ALLIANCE OF
WOUND CARE
STAKEHOLDERS
POWER THROUGH COLLECTIVE ADVOCACY

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Dear Doctors Ballyamanda, Lalla, Hoover and Jenny,

On behalf of the members of the Alliance of Wound Care Stakeholders ("Alliance"), I am expressing our substantive concerns regarding the Durable Medical Equipment Medicare Administrative Contractor (DMEMAC) Contractor Advisory Committee (CAC) Topical Oxygen Therapy (TOT) meeting held on December 11, 2024. The Alliance is a nonprofit multidisciplinary trade association of physician specialty societies, clinical and patient associations, wound care provider groups, wound care clinics and business entities operating in the wound care area. Our mission is to promote quality care and access to products and services for people with wounds through effective advocacy and educational outreach in the regulatory, legislative, and public arenas.

The DME MACs had received requests from Inotec AMD Inc. and ALSTON & BIRD Law Firm (representing a group of wound care specialists) to revise the Oxygen and Oxygen Equipment LCD to include language indicating that Topical Oxygen is reasonable and necessary for wound healing therapy for treating Diabetic Foot Ulcers (DFU). The purpose of this Specialty Focused CAC was to discuss the scientific evidence for both the Continuous and Intermittent TOT approaches underlying the requested LCD revisions.

Our understanding of the purpose of the Contractor Advisory Committee meeting stems from Chapter 13 of the Program Integrity Manual which advises that Medicare Administrative Contractors shall use available evidence of general acceptance by the medical community, such as published original research and peer reviewed medical journals, systematic reviews and meta-analyzes, evidenced based consensus statements, and clinical guidelines to help form an opinion. CAC members' role is advisory in nature, and comments, opinions on the evidence and literature are made to assist Contractor Medical Directors in determining if a proposed LCD should be developed and its potential content. This function supplements the Medicare Administrative Contractors internal expertise and ensures an unbiased and contemporary consideration of the state of the art, technology, and science.

These reconsideration requests included a plethora of new scientific studies, guidelines and consensus documents which were published after the previous 2019 Topical Oxygen Therapy (TOT) CAC meeting.

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Having listened to and participated in many previous CAC meetings, our expectations were that we would have a full two-hour meeting of subject matter experts addressing the key questions and a robust discussion of the strength of the new evidence supporting their answers. However, the Alliance leadership and members who listened to the meeting were surprised and dismayed with what we heard instead: an extremely biased and unsettling lightning quick discussion that did not address much of the new evidence and began with a negative undertone being established by the Chairperson that was palpable throughout the entire meeting. The discussion of evidence that did take place occurred too quickly to be meaningful.

We strongly encourage the DMEMACs to discount the results of this TOT CAC meeting due to the procedural and substantive concerns discussed in detail in this letter. Four important issues include:

1. The design of the CAC meeting was flawed since the intent of the CAC (as stated above) was to have a full discussion of the strength of all the new evidence (i.e., RCTs, clinical practice guidelines) presented in the reconsideration requests, which did not occur. There was no verbal discussion of the evidence provided to CAC members nor was there a power point presentation highlighting the evidence being reviewed by the CAC, as is common. As such, the public was aware of the new evidence being reviewed since the 2019 CAC meeting and it is unclear whether the CAC members received and reviewed all the new evidence.
2. Due to time constraints, the subject matter experts were not able to fully address an accurate assessment of the evidence base supporting TOT use in DFUs. This CAC meeting deserved the focus and time necessary for the subject matter experts to first understand and then adequately **discuss the evidence in context of the wound care space**. We believe that the additional time to conduct a full discussion of the evidence in the appropriate context would have positively changed the voting scores of the CAC members.
3. There was an improper voting procedure in that Dr. Ballyamanda announced that one of the CAC members voted twice which could have negatively impacted the final vote of the key questions.
4. The updated results were not made publicly available before the conclusion of the meeting. The public had the right to know who voted twice and be presented with the updated recalculated vote at the end of the meeting.

Our concerns as stated below address the need for discussion of the new evidence, the make-up of the CAC members and procedural issues.

Lack of Discussion of the New Evidence

The requesters of the reconsideration have been waiting many years in order to have the CAC consider new evidence for TOT. Just as importantly, the wound care community has been waiting this same amount of time to have this new evidence reviewed so coverage for TOT be established once deemed sufficient. TOT is a therapy that clinicians want to use on their patients given the ever-growing body of evidence and its success in resolving nonhealing wounds.

