated that the HCPCS codes for topical oxygen therapy are designated as DME jurisdiction.[27] Therefore, the DME MACs are best situated to review and consider the totality of the evidence and specifically determine coverage criteria for the two available TOT treatment options.

The Carter SRMA also applied the most rigorous form of risk of bias assessment, GRADE, and meta-analysis in assessing the four TOT RCTs, which clearly demonstrated that the study with the most robust design

and lowest risk of bias was the Frykberg RCT[28]. This study is consistently awarded with the lowest risk of bias score, utilizing the respected Cochrane Collaboration's tool for assessing risk of bias in RCTs.

Table 4. *Final summary table risk of bias judgment for complete wound healing outcome at 12 weeks*

Study	*Domain 1*	*Domain 2*	*Domain 3*	*Domain 4*	*Domain 5*	*Overall*
Driver *et al.*[11]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Frykberg *et al.*[15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Niederauer *et al.*[14]	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
Serena *et al.*[13]	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns

The Frykberg (Intermittent TOT device) RCT also demonstrated the most significant Relative Risk benefit in healing DFUs at 12 weeks, with a low-end confidence interval well above 1, demonstrating high statistical confidence of positive complete healing outcomes.

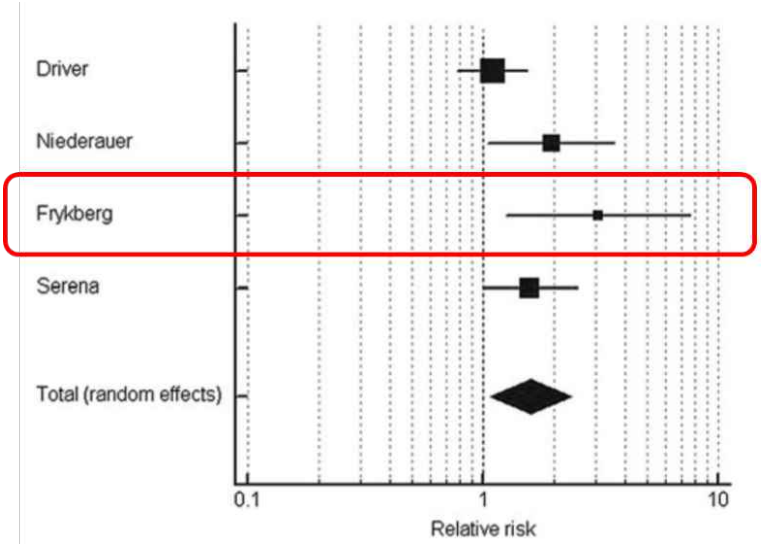
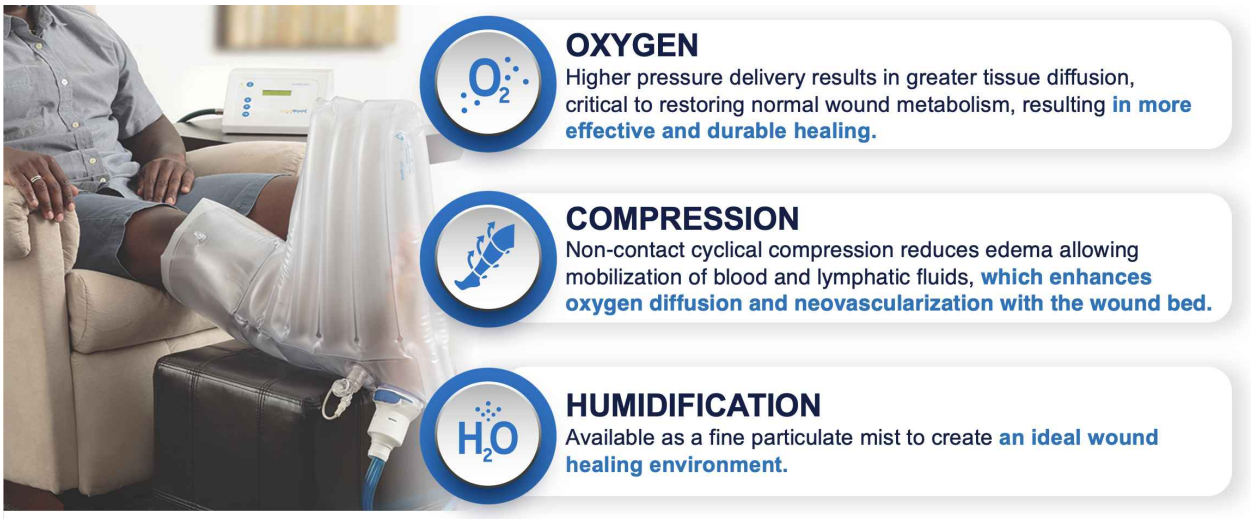


Figure 2. Forest plot for the random-effects model including all studies.

