Tamara Syrek-Jensen, Esq., Director
Coverage and Analysis Group (CAG)
The Centers for Medicare and Medicaid Services (CMS)
7500 Security Blvd.
Baltimore, MD 21244

March 16, 2015

Dear Ms. Syrek-Jensen,

EO2 Concepts, Inc. is pleased to submit the following information as a formal request for an internal review of the National Coverage Decision (NCD) for Hyperbaric Oxygen Therapy (20.29) with respect to Section C, "Topical Application of Oxygen".

Since NCD 20.29 was published in 2003, new devices that provide a continuous diffusion of oxygen (CDO) were yet to be developed and hence, the NCD could not consider this evolution of oxygen therapy and the documented advances to wound treatment.

The attached library of mostly peer reviewed articles provides documentation of the role of oxygen, it's mechanism of action and the effectiveness of CDO treatment on open hard-to-heal wounds. We believe these studies provide overwhelming evidence of the effectiveness of CDO and will enable CMS to move forward to amend the NCD.

We appreciate your time and consideration of this request. Please feel free to contact me, or Jennifer Summa with Baker Donelson at 202-508-3408 if you have any questions or need additional information.

Sincerely,

Joe Moffett

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1. Position of CDO in NCD 20.29

Current position and language:

National Coverage Determination (NCD) for Hyperbaric Oxygen Therapy (20.29)
Item/Service Description CIM 35-10

For purposes of coverage under Medicare, hyperbaric oxygen (HBO) therapy is a modality in which the entire body is exposed to oxygen under increased atmospheric pressure.

Indications and limitations of coverage:

A. Covered conditions
B. Non covered conditions
C. Topical application of oxygen
   (1) This method of administering oxygen does not meet the definition of HBO therapy as stated above.
   (2) Also, its clinical efficacy has not been established. Therefore, no Medicare reimbursement may be made for the topical application of oxygen.

Request

The company requests an internal change to NCD Hyperbaric Oxygen Therapy 20.29 to clarify section C the definition of "Topical Application of Oxygen" to "Topical Hyperbaric Chamber for Extremities". The purpose of the clarification is to allow Continuous Diffusion of Oxygen (CDO) therapy to be taken out of NCD 20.29 because CDO would not meet the new definition of "Topical Hyperbaric Chamber for Extremities".

The supporting arguments:

1. Physical

CDO is not administered to the whole body of a patient in a chamber, nor a part of a body in an extremity chamber.

- The patient is not required to travel to a site that has a dive chamber.

CDO therapy does administer oxygen to only the body part that has a wound and uses a dressing to distribute the oxygen and collect the exudate. There is no chamber and patient can be treated at home. CDO is wearable.

CDO does not systemically provide high flow hyperbaric oxygen to patients.

- CDO does not have the same potential risks and complications of hyperbaric oxygen.

CDO therapy does deliver low flow normobaric oxygen and has no known complications.

CDO is not intermittent with 90 minute daily dives.

- CDO therapy is continuous (24 hours per day, 7 days per week) oxygen treatment.

CDO does not require a physician present for supervision or risk management.

- CDO therapy can be managed by low intensity caregivers, including family members.

CDO does not belong in a service code for physicians. For consideration, physicians may and do setup the device and change dressings in their facilities. On going management of the device is limited to routine office and or home nursing visits to follow progress. Dressing changes, debridement and other care regimens are required, whether in an acute or chronic setting dependent on wound type and status. In many cases, dressing changes can be performed by a family member or other care taker.

CDO therapy is maintained by onboard monitoring for constant oxygen output and patency of the system. Dressing changes are managed similar to other multilayered absorbent dressings in the acute or chronic (home) settings. There are different sizes, adhesive and absorbent dressing options dependent on clinical requirements. CDO therapy can also be used to support other clinical interventions to good effect[1], such as grafts and antibiotics. CDO cannot be used with petroleum based salves or ointments.

Lastly, the technology has limited opportunity to prove commercial viability with a non-payable code in a fee for service healthcare delivery system in the US. However, the technology is available to the Veterans Administration Healthcare and Indian Healthcare Systems, as the technology has been awarded a contract on the Federal Supply Schedule. This has facilitated our ability to develop data similar to the Dr. Couture paper published this year on 32 of his patients. More studies are expected from the VA and now Indian Health facilities, given this opportunity for commercialization.

