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I. INTRODUCTION

The Centers for Medicare & Medicaid Services (“CMS” or “you”) has a long-standing National Coverage Determination (“NCD”) for Hyperbaric Oxygen Therapy (20.29) (“NCD 20.29”) that provides coverage for hyperbaric oxygen treatment under certain circumstances. Even though topical oxygen is not hyperbaric oxygen, the NCD adds a final paragraph that states, with regard to topical application of oxygen, “This method of administering oxygen does not meet the definition of HBO as stated above. Also, its clinical efficacy has not been established. Therefore, no Medicare reimbursement may be made for the topical application of oxygen.”

EO2 Concepts, Inc. (“EO2”) submitted to CMS a request for a reconsideration of NCD 20.29 on March 15, 2015. EO2 requested, (1) a reconsideration of NCD 20.29 and the removal of Continuous Diffusion of Oxygen (“CDO”) therapy from this NCD; and (2) 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. EO2’s formal request is:

[An] internal change to [NCD 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 [CDO] to be taken out of NCD 20.29 because CDO would not meet the new definition of “Topical Hyperbaric Chamber for Extremities.”¹

CMS may consider a request to revise an existing NCD only if the requester presents: (1) additional scientific evidence that was not considered during the most recent review along with a sound premise by the requester that new evidence may change the NCD decisions; or (2) plausible arguments that CMS’s conclusion materially misinterpreted the existing evidence at the time the NCD was decided.^{2/} Because CMS proceeded to open NCD 20.29, under its authority in Section 1862(a)(1) of the Social Security Act, we therefore assume that one, or both, of these reconsideration standards have been met by EO2’s request.

CMS expanded the EO2 reconsideration request and is reconsidering section C in its entirety and solicited comments regarding the clinical efficacy of topical oxygen. You further clarified that CMS is considering coverage of topical oxygen as part of the reconsideration process and that information to be considered as part of that decision process should be provided within the open comment period, closing August 11, 2016. GWR Medical, Inc. (“GWR” or “we”) is responding timely to the August 11th comment deadline. All **ATTACHMENTS** referenced in our comments will be separately emailed within the deadline for comment, in multiple numbered emails, and also sent to CMS on a compact disk for delivery August 12, 2016. Per your instructions we have sent separately a disk of attachments that should be considered as part of the GWR comment package.

EO2 included certain references, primarily aimed at identifying the clinical experience of their specific topical oxygen technology. In general, GWR agrees with the premise of many of those cited references insofar as they support our consistent argument that topical oxygen has

^{1/} EO2 Request Letter, **ATTACHMENT 1**.

^{2/} Medicare Program; Revised Process for Making National Coverage Determinations, 78 Fed. Reg. 48167 (Aug. 7, 2013). **ATTACHMENT 2**.

sufficient clinical evidence to support a CMS determination to cover topical oxygen treatment. Our comment submitted below will, among others, clearly demonstrate the following points:

- Topical oxygen treatment is not the same as Hyperbaric Oxygen treatment.
- Topical oxygen is safe and effective for FDA-cleared indications.
- Topical oxygen has historically received inconsistent scrutiny among federal agencies (i.e., FDA and CMS).
- Sufficient clinical information exists for CMS to provide coverage for TO as reasonable and necessary for the treatment of illness or injury. In fact, TO is safer than other wound treatment modalities such as negative pressure wound therapy and systemic hyperbaric wound treatment.
- NCD 20.29 is not applicable to topical oxygen and it would be more appropriate for CMS to consider a separate NCD for topical oxygen.

GWR appreciates the opportunity to submit comments regarding the reconsideration of Section C, NCD 20.29 and looks forward to continued discussions about Medicare coverage of topical oxygen as a safe and effective wound care treatment that is reasonable and necessary for a Medicare beneficiary population.

II. WHAT IS TOPICAL OXYGEN?

Oxygen treatment for wounds first emerged in the 1960s. Since then, a number of different definitions and descriptions have been used by government agencies, health care institutions, and scientific literature to characterize the differences between the multiple oxygen treatment modalities; some of which overlap. We think it is important to review the various definitions in order to have an understanding that topical oxygen is in fact, not at all similar to hyperbaric oxygen.

Hyperbaric Oxygen Therapy (“HBO”)

- CMS states, “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.”^{3/}
- FDA regulations: “**Hyperbaric chamber.** A hyperbaric chamber is a device that is intended to increase the environmental oxygen pressure to promote the movement of oxygen from the environment to a patient’s tissue by means of pressurization that is greater than atmospheric pressure. This device does not include topical oxygen chambers for extremities.”^{4/}

^{3/} Centers for Medicare and Medicaid Services, Medicare Benefit Policy Manual, CMS Pub. 100-02, Chap. 1, Sec. 20.29 (Rev. 48, Mar. 7, 2006); available at <http://www.cms.hhs.gov> - last checked Aug. 9, 2016 and found under Regulations and Guidance > Manuals > Internet-Only Manuals (IOMs).”