Clinical Evidence Specific to Intermittent TOT

The primary provider of Intermittent TOT is Advanced Oxygen Therapy Inc. (AOTI). AOTI's TWO2 therapy (Hyper-Box) device is FDA 510(k) cleared (K080966) and meets the Intermittent TOT category criteria. It is unique in that it is a patient applied at-home therapy, which provides a multi-modality approach that combines higher cyclical pressure oxygen, with non-contact compression and humidification. The graphic below illustrates the uniqueness of this approach:



As described below, this multi-modality intermittent treatment approach has been demonstrated in both RCT and RWE studies to not only heal DFUs at a higher efficacy at 12-weeks, but to provide more durable healing, such that the ulcers remain closed longer, resulting in significant reductions in hospitalizations and amputations over 12-months.

The Frykberg RCT is **a double-blinded, placebo-controlled RCT** on TWO2 therapy, published in the leading journal (by impact factor) in the diabetes space, *Diabetes Care*, in October 2020.[28] This study was conducted by diabetic foot experts from across the USA and Europe utilizing a protocol that was reviewed and highlighted in the 2017 CMS Decision Memorandum (CAG-00060R)[26] as an example of the level of evidence and study design that CMS would like to see to help demonstrate efficacy for future wound care coverage determinations, as it addressed all the patient selection, blinding, run-in, ethical, and control of optimal SOC concerns that commonly plague wound care studies. All analysis was conducted solely using the most stringent Intention-To-Treat (ITT) approach. Recently, this study was further honored by being selected as one of "Top 4 Studies over the last 4 years" at the 9th International Symposium on the Diabetic Foot (ISDF) in the Hague, the Netherlands.[29]

The recent SRMAs discussed above all included this specific RCT in their analysis and have recognized the robustness of the study design and its execu on. The Frykberg RCT looked at a more severe and real-world representa ve DFU pa ent popula on of Medicare age. Unlike the CDO (Con nuous TOT) RCTs that focused on nonischemic superficial ulcers assessed under the Wagner classifica on, the Frykberg study looked at ulcers mee ng University of Texas grades 1 – 2, A – D. These are ulcers penetra ng to muscle and tendon, which could also have moderate degrees of ischemia and infec on. Assessing the level of ischemia in the ac ve TWO2 treated pa ents in the Frykberg RCT u lizing the Interna onal Working Group on the Diabe c Foot guidelines,[30] more than half of the DFUs in this RCT were at least moderately ischemic and healed in similar propor ons to those nonischemic ulcers, as is illustrated in the table that follows:

Ischemia Level	n	Healed (n) at 12 Weeks	Healed %
Normal	17	8	53.00%
Moderate	18	7	47.00%
Severe	1	0	0%
Total	36	15	41.70%

The key takeaways from this study include:

- **A robust run-in was utilized with optimal SOC**, which meant that only DFUs not on a proven healing trajectory with optimal SOC alone to be randomized into the active phase of the study. This resulted in only hard-to-heal failures of SOC-treated ulcers being randomized into the study.

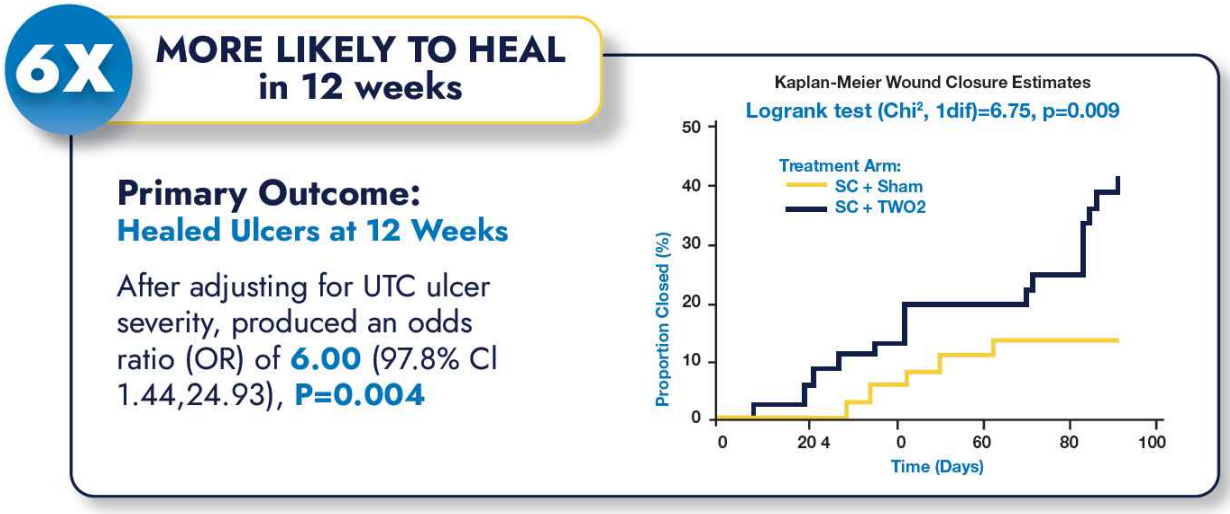
- **This study utilized a stringent Group Sequential Design (GSD)** that allowed for pre-determined blinded analysis of the primary outcome at three points.[31] This resulted in **far harder to achieve significance value of 97.8% (p = 0.022**) and mandated that the independent data monitoring committee end the study if significance is achieved at any of the a priori analyses points. GSDs are utilized both when the magnitude of the treatment effect is uncertain and for ethical reasons, so that once an outcome is proven statistically, patients are no longer subjected to the other treatment arm and put at higher risk, in this case, of amputation and even death.