This CAC meeting deserved the focus and time necessary for the subject matter experts to first understand and then adequately **discuss the evidence in context of the wound care space**. In many other CAC meetings, the meeting commenced with a review and discussion of the new evidence that would include a summary PowerPoint presentation by the lead authors, allowing all to achieve a better understanding and adequate

exploration of the subject matter at hand. However, unfortunately, this did not take place. In fact, most of the evidence that was submitted for review by the requestors of the reconsideration was not discussed at all. Therefore, it is unclear whether any of this evidence was reviewed by the CAC and to what level, since none of the evidence reviewed was made publicly known.

Patients with DFUs often exhibit multiple comorbidities such as diabetes, heart failure, chronic kidney and vascular disease, thereby the patients' bodies respond differently at times to various wound healing technologies. These complexities and comorbid conditions often impact the number of patients that can meet needed inclusion criteria to be enrolled into wound care RCTs. In the recently published final LCD for *Skin Substitute Grafts/ Cellular and Tissue-Based Products (CTP) for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers*[i], other wound care treatments used in the same DFU indication the MACs established clear precedent as to adequate RCT enrollment size and quality acceptable to achieve coverage. The RCTs being examined for TOT clearly meet these established criteria. We believe it is paramount to the integrity of the process that consistent evidence assessment standards be applied when making coverage decisions for the same clinical indication.

As the CAC reviewed the evidence, it appears that neither inclusion/exclusion criteria based on the complexities and comorbid conditions of wound care patients nor the consistent evidence assessment standards were taken into consideration during the discussion.

We have concerns that the following pertinent new evidence was not discussed during the call:

- One of the key questions raised was whether TOT is generally accepted by the medical community. TOT **is** accepted by the medical community as is evidenced by its use and recommendation in numerous clinical practice guidelines (CPG) and consensus documents.[ii],[iii],[iv],[v],[vi] Yet, none of those guidelines were specifically discussed during the call:

    1. The American Diabetes Association (ADA) in February 2022 published a clinical compendium stating that the "evidence supporting TOT's efficacy in healing chronic DFUs can no longer be disputed" and supported this with the inclusion of TOT, with their highest "A" GRADE level recommendation, in their standards of care CPG for chronic DFUs from 2023 onwards.[vii]
    2. Additionally, medical experts in the field of wound healing (including vascular surgeons, critical care physicians, podiatric surgeons, and others) published a consensus treatment guideline in September 2021 that concluded patients with DFUs would likely benefit from application of TOT.[viii]
    3. These various CPG updates all reflect the results of published RCTs, meta-analyses, and systematic reviews that have consistently identified statistically significant complete healing outcomes for patients with DFUs treated with TOT.[ix]

- In addition to the guidelines and consensus documents, other evidence was submitted but not discussed during the TOT CAC call. We have provided some of that evidence below and underlined words or phrases that tied to the key questions. This evidence includes but is not limited to:

    - The 2021 RCT by Serena et al among others which took into account the recommendations made in the 2017 CMS Hyperbaric Oxygen (HBO) Therapy (Section C, Topical Oxygen) Decision Memorandum (CAG-00060R).[x] In the Serena trial, only patients who were strong candidates for advanced wound care were selected for participation. The inclusion criteria mandated that <u>all subjects exhibit 4 weeks of clear</u>

non-healing. Wounds demonstrating more than a 20% healing rate in the first two weeks were excluded. Those patients who remained were subjected to a comprehensive 2-week protocol, which included precise sharp debridement, effective reduction of bacterial load, and total contact casting. Once again, any wounds achieving over 20% healing during this secondary two-week period were excluded from the study. This meticulous 4-week run-in period was strategically implemented to eliminate any wounds that might show improvement due to standard care alone, thereby strengthening the integrity of the data and bolstering the reliability of the conclusions drawn.

Furthermore, 54.5% of all patients enrolled in the Serena trial were over 65 years of age, reinforcing the notion that these outcomes are highly applicable to the Medicare population. This significant representation enhances the relevance of the findings for older adults, ensuring that the benefits of the treatment can be effectively translated to this specific demographic.

The results of this RCT reveal a statistically significant rate of complete wound closure between the two study cohorts, indicating that this finding is unlikely to be due to chance. Statisticians typically consider a sample size of 30 or fewer to be small. However, this study's inclusion of 145 randomized subjects provides robust power for the investigation. Even as the CAC Chairperson emphasized the narrative of a small sample size, the undeniable statistical significance remains. It's crucial to also evaluate the effect size, clinical relevance, and the ability to replicate results seen in other submitted evidence.