Available technology in 2003 to drive NCD 20.29 update

At the time of the 2003 NCD update, only HBO and topical oxygen extremity chambers were available to the market: CDO therapy or devices did not yet exist. Devices using topical oxygen extremity chambers did employ various chambers, were applied just like HBO with daily 90 minute dives, and provided pressure above atmospheric pressure. These devices didn't allow patient ambulation or wearability, but could be used in a home environment.

The August 2002 CMS Decision Memorandum published prior to the issuance of NCD 20.29 detailed the proposed NCD for Hyperbaric Oxygen Therapy with no mention of "Topical Application of Oxygen". Therefore, the intent of the NCD update was to address topically applied oxygen via topical oxygen extremity chambers. The updated NCD position was also supported by a 2005 paper written by the Undersea & Hyperbaric Medical Society, which only described and referenced the Society's opposition to topical oxygen extremity chambers.

TransCu O_2 did not receive FDA clearance until 2009. The NCD did not consider this novel next step in the evolution of oxygen therapy and therefore made no mention of this mechanism of action or application outside the use of chambers.

2. Technology Description

TransCu O_2® is a **wearable** and **completely silent** continuous low flow oxygen delivery system for difficult to heal wounds. The system is comprised of two major components.

- First, the wearable device is a battery (rechargeable) operated, low flow oxygen concentrator. It uses a charged proton exchange membrane and an electrochemical process to produce humidified pure oxygen. The oxygen output is at normobaric pressures and is therefore not hyperbaric. What sets the technology apart from predicate devices is that the clinician can set an appropriate oxygen flow rate based on the size of the wound, and the device servo controls the flow rate independent of ambient humidity conditions. The actual flow rate is always displayed for the clinicians for reference of proper operation. The technology also has a pressure transducer that continuously monitors the pressure on the oxygen delivery tubing to validate to the clinician the tubing and dressing are patent. Therefore, the capillary bed is not subject to pressure that could collapse the vascular bed, thereby inadvertently interfering with the proper perfusion of the wound bed. An alarm is sounded for the clinician if the pressure exceeds the reported level of capillary collapse in the literature[2]. It is these advances in the technology that are likely a big part of the clinical performance differences over predicate devices or topical extremity chambers.

- Second, the system's OxySpur™ dressings channel the oxygen to all parts of the wound area to optimize the oxygen application to the entire wound bed. The design also provides offloading of the pressure associated with the insertion of the perforated cannula, thereby protecting the periwound from pressures that could break down the skin.

- The technology has real advantages for application in rural communities that can't get to wound clinics regularly and can be managed in the home environment with less intensive clinical oversight and management. 90% of the patients in the patient registry and greater than 95% in the Randomly Controlled Trial (RCT) did not require home nursing.

3. Supportive Science

TransCu O_2 employs Continuous Diffusion of Oxygen (CDO) therapy and is a FDA cleared system that promotes wound healing, providing continuous therapy while supporting more normal quality daily life. Indications for use in FDA clearance include skin ulcerations resulting from diabetes, venous stasis, post surgical infections, gangrenous lesions, pressure ulcers, infected residual limbs, skin grafts, burns and frostbite.

CDO therapy is a method intended to promote the body's natural healing of chronic or acute wounds that fail to heal without advanced clinical intervention. This is accomplished by maintaining a high oxygen concentration in the dressing above the wound bed and continuously diffusing the oxygen through a moist wound media to the

wound bed. The oxygen delivery is both continuously applied and Henry's law of partial pressure (concentration) gradients moves the oxygen from the high concentration area above the wound to the low concentration area in the wound bed. This physiologic process is at work in both internal and external respiration.