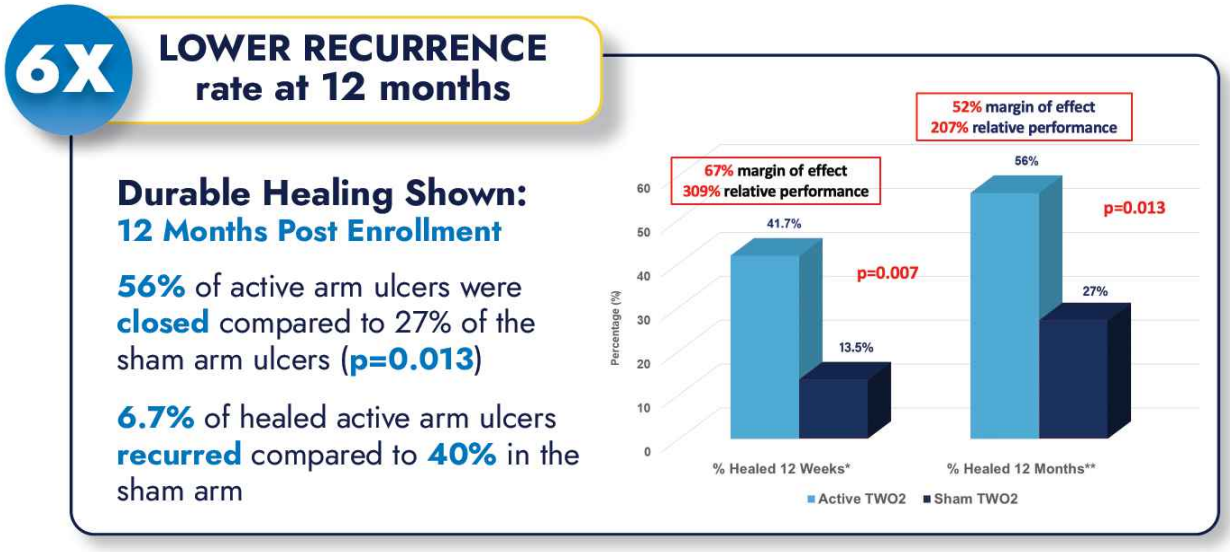
- **This study achieved overwhelming superiority** at the first a priori analysis point **due to the large (68%) margin of effect and 309% relative performance**, resulting in an Odds Ratio (likelihood of the outcome) of **4.57 (1.19, 17.57), p = 0.010** in favor of TWO2 therapy plus SOC over SOC alone. When adjusted for ulcer severity, the Odds Ratio increased to **6.00 (1.44, 24.93), p = 0.004**.

- **With respect to the primary outcome of healing at 12-weeks**, TWO2 was shown to be superior in healing DFUs compared to optimal SOC with 41.7% of Active TWO2 vs only 13.5% of Sham TWO2 ulcers healing (**Pearson Chi^2=7.27, (1df) p = 0.007**). The low Sham healing rate demonstrates the effectiveness of the run-in, with only hard to heal ulcers being randomized, and as would be expected, few resultingly healing in the SOC-only arm.

- **The resultant healing is more durable.** Although long term recurrence in chronic wounds has never been a requirement for Medicare coverage, and we know of no covered product that provided data on this previously, this RCT additionally included a **12-month follow-up to explore the durability of healing** with TWO2 therapy. At 12 months, a significantly higher number of TWO2 wounds were healed compared to the SOC. Specifically, 56% of active arm ulcers were closed compared with 27% of the sham arm ulcers (p = 0.013), which combined to give a substantial **six-fold lower recurrence rate.**

The following graphs illustrate the 12-week, and 12-month healing outcomes from this study:





- **Generalizability to the Medicare population** was addressed in this study with the **average age** in the TWO2 arm being **64.6 and with the majority of patients being over 65**. In addition, there is a significant Medicare population under 65 with disabilities and End Stage Renal Disease, and the eligibility criteria of this study were designed to **include patients with a broader range of comorbidities** commonly seen in patients with chronic wounds. This included both neuropathic and neuroischemic DFU penetrating as deep as to muscle and tendon, which could also be infected (University of Texas Grades 1-2, A-D). Additionally, racial and ethnic diversity in this study mirrored that seen generally in the population.