- Regarding the durability of healing, Al-Jalodi et al conducted a follow-up study involving all subjects from the Serena diabetic foot ulcer (DFU) randomized controlled trial (RCT) who achieved healing during the trial period. Subjects from both study arms were evaluated 12 months after their wounds completely closed. The results were promising: 78% of those in the continuous topical oxygen therapy group remained healed after one year, compared to just 60% of the standard of care (SOC) group. Notably, this important follow-up study was not mentioned during the CAC discussions.

- The discussion of the Frykberg study ("A Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen Therapy in the Treatment of Chronic Diabetic Foot Ulcers: The TWO_2 Study") was conducted completely out of context with RCTs in the wound care space. The study utilized a robust prospective group sequential design to balance ethical considerations with meeting statistical significance, with enrollment of similar size to those RCTs deemed acceptable for coverage in CMS's recent CTP LCD for DFUs. It included all of the recommendations and was highlighted as an example of CMS's desired study design in the 2017 Decision Memorandum (CAG-00060R), Additionally, the majority of enrollees were of Medicare age and matched the demographic mix seen in this population.

  Uniquely, this RCT demonstrated more durable benefits with statistically significant complete wound healing at both 12 weeks and 12 months, and a far lower 12-month ulcer reoccurrences, across a broad range of severity DFUs. The study also assessed the impact on the patient's quality of life (QOL) utilizing the Cardiff Wound Impact Schedule (CWIS) https://www.wwic.wales/research/cardiff-wound-impact-schedule-cwis, a validated assessment tool that measures the impact of chronic wounds on a patient's QOL, which demonstrated that QOL improved substantially for patients whose ulcers healed with the active treatment across all functional domains.

- In what is the most robust and complete TOT systematic review and meta-analysis conducted by Marissa Carter et al., in 2022, which utilized the CMS recommended GRADE assessment approach, the Frykberg study was assessed to have a low risk of bias across all domains. The Carter review also included a forest plot of the relative risks of complete healing for all the TOT RCTs, where the Frykberg study lower confidence interval clearly still shows positive treatment effect, further proving the adequate powering of the study and the statical rigor of the outcome. The study was additionally awarded in 2023 one of the top 4 studies on the Diabetic Foot in the past 4 years by the International Symposium on the Diabetic Foot.

- Another high quality and supportive real-world study that was not discussed was that by Yellin 2022 ("Reduced Hospitalizations and Amputations in Patients with Diabetic Foot Ulcers Treated with Cyclical Pressurized Topical Wound Oxygen Therapy: Real-World Outcomes")[xi] where the 12 month durability of healing was further explored in 202 comorbid DFU patients of Medicare age and demographics, demonstrating substantial statistically significant reductions in amputations and DFU related hospitalizations over 12 months. Well-designed real-world studies contribute meaningful clinical insights, which cannot always be garnered from high quality RCTs, as to treatment effectiveness and generalizability across the broader very comorbid Medicare patient population.

We submit that the evidence that should have been reviewed is robust and more than sufficient to allow for the DME MACs to move forward with covering TOT in the Oxygen and Oxygen Equipment LCD.

TOT CAC Member Selection

The TOT CAC was comprised of 8 members- only four of which were clinicians and subject matter experts, with one of those being arbitrarily designated as an industry representative and not able to cast a vote. In other CACs, most if not all of the members are physicians or clinicians who are subject matter experts first rather than statisticians or evidence experts. Therefore, we were concerned that only a small number of the voting CAC representatives really understood contextual relevance or had any experience in wound care, or in using these important new technologies. In fact, Dr. Mandrekar, a Ph.D. statistician, even stated in the introduction that "he has never treated a patient and has no understanding of the complexities of wound care."

We were surprised to hear as the CAC members were being introduced that one of the most knowledgeable wound care subject matter experts, Dr. Matt Regulski, was designated the industry representative and therefore not permitted to vote. We believe that the DMEMACs should not have selected him as the industry representative and either have chosen someone who does work for industry or a well-known researcher on TOT such as Dr. Marissa Carter who served in this capacity in the 2019 TOT CAC. Dr. Regulski's expertise is that of a practicing clinician who has treated patients with diabetic foot ulcers for over 20 years. We believe that Dr. Regulski should have been left as a voting CAC member given his expertise not only in the field of wound care but in wound care evidence.