^{4/} 21 C.F.R. § 868.5470(a) (2016).

- The scientific literature makes it clear that HBO includes two key components: (1) high (2-3 atmospheres) pressure and close to 100% oxygen.^{5/}
 - HBO is defined by having a patient breathe 100% oxygen inside a treatment chamber as a pressure greater than sea level, usually in the range of 1.4-3.2 ATA.^{6/}

Topical Oxygen Therapy (“TO”) or Topical Oxygen Wound Therapy (“TOWT”)

- FDA regulations: “**Topical oxygen chamber for extremities.** A topical oxygen chamber for extremities is a device that is intended to surround a patient’s limb and apply humidified oxygen topically at a pressure slightly greater than atmospheric pressure to aid healing of chronic skin ulcers such as bedsores.”^{7/}
- The scientific literature describes TO as “pure oxygen is locally administered to an affected region of the body at 1.03 atmospheres of pressure.”^{8/}
- Alternatively, TO is the external application of oxygen to a wound in order to increase oxygen in the wound space. This is usually accomplished by shrouding the wound site, usually a limb, with a disposable or reusable device or appliance into which oxygen is pumped. Device may be filled with gas at pressures slightly above 1 atmosphere.^{9/}
- Described in more detail in Section V, the GWR TO technology delivers oxygen directly to an open moist wound at a pressure slightly higher than atmospheric pressure to promote wound healing.

Topical Hyperbaric Oxygen (“THO”)

- This is an outdated term that is synonymous with TO and, in our opinion, is inadequate to describe TO devices and treatment. One author stated that, “The two primary methods of oxygen-based therapies used to treat wounds were Hyperbaric Oxygen (HBO) and Topical Hyperbaric Oxygen (THO), the term used initially in the literature and more recently shortened to “Topical Oxygen” (TO).^{10/}

Topical Pressurized Oxygen

- Method of delivering pressurized and humidified oxygen directly to the wound bed to support the healing of chronic and hypoxic wounds.

^{5/} Sen, C.K., Khanna, S., Gordillo, G., Bagchi, D., and Roy, S. “Oxygen, Oxidants, and Antioxidants in Wound Healing: An Emerging Paradigm.” *Annals of the New York Academy of Sciences* 957 (2002): 239-249. **ATTACHMENT 26**, Resource 15.

^{6/} Piantadosi, C.A. “Topical Oxygen is Not Hyperbaric Oxygen (HBO₂).” *Undersea and Hyperbaric Medical Society, Inc.* 30.4 (2003): 267-269. **ATTACHMENT 26**, Resource 12.

^{7/} 21 C.F.R. § 878.5650(a).

^{8/} Sen, C.K., Khanna, S., Gordillo, G., Bagchi, D., and Roy, S. “Oxygen, Oxidants, and Antioxidants in Wound Healing: An Emerging Paradigm.” *Annals of the New York Academy of Sciences* 957 (2002): 239-249. **ATTACHMENT 26**, Resource 15.

^{9/} Piantadosi, C.A. “Topical Oxygen is Not Hyperbaric Oxygen (HBO₂).” *Undersea and Hyperbaric Medical Society, Inc.* 30.4 (2003): 267-269. **ATTACHMENT 26**, Resource 12.

^{10/} Howard, M.A., Asmis, R., Evans, K.K., and Mustoe, T.A. “Oxygen and Wound Care: A Review of Current Therapeutic Modalities and Future Direction.” *Wound Repair and Regeneration* 21 (2013): 503-511. **ATTACHMENT 26**, Resource 9.

Topical Continuous Oxygen Therapy

- The delivery of non-pressurized, non-humidified oxygen to the open wound via a cannula placed over the wound with a dressing topper.^{11/} This therapy appears to be the same as EO2's treatment modality, CDO.

Continuous Diffusion of Oxygen ("CDO")

- Portable devices that deliver oxygen continuously at normospheric pressure, directly to the wound site covered with an occlusive moist wound dressing. Also called "transdermal oxygen therapy."^{12/}
- Delivery of oxygen directly to the wound through a cannula placed underneath a moist wound therapy dressing. The thin film dressing maintains a moist wound environment and protects the wound from external contamination.^{13/}

These sources demonstrate that, while experts agree on the definition of HBO, five separate terms exist to describe TO. It is possible that the multitude of terms used to refer to TO may have limited clinical evidence searches used to support previous TO technology assessments, as a literature review may have been inadvertently narrowed to "hyperbaric" or "pressurized" TO. In fact, the Technology Assessment for NCD 20.29 conducted in 2001 referred to this type of treatment as "topical hyperbaric oxygen" or "THO," even though it was unclear whether "hyperbaric" was a required search term in the TA process.^{14/} Therefore, we believe important supportive studies may have been overlooked in 2001.