- **Quality-Of-Life (QOL**) was addressed by employing the Cardiff Wound Impact Schedule (CWIS) throughout the study, a well-validated, wound care-focused QOL survey, which demonstrated that **QOL improved substantially for patients whose ulcers healed with TWO2** across all functional domains. This improvement was seen in both full and partial responders.

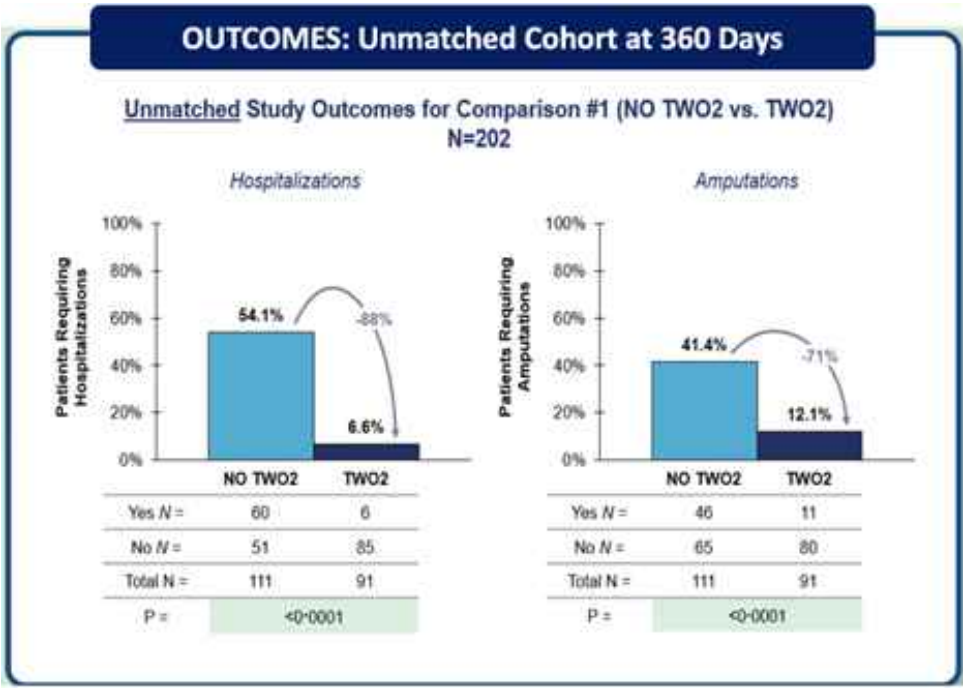
A high-quality RWE study was conducted following the RCT discussed above by Jessica Izhakoff Yellin, et al.[32] and was published in September 2022 in *Advances in Wound Care*, the leading journal (by impact factor) in the wound care space and the official journal of the Wound Healing Society. It is not possible to capture all real-world heterogenic populations within any one RCT and to also look at the effect of long-term healing outcomes on hospitalizations and amputations, making it sometimes difficult to assess the generalizability of a study's findings to the broader Medicare and Medicaid populations. This RWE study therefore evaluated **whether the more durable complete healing outcomes** associated with TWO2 (Intermittent TOT), as seen in the RCT, were both **reproducible and generalizable** to a very comorbid patient population, as experienced within the Veterans Administration integrated delivery network.

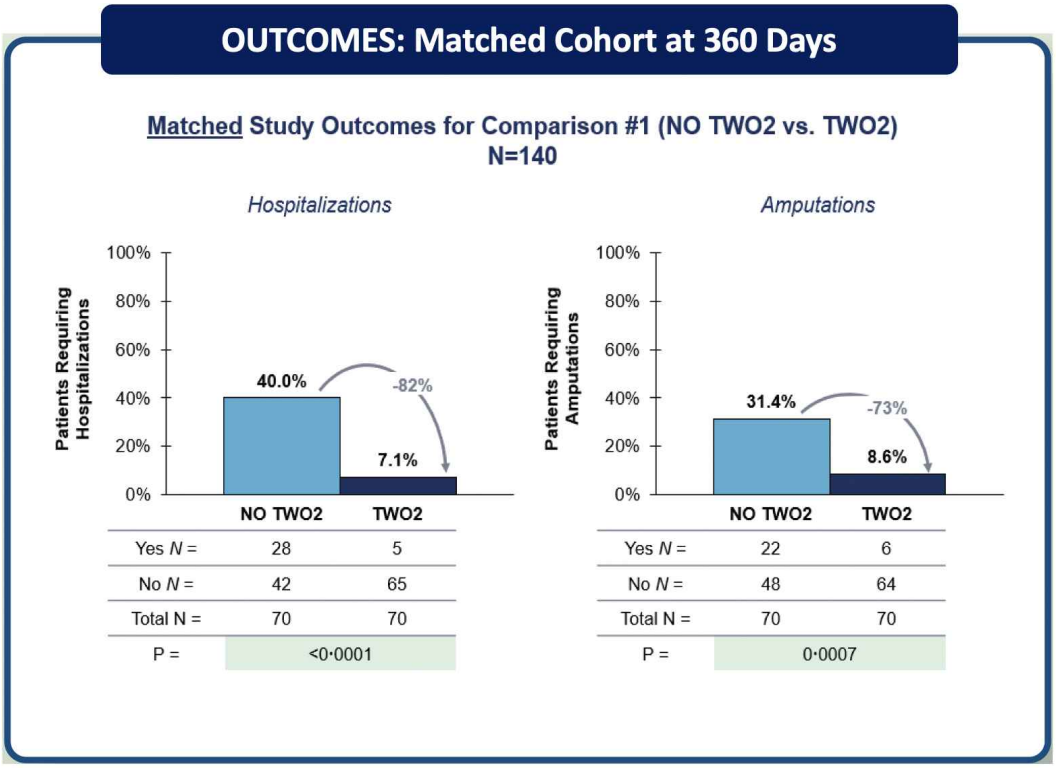
This study data mined the comprehensive patient records of **over 200 DFU patients across two geographically dispersed** Veterans Administration medical centers with a **wide variation of ulcer severities and common comorbidities**, to see if there were any significant differences in meaningful outcomes, such as DFU-related **hospitalizations and amputations over a 12-month period** when they either received, or did not receive, TWO2 therapy.