Concerns with Procedural Issues

The Alliance has the following concerns with procedural issues related to the TOT CAC meeting:

- In other CAC meetings, many times the CAC medical directors serve as the moderator and state the key questions so as to have an objective and unbiased approach. Instead, the same person served as the chair in both this and the 2019 TOT CAC. We would have thought since she had served in this capacity previously, she would have known about the topic and would not only have encouraged a more in-depth discussion of the new evidence but also would have stated the correct title of the CAC meeting. Unfortunately, it appeared she was unaware that the CAC meeting was for "topical" oxygen therapy since she kept referring to it as "total" oxygen therapy and unfortunately, none of the medical directors provided any corrections throughout the meeting. It was disconcerting that after waiting over two years for this meeting to take place not only was the evidence not discussed but the name of the meeting was not referred to correctly. Both these issues set a very problematic tone from the start of the meeting.
- The meeting started close to 20 minutes late – which impacted the ability of the CAC members to discuss the evidence in any meaningful way as the meeting was cut short and did not provide sufficient time to discuss the evidence – which was the purpose of the CAC TOT meeting. For those of us listening, we were simply surprised and dismayed that there was not enough time to have a full discussion of the evidence when the key questions were being discussed. In fact, the chair only allowed **at most a minute per CAC member and sometimes as little as 30 seconds to "discuss evidence" for both continuous and intermittent oxygen to address the 8 questions posed for each approach**. The chair should have been able to figure out a way to either add 20 minutes to the end of the meeting so that the CAC members were not rushed in delivering their answers or find a way to allow for each member to be able to discuss the evidence in a more detailed manner - highlighting any studies that were strong in general before moving to the key questions. By not being able to have meaningful discussion of the new evidence, we view this as a failure of the DMEMACs to uphold the standards set up by Chapter 13 of the Program Integrity Manual when a CAC is conducted. This is unacceptable.
- In contrast, the chairperson afforded herself several minutes of continuous uninterrupted time at the beginning of meeting to discuss her uncontextualized views of the evidence which not only took time away from the overall time of the CAC meeting evidence discussion, it was more time than the 30 seconds to a minute she afforded other CAC members. Given that the meeting had already started late, this was also mystifying and problematic to those listening.
- When the votes on the key questions took place and the results were reviewed, albeit briefly – Dr. Ballyamanda recognized and stated that someone voted twice. It appeared that Dr. Redberg offered up that she may have been the member of the CAC which voted twice. This could have negatively skewed the final vote. Yet, it was not disclosed as to who voted twice nor were the new results reviewed with the public. The only comment made by Dr. Ballyamanda was that "it won't make a difference." If Dr. Redberg voted twice, as the voting screens indicated, since there were 8 votes counted for each question, it actually would have made a difference. The results should have been recalculated and announced during the call. As stated in the beginning of this letter, the DMEMACs need to resolve and address these concerns before finalizing the CAC responses and posting them online.

Conclusion

To conclude, the Alliance has substantive concerns with the TOT CAC meeting including:

- The meeting started 15-20 minutes late, which rushed the entire agenda and allowed the CAC subject matter experts virtually no time to review/discuss the new evidence when answering the key questions, which was the entire purpose of this meeting.

- Instead of a well-respected wound care clinician who is also knowledgeable about the research, the DMEMACs should have designated as an "industry representative" someone who actually works in industry or a well-known researcher on TOT such as Dr. Marissa Carter who served in this capacity in the 2019 TOT CAC. Dr. Regulski should not have been designated as the industry representative.
- The Frykberg RCT was the only evidence discussed yet it was dismissed as being too small, despite being adequately powered with a positive lower confidence interval and being of similar size to other studies in the wound care space deemed acceptable to CMS for positive coverage decisions. The fact that this award-winning study showed statistically significant 12 week and 12-month complete healing outcomes, and QOL improvements, on majority Medicare age/demographic patients, was neither understood or expounded accurately by the non-wound care experienced CAC members.
- The large Yellin follow-on real world evidence study was not discussed. This study further supported the durable healing outcomes from the Frykberg RCT in a broad comorbid Medicare age patient population and demonstrated significant 12-month reductions in life altering and expensive amputations and hospitalizations.
- In the 200-patient retrospective study by Kaufman, the compelling evidence showcases that continuous topical oxygen therapy (cTOT) significantly accelerates healing in chronic wounds of all origins. Notably, the use of cTOT in chronic diabetic foot ulcers (DFUs) triggered a marked healing response, highlighting the critical role of oxygen in the wound healing process for these patients. These findings are particularly impressive considering that this real-world cohort had a larger mean baseline wound size and greater complexity compared to other studies on cTOT. Furthermore, a majority of the patients were frail, grappling with multiple comorbidities, including underlying peripheral artery disease. This study strengthens the growing body of evidence that confirms cTOT as an effective solution for challenging, hard-to-heal chronic DFUs.
- The Serena DFU RCT and his follow-up durability study offer vital new evidence contained in the NATROX Wound Care reconsideration request. It is troubling that the CAC did not engage in any discussion about the outcomes of these significant studies. This absence of dialogue calls into question the thoroughness with which relevant data was considered in the decision-making process.
- Finally, it seems the voting process was flawed with an obvious critic possibly voting two times. It seems that this would skew the data yet it is unknown to the public who voted twice as well as the results of the final corrected vote.