Scientific documentation on oxygen therapy in the literature offers evidence that oxygen in wound care:

A. Increases Cell Metabolism and Energy Production
    a. If oxygen levels are too low (<20 mmHg pO_2):
        i. Cells convert to anaerobic metabolism - survival mode
        ii. Healing activities & collagen production impaired[3,4,5]

B. Increases Rate of Cell Proliferation and Reepithelialization
    a. Fibroblast proliferation and protein production reported to be optimal at 160 mmHg pO2 (2-3 fold higher than normal)[6]

C. Increases Collagen Synthesis and Tensile Strength
    a. Increased collagen deposition[7,8,9,10] (faster repair)
    b. Increased tensile strength[11,8,12] (reduced recurrence)
    c. Increased collagen organization[13] (reduced scarring)

D. Increases Anti-Bacterial Activities
    a. Oxygen is essential for respiratory burst, the production of reactive oxygen species (ROS), such as O_2^- & H_2O_2[14,15,16]
        i. Leukocyte activity is directly proportional to local oxygen concentration[17]
    b. Optimal ROS production is seen at oxygen levels of greater than 300 mmHg[16]
        i. Can only be achieved with supplemental oxygen[18]

E. Increases Angiogenesis & Promotes Revascularization
    a. Oxygen levels directly affect the rate & quality of new blood vessel growth[19,20,21,22]

- The company's first published article in the peer reviewed ***International Wound Journal; "Low flow oxygenation of full-excisional skin wounds on diabetic mice improves wound healing by accelerating wound closure and reepithelialization"***[13]

In this double-blind, randomized study with a sham control, the authors explored the hypothesis that providing diabetic skin wounds only locally, yet continuously, with a saturated oxygen environment at ambient pressure and at low oxygen flow rates (CDO) improves wound healing. The authors report that CDO treatment dramatically accelerated reepithelialization and wound closure of full excisional skins wounds in diabetic mice.

Two full-excisional dorsal skin wounds were generated on 15-week-old diabetic db/db mice and treated for 10 days in 20 mice divided into two treatment arms. Mice in both arms received identical treatment, with the only difference being that the control group received no oxygen and the active group received continuous pure oxygen (>99.9%) at low flow rates (3 ml/h).

After 6 days, oxygen treatment resulted in a statistically significant (p=0.022) mean reduction of the original wound size by 60.2% as compared with only 45.2% in wounds on control mice that did not receive pure oxygen.

After 10 days, oxygen-treated wounds were 83.1% closed compared with 71.2% in wounds on control mice (p=0.008). Furthermore, at 10 days reepithelialization was complete in over 57% of wounds receiving CDO treatment as compared to 25% in the control group, with significant differences in the remaining epithelial gap size (p=0.006). The authors conclude that CDO therapy "significantly accelerates wound closure and reepithelialization" and state further that while oxygen-based therapies have proven effective in treating chronic and difficult-to-heal skin wounds, the current intermittent therapeutic approaches suffer from major limitations and they do not allow for mobility or continuous wound treatment.

- The company's second peer reviewed journal article was published in the ***Wound Repair and Regeneration Journal: "Oxygen and Wound Care: A Review of Current Therapeutic Modalities and Future Direction"[23].***

  This article presents historical and current understanding of the role of oxygen in wound healing, as well as comparing and contrasting the various modalities of applying oxygen therapy. Howard, Asmis, Evans, and Mustoe clearly point out the advancements made in the technology offered in CDO versus other methods of action used in oxygen-based therapies. They clearly define the differences in the mechanism of action of the various oxygen modalities and conclude more precise nomenclature and categorization is necessary to adequately communicate the differences between the modalities.

  This subset of scientific evidence identifies the role of oxygen in wound healing and the various mechanisms of action substantiated by both controlled and anecdotal evidence. The references are mostly 3rd party publications, but establish credence in the company's work to the science behind the technical advancements.

4. Specific Clinical Support

CDO therapy has to date consistently demonstrated clinical evidence of improved outcomes, as compared to covered technologies and interventions:

- Most other advanced modalities, like negative pressure devices and hyperbaric oxygen treatments, do not bring wounds to full closure. Additional treatments such as sutures, flaps, grafts, and advanced wound dressings are often required to achieve full closure. Worst of all, failed advanced modalities can end in amputation of extremities, which are

very costly and also have a 45% (neuropathic) and 55% (ischaemic ulcers) mortality rate for patients in 5 years[24].

- The company defines a successful outcome as 100% re-epithelialization without weeping.