And yet, any difference between the five TO technologies listed above is belied by the commonality among the definitions and by FDA's classification of all five technologies into one regulation:

21 C.F.R. § 878.5650 Topical oxygen chamber for extremities.

(a) Identification. A topical oxygen chamber for extremities is a device that is intended to surround a patient's limb and apply humidified oxygen topically at a pressure slightly greater than atmospheric pressure to aid healing of chronic skin ulcers such as bedsores.

(b) Classification. Class II (special controls). The special control for this device is FDA's "Class II Special Controls Guidance: Topical Oxygen Chamber for Extremities." See §878.1(e) for the availability of this guidance document.

FDA has classified all TO devices, whether an inflatable plastic chamber to surround the wound area and affected extremity with pure oxygen, or a cannula that continuously diffuses

^{11/} Orsted, H.L. and Poulson, R. "Evidence-Based Practice Standards for the Use of Topical Pressurised Oxygen Therapy." *International Wound Journal* 9.3 (2012): 271-284. **ATTACHMENT 26**, Resource 11.

^{12/} Howard, M.A., Asmis, R., Evans, K.K., and Mustoe, T.A. "Oxygen and Wound Care: A Review of Current Therapeutic Modalities and Future Direction." *Wound Repair and Regeneration* 21 (2013): 503-511. **ATTACHMENT 26**, Resource 9.

^{13/} Couture, M. "Does Continuous Diffusion of Oxygen Have Potential in Chronic Diabetic Foot Ulcers?" *Podiatry Today* 28.12 (2015). **ATTACHMENT 26**, Resource 2.

^{14/} AHRQ, Technology Assessment: Hyperbaric Oxygen Therapy in Treatment of Hypoxic Wounds, 2001. **ATTACHMENT 3**.

oxygen over the wound area under a moist dressing, under this single medical device regulation. The only regulation applicable to technology intended to deliver oxygen directly to a wound, without also raising the oxygen content of circulated blood (i.e., as with HBO), is 21 C.F.R. § 878.5650. Although the mechanical action of HBO includes the effects of both respired oxygen and topical oxygen, there does exist this separate FDA regulation for topical oxygen as an independent treatment. To further illustrate this, **Table 1**, below, represents all of the entities currently registered with FDA to manufacture or develop devices cleared for commercial use under 21 C.F.R. § 878.5650 (product code KPJ).

Establishment Name & Location	Registration No.	Current Registration Year	Manufacturer Type	Listed Devices
Allied Healthcare Products, Inc. Missouri, USA	1924066	2016	Specification Developer	Chamber, Oxygen, Topical, Extremity – Topical Oxygen Sleeve
AOTI Ltd. Ireland	3006538358	2016	Manufacturer	Chamber, Oxygen, Topical, Extremity – Topical Wound Oxygen (TWO2) Chamber
Electrochemical Oxygen Concepts Texas, USA	3008139322	2016	Manufacturer Complaint File Establishment	Chamber, Oxygen, Topical, Extremity: - OxySpur Diffusion Dressing, - TransCu O2 Extension Set - TransCu O2 Oxygen Generator - TransCu O2 System
GWR Medical, Inc. Pennsylvania, USA	3008847017	2016	Specification Developer	Chamber, Oxygen, Topical, Extremity: - O ₂ Boot - O ₂ Sacral
Neogenix, LLC (dba Ogenix) Ohio, USA	3004036118	2016	Manufacturer Specification Developer	Chamber, Oxygen, Topical, Extremity – EPIFLO
Numotech, Inc. California, USA	2030595	2016	Specification Developer	Chamber, Oxygen, Topical, Extremity – Numobag
Sparton Medical Systems Ohio, USA	3003144120	2016	Contract Manufacturer	Chamber, Oxygen, Topical, Extremity
Xennovate Medical Ohio, USA	3004089989	2016	Contract Manufacturer	Chamber, Oxygen, Topical, Extremity – OxySpur Oxygen Diffusion Dressing

Table 1. Entities currently registered with FDA to manufacture or develop devices cleared for commercial use under 21 C.F.R. § 878.5650.

This chart demonstrates that FDA considers traditional TO technologies (e.g., GWR’s O₂Boot) and CDO as part of the same overarching device category, and therefore, under the same definition. In fact, EO