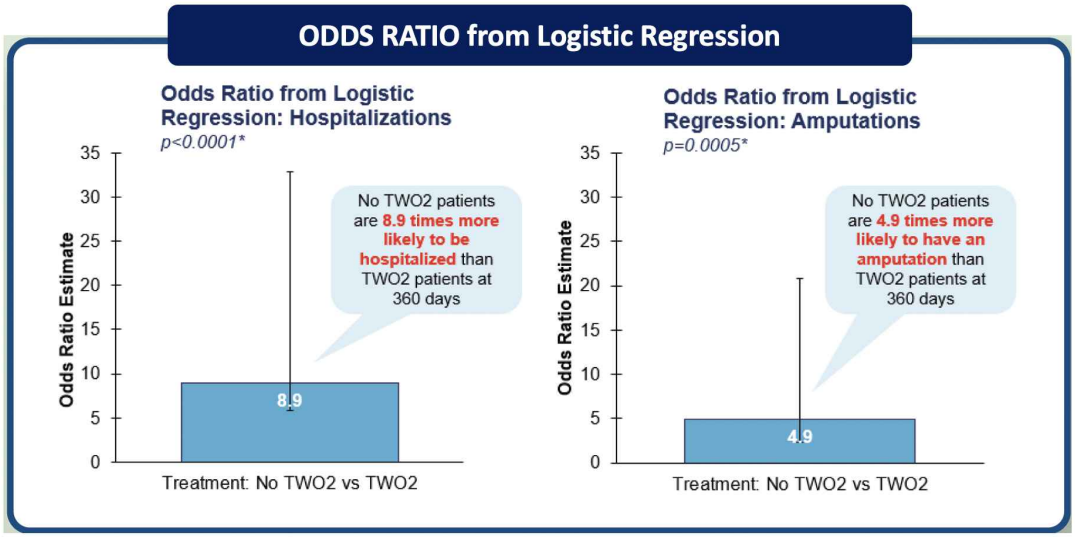
The raw, unmatched outcomes demonstrated an **88% reduction in hospitalizations and 71% reduction in amputations** in the patients who received TWO2 compared to those who did not receive TWO2 over a 12-month period. When the retrospective study arms were matched using statistically recommended propensity scoring, this significant difference remained, with an **82% reduction in hospitalizations and 73% reduction in amputations**.

Additional logistic regression analysis was conducted on the matched study outcomes (hospitalization vs. no hospitalization, and amputation vs. no amputation), which demonstrated a **nearly ninefold greater risk of wound-related hospitalization** (OR: 8.667; 95% CI: 3.101, 24.219; p < 0.0001) and **nearly fivefold greater risk of amputation** (OR: 4.887; 95% CI: 1.840–12.985; p = 0.0015) for patients who did not receive TWO2 compared with those who received TWO2 over a 12-month period.

The following charts illustrate these more durable healing outcomes:



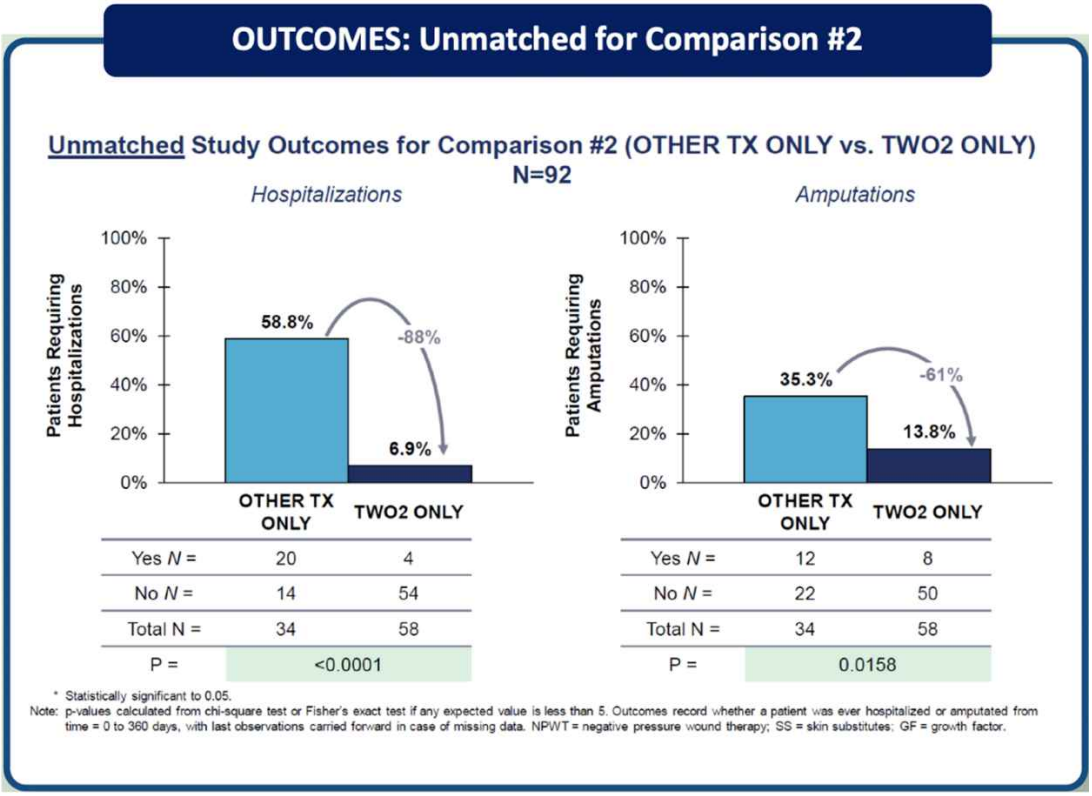




Sub-analysis was conducted that compared patients who had received only TWO2 and no other adjunctive wound care therapies (TWO2 ONLY) with those receiving other Medicare covered adjunctive modalities, such as Skin Substitutes (SS), Negative Pressure Wound Therapy (NPWT), and Growth Factors (GF), but not TWO2 (OTHER TX ONLY), to evaluate whether TWO2 was superior to these common already reimbursed adjunctive treatments. Like in the preceding analysis, patients in each cohort received appropriate SOC irrespective of any adjunctive therapies, including TWO2.

The results demonstrated that TWO2 had superior outcomes over other adjunctive wound care therapies, with the TWO2 ONLY arm achieving an **88% reduction in hospitalizations** (6.9% vs. 58.8%, $p < 0.0001$) and

61% reduction in amputations (13.8% vs. 35.3%, p = 0.016) over a 12-month period, compared to SS, NPWT, or GF.



Looking further at the demographics and comorbidities of these DFU patients, the mean age was shown to be approximately 67 years, and more than half were minorities. Additionally, the TWO2 healing outcomes held consistent across the wide range of comorbidities and wound severities encountered. About 20% of the DFUs were classified as the most severe Wagner grade 3 (deep ulcer with abscess osteomyelitis) and 4 (gangrene of toe or forefoot), and many included a myriad of commonly encountered comorbidities. Most study participants had less than optimally controlled HbA1c levels although other studies have shown this does not significantly influence healing outcomes[33], about 80% had Peripheral Artery Disease (PAD), and many were in severe stages of Chronic Kidney Disease (CKD) or even End Stage Renal Disease (ESRD), as illustrated in the table below:

CKD/ESRD Status

	TWO2	NO TWO2
Normal	**1**	**19**
Stage I/II	**23**	**24**
Stage III	**45**	**31**
Stage IV/V	**12**	**16**
Dialysis	**10**	**21**

Physician Society Evidence Based Clinical Practice Guidelines (CPG) and Standards of Care

As the body of evidence in support of TOT in healing DFUs has expanded significantly over the last few years, the leading clinical societies have begun to update their CPGs to reflect the current state of the science with positive recommendations for the use of TOT in DFUs. This has included the American Diabetes Association (ADA), who in 2022 formed a global DFU expert editorial board and published a New Evidence-Based Therapies for Complex Diabetic Foot Wounds compendium[34] that details the extensive evidence base that now exists for all TOT devices. This ADA-published guidance also highlights and recommends TOT usage for DFUs. Recently, the ADA has incorporated these recommendations into their 2023 Standards of Care CPG, where they recommend that *"For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with RCT proven advanced agents should be considered"* including *"topical oxygen therapy"*.