- Interim results from a **Tier 1 Diabetic Foot Ulcer study** show statistically significant results at an interim analysis. The interim results were published online in ***Wound Medicine* in *May of 2015***[25]. The rigor of this study is rare in the medical device world and modeled after a pharmaceutical trial. It is a double-blind, prospective, randomly-controlled trial with a sham and an active arm. Both arms receive identical treatment (device, dressings, etc.) and the devices are functional in both arms. However, the oxygen does not flow to the wound in the sham arm.

  David Armstrong DPM, MD, PhD of the University of Arizona is the overall principal investigator for this study.

  In an unpublished interim statistical report by the biostatistician, Joel Michalek, PhD, of the University of Texas Health Science Center San Antonio (UTHSCSA)[26], the interim analysis of the current study shows that CDO demonstrates statistically significant results (p=0.019) with 56% closure in the active arm and 20% closure in the sham arm.

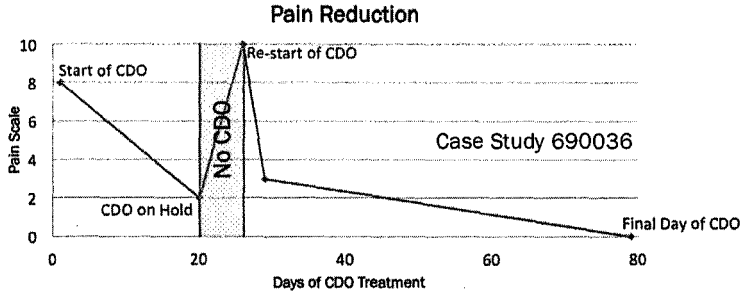
  These results compare favorably to other advanced wound therapies, which are currently covered by CMS, as shown in the table below. It is important to note that the CDO study highlighted below uses full closure (defined as full reepithelialization with no weeping) as the primary outcome, whereas the other comparative non-CDO studies in the table below were allowed other additional interventions to attain the end point of full closure.

Study	Wound Type	Test Device	Comparator	N	Study Length (weeks)	Wound closure (%)		
						Test	Control	p-value
Blume et al 2008[27]	DFU	VAC	MWT with alginates, foams, hydrocolloids, or hydrogels	335	16	43%	29%	0.007
Armstrong et al 2012[28]	DFU & VLU	Snap	VAC	83	12	50%	52%	N/A
Marston et al 2003[29]	DFU	Dermagraft	Saline-moistened gauze	245	12	30%	18%	0.023
Edmonds 2009[30]	DFU	Apilgraf	Non-adherent dressing	71	12	52%	26%	0.049
Armstrong 2015[25,26]	DFU	TransCu O_2	MWT with specific foam & thin film, optional alginate	50	12	56%	20%	0.019

- Dr. Mark Couture (Central Texas Veteran's Healthcare Administration, Temple, TX): an IRB approved retrospective analysis of 25 patients in a Veteran's Healthcare Administration environment. As Published in ***Podiatry Today***[1], results show 68% full closure, both as a stand alone and adjunctive therapy. The author found that CDO improves wound healing potential, even in wounds receiving advanced tissue/skin

substitute applications. These outcomes are also compared to outcomes in other published studies, as well as EO2's registry. Reprints available (EO2 White Paper 690080).

- Dr. Stephanie Wu (Rosalind Franklin University, Chicago, IL): prospective study looking at wound closure, pain reduction (VAS), reduction of inflammatory cytokines (Luminex bead-based xMAP technology 18 cytokine analysis), VEGF, genetic markers (RNA expression of wound biopsies, as well as Targeted Quantitative PCR), quality of life/activity levels, bio-burden reduction. A case study from Dr. Wu's first patient (prior to the study) has been published in Podiatry Today[31]. This case demonstrates a marked pain reduction upon application of CDO. See graph from EO2 Case Study 690036: pain reduced from 8 to 3 upon application, rose to 8 upon withdrawal of CDO during treatment, then reduced quickly to 3 upon reapplication of CDO.



- Dr. Gabriel Urrea-Botero (Gonzaba Medical Group, San Antonio, TX): retrospective analysis on the impact of CDO in chronic toe ulcer healing for 20 patients. As Published in Podiatry Today[32], results include an overall success rate (full closure) of 74% on wounds that were unresponsive to other therapies, which compares very well to the EO2 registry (eo2.com). The author highlights a chief benefit being that of high patient compliance (95%), which he attributes to the device's ease of use, the noticeability of improvement within a short period of time, and the reduction of pain. Reprints available (EO2 White Paper 690076).