It is imperative that CMS provide coverage for products that are proven to help heal diabetic foot ulcers– especially when there is a significant body of clinical evidence to support their use. TOT is a necessary addition to the treatment options for clinicians, complimenting their limited existing covered options. The continued delay of not moving forward with issuing a positive coverage decision for TOT increases the risk of negative health outcomes for some of the most at-risk Medicare patients, particularly among racial and ethnic minority populations that suffer from disproportionately higher rates of diabetic complications, including foot ulceration, amputation, and diabetes-related death and disability.[xii]

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In the beginning of this letter, we stated that the purpose of the CAC meeting, in alignment with Chapter 13 of the Program Integrity Manual, allows for discussion of the available evidence of general acceptance by the medical community, such as published original research and peer reviewed medical journals, systematic reviews and meta-analyzes, evidenced based consensus statements, and clinical guidelines and that the CAC is advisory in nature and should be unbiased.

Thus, we were very enthusiastic that the DMEMAC medical directors were planning to convene a CAC meeting on topical oxygen. We had high expectations that once we saw the agenda, there would be a full two-hour meeting of subject matter experts addressing the key questions and a robust discussion of the strength of the new evidence supporting their answers. However, after listening to this meeting, we believed that we needed to send a letter with our concerns which allowed us to come to the conclusion that the TOT CAC failed to meet those standards set forth by the purpose of the CAC.

We strongly encourage the DMEMACs to discount the results of this TOT CAC meeting due to the procedural and substantive concerns discussed in detail in this letter. Specifically, we also suggest that the DMEMACs need to resolve and address these concerns regarding the voting before finalizing the CAC responses and posting them online.

Instead, we recommend that the DME MAC medical directors rely more on their independent assessment of the new RCTs, clinical practice guidelines and additional real-world evidence that is outlined in this letter and in the reconsideration requests, in context of the wound care space and recent coverage decisions for treatments in the same DFU indication, so that Topical Oxygen can be assessed as a reasonable and necessary wound healing therapy in the Oxygen and Oxygen Equipment LCD.

Thank you for your consideration. We request a further discussion about our concerns at your convenience.

Sincerely,

Marcia Nusgart R.Ph.

Marcia Nusgart, R.Ph.
Chief Executive Officer

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[i] *https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=35041*
[ii] *Chen, P. et al. www.iwgdfguidelines.org (2023)*
[iii] *Lavery, L. A. et al. WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines. Wound Repair Regen. 2024; 32:34-36*
[iv] *ElSayed, N. A. et al. 12. Diabetes Care **46**, S203–S215 (2023)*
[v] *ElSayed, N.A. et al. 12. Diabetes Care 47 (Suppl. 1):S231–S243 (2024)*
[vi] *Frykberg, R. et al. Use of Topical Oxygen Therapy in Wound Healing. J Wound Care **32**, S1–S32 (2023).*
[vii] *Andrew J.M. Boulton, David G. Armstrong, Magnus Löndahl, Robert G. Frykberg, Frances L. Game, Michael E. Edmonds, Dennis P. Orgill, Kimberly Kramer, Geoffrey C. Gurtner, Michael Januszyk, Loretta Vileikyte; New Evidence-Based Therapies for Complex Diabetic Foot Wounds. ADA Clinical Compendia 22 February 2022; 2022 (2): 1–23. https://doi.org/10.2337/db2022-02.*

[viii] *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;30(Suppl. 9): S30–S34.*
[ix] *See, e.g.,*

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[x] *https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=286*
[xi] *Yellin JI, Gaebler JA, Zhou FF, et al. Reduced Hospitalizations and Amputations in Patients with Diabetic Foot Ulcers Treated with Cyclical Pressurized Topical Wound Oxygen Therapy: Real- World Outcomes [published online ahead of print, 2021 Dec 6]. Adv Wound Care (New Rochelle). 2021;10.1089/wound.2021.0118. doi:10.1089/wound.2021.0118;*
[xii] *Sharpe J.E., DOI: 10.23937/2377-3634/1410120*

c.c. Will Harris (Office of the Administrator), Tamara Syrek Jensen, Director Coverage and Analysis Group (CAG), Elizabeth Truong, Karen Reinhardt, CAG Staff