This recommendation is made with the ADA's highest "**A**" Grade rating. The ADA states that "*Recommendations with A level evidence are based on large well-designed clinical trials or well-done meta-analyses. Generally, these recommendations have the best chance of improving outcomes when applied to the population for which they are appropriate*."[35]

In 2021, 23 clinical leaders in the field of wound healing from across the USA assembled as an expert panel for an interactive assessment to develop guidelines for the use of TOT in the treatment of hard-to-heal wounds based on the accepted Delphi consensus approach. This resulted in the publication of the *Guidelines for the use of topical oxygen therapy in the treatment of hard-to-heal wounds based on a Delphi consensus*, which recommended that TOT should be incorporated into clinical practice as an evidence-based treatment for chronic DFUs.[36]

The International Working Group for the Diabetic Foot (IWGDF) meets every four years to update their CPG and convened on May 13, 2023, in the Hague, the Netherlands at the ISDF to issue their 2023 guidelines for treating the Diabetic Foot,[37] which like the ADA guidance cited above, now includes a positive TOT adjunctive treatment recommendation in non-healing DFUs.

In 2017 the European Wound Management Association (EWMA) published a CPG entitled Use of oxygen therapies in wound healing, with special focus on topical and hyperbaric oxygen treatment.[38] This guidance, although published prior to the publication of the most recent RCTs and SRMAs assessing TOT therapy, recommended TWO2 therapy for use with non-healing DFUs with a 1B evidence rating utilizing the GRADE methodology.

The Wound Healing Society (WHS) is in the process of updating its 2016 Diabetic foot ulcer treatment guidelines[39] and is expected to include a level 1 evidence-based recommendation for the use of TOT in DFUs, consistent with those cited above.

The Society for Vascular Surgery, in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine is commencing updating their CPG for management of the diabetic foot.[17] This guideline is being updated to incorporate the current state of the science and consistent with the ADA, IWGDF, and EWMA CPGs and is expected to include a consistent positive recommendation for the use of TOT in DFUs.

Issues Related to Health Disparities

It is well understood and was highlighted by CMS recently in CY 2023 PFS Proposed Rule (CMS-1770-P), that low socioeconomic and minority populations in the USA are disproportionately represented among those diagnosed with diabetes and subsequently with DFUs.[40] These beneficiaries experience complications arising from diabetes at higher rates and consequently use emergency and inpatient services more frequently.[41] Furthermore, diabetes is more prevalent among ethnic minorities, as the non-Hispanic White population has the lowest prevalence of diagnosed diabetes.[42] These disparities make it even more important to ensure that minority populations have access to appropriate resources and tools to best manage their condition, including as it relates to subsequent comorbidities associated with diabetes, such as DFUs.

African American, Hispanic, and American Indian/Native Alaskan individuals with DFUs have a several-fold greater risk of amputation than their White counterparts.[43] A recent 2022 study identified that within the USA, individuals identifying as Black undergo amputation at more than twice the rate of individuals identifying as non-Hispanic White, while those in rural areas have a nearly 35% increased likelihood of major leg amputation compared to their urban counterparts. Access to care has been identified as one of the main reasons for such inequalities.[44]

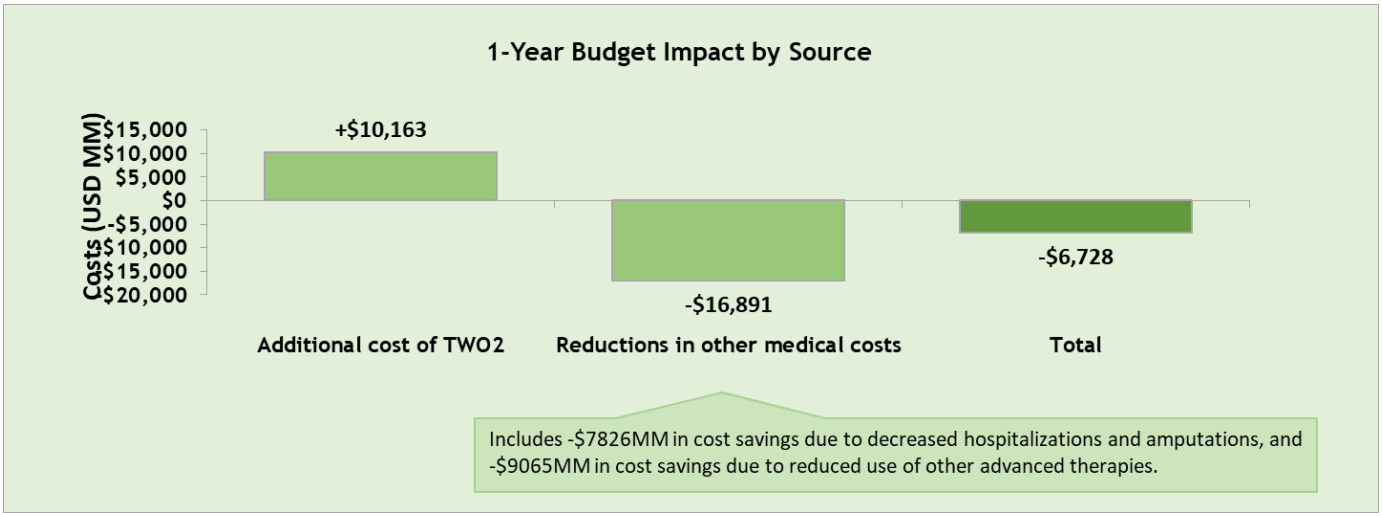
We believe that coverage of Intermittent TOT, which is applied by the patient at home, will greatly support and improve beneficiary access among minority and other underserved Medicare beneficiaries, especially those dually eligible for Medicare and Medicaid. We believe the clinical evidence presented supports ensuring this coverage and access, and we strongly expect that this will help to address many of the disparities that exist, improving health equity for these patients in the process, especially as they relate to limb amputations and the subsequent costs associated with these preventable adverse outcomes.