- Dr. Larry Leverett (Plastic Surgeon in Phoenix, AZ): retrospective case report consisting of two cases in which CDO was used successfully to salvage acutely ischemic surgical tissues. Successful salvage of tissues was expected and seen relatively quickly. Patient satisfaction was extremely high. Submitted for publication.

- Dr. Larry Lavery (University of Texas Southwestern Medical Center, Dallas, TX): prospective study investigating perfusion changes in the wound bed (using Hyperspectral imaging (Hyper Med), Skin Perfusion Pressure measurements (Vasa med) and Transcutaneous oxygen measurements), changes in inflammatory cytokines (IL-6, IL-8, TNF-α) and growth factors (VEGF, PDGF, IGF, TGF-β), and reduction in bioburden. IRB approved, in progress.

- Dr. Joseph Mills (Baylor College of Medicine, Houston, TX): prospective study investigating perfusion changes in the skin perfusion (ABI, Toe Pressures and Waveforms (pulse volume recordings) on both extremities, as well as SensiLase system

(Väsamed) to measure Skin Perfusion Pressure), wound associated pain, and in quality of life/physical activity levels. IRB approved, in progress.

- The company's post-market surveillance registry of 945 patients demonstrates a success rate of 74% in 59 days in the field. This success rate is on very difficult wounds that have already been unresponsive to other advanced therapies such as NPWT and HBO and had been open for an average of 359 days (as a new technology, CDO is typically initially tried as a last resort for challenging, unresponsive wounds).

- An article from **Advances in Skin and Wound Care in August of 2008**[33] presented the 5-year average of direct DFU wound care costs per modality per patient. The costs ranged from $47k to $21k per modality per patient. The travesty is that the published closure effectiveness of the various modalities was 30 to 70%. Said differently, the healthcare system endured the cost of the modality failures 70% to 30 % of the times. This makes CDO at an average cost of $5,500 appear to be a significantly more cost effective alternative to other advanced modalities. Consider the cost of amputation and the difference is even larger both in cost and quality of life. In 5 cases in the Indian Health System the patients were scheduled for surgery to remove the feet above the ankle, when all the surgeons decided to apply CDO. After the first week of treatment with CDO, one patient's wound had closed 60% and the other 4 patients showed significant improvement, and the surgeons cancelled all 5 patient's surgeries.

- The research and clinical endpoints of any CDO application is full closure – stop spending money. The greatest expense of wound care is in the sometimes lengthy formulary application to find the right interventions. Very few technologies consistently choose and implement full closure in their research protocols or anecdotal use guidance without secondary interventions.

5. Summary

Over the last 5 years, the TransCu O_2 System and the associated CDO therapy have been studied scientifically and clinically to understand its efficacy and utility to bring hard to heal acute and chronic wounds to closure. The company has committed most of its resources to demonstrating the clinical efficacy of CDO, and has limited it's marketing to both carefully control the messaging and build clinical confidence in a highly fragmented industry with limited standards of care.

The technology has amassed a plethora of various data ranging from a 945 patient registry to a Tier 1 level of evidence randomly controlled trial (RCT) with an arduous lead-in to single out truly chronic wounds. The published interim report and follow up of the UTHSCSA report showed statistically significant results. In a second statistical check by an independent statistician on the outcomes of the RCT, the completion of the study has a 96.7% Bayesian predictive probability of a successful outcome. The subsequent published articles and case study reports referenced in this document have all demonstrated consistent positive outcomes to a similar degree: CDO produces outcomes non-inferior to covered and reimbursed technologies.

In the aforementioned clinical support material, the company expects more affirmation of not only the same positive clinical outcomes, yet also a further understanding of the physiologic reasons for these outcomes.

The clinicians who have used this technology believe they have data and understanding to integrate this into their practices and want an opportunity to use this technology for the improvement of their clinical outcomes in wound care.

The company requests a reconsideration of NCD 20.29 and the removal of CDO from this NCD.

We also request CMS provide more descriptive language of the technology that CMS intended to exclude from coverage that is technically in alignment with the definition of hyperbaric devices. This therefore, would afford CDO the opportunities of coverage from CMS other than NCD.

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