Cost Effectiveness of Intermittent TOT

While determining coverage is dependent on the "reasonable and necessary" standard consistent with clinical evidence and standards of care, we wanted to raise the cost effectiveness of covering Intermittent TOT in the treatment of DFUs. In particular, the proven, long-term efficacy of Intermittent TOT (TWO2) will reduce overall costs associated with beneficiaries suffering from DFUs. This is based on extrapolation of the more durable healing exhibited when this therapy is utilized. TWO2 therapy, which is a patient self-applied at-home therapy, has shown in both randomized and real-world studies to be as much as six-times more effective in healing DFUs compared to optimal SOC, with similar reductions in ulcer recurrence, which resulted in a substantial 88% reduction in hospitalizations and 71% reduction in limb amputations over 12 months.

A Budget Impact Model (BIM) developed by a leading health economics consulting group, Health Advances Inc.[45], suggests that such savings could be substantial for CMS across both the Medicare and Medicaid populations. The conservative estimate shows cost savings that exceed $6.7 billion per year, as is illustrated in the following chart:

	Total 1-year costs	Average cost per non-healing DFU patient	Cost per member per month (PMPM)
Current scenario	$43,427,071,704	$38,458	$25.80
Projected scenario with TWO2	$36,698,822,615	$32,500	$21.80
Budget impact	**-$6,728,249,089**	**-$5,958**	**-$4.00**
Change (%)	**-15.5%**	**-15.5%**	**-15.5%**



This estimate was determined as follows:

- The combined Medicare and Medicaid enrolled adult population of 140.27 million (as estimated by CMS in 2021)[46]
- An adult diabetes prevalence rate is 25% in Medicare and 9% in Medicaid (as estimated by CMS)[47,48]
- Incorporating the estimated rate of DFU prevalence in this diabetic population[49]
- Identifying the current estimated costs of treating these Medicare and Medicaid enrollees suffering from DFUs with SOC and existing CMS covered adjunctive modalities (NPWT, CTPs, HBO etc.)[50]
    - Monthly cost of Negative Pressure Wound Therapy (NPWT)[51]
    - Monthly cost of Cellular Tissue-Based Products (CTPs)[52]
    - Monthly cost of HBO[53,54]
    - Treatment duration of Negative Pressure Wound Therapy (NPWT)[51]
    - Treatment duration of Cellular Tissue-Based Products (CTPs)[55]
    - Treatment duration of HBO[54]
    - Proportion of patients on NPWT, CTPs, and HBO[56]
- Extrapolating the projected costs of treating these patients under SOC, including avoidable hospitalizations, lower extremity amputations, and other adverse outcomes[57]
- Comparing the above-calculated amount with the savings experienced by covering TWO2 therapy at the current reimbursed rate in New York Managed Medicaid conservatively estimating only a 50% adoption rate by prescribers/patients.

Other Payer Coverage of Intermittent TOT

Intermittent TOT is currently covered and reimbursed throughout the Veterans Administration via a Federal Supply Schedule Contract,[58] and New York, Arizona, and New Jersey state Medicaid programs under HCPCS code A4575. Multiple Medicaid managed care organizations cover Intermittent TOT, including Emblem Health Managed Care NY, Healthfirst Managed Care Insurance, and Community Health Choice Managed Care Plan. Given the success and coverage under the Veterans Administration and state Medicaid programs, we believe Intermittent TOT should be similarly covered by Medicare.

To date, thousands of patients have received TWO2 therapy with an estimated 2 million TWO2 treatments being applied by patients safely at home.

CONCLUSION

We thank you for your consideration of this request and look forward to working with you on ensuring Medicare beneficiaries have access to proven therapies to treat DFUs that have failed to heal with optimal SOC. We strongly believe that Medicare beneficiaries should have access to this therapy to improve healing and avoid long-term adverse outcomes associated with hospitalizations and amputations. We also believe that TWO2 therapy, which is applied by the patient at home, has the potential to significantly improve patient access to care and help address some of the racial and social-economic health inequities that exist today.

Should you have any questions or if you would like to discuss further, please contact Brian Lee at brian.lee@alston.com or (202) 239-3818.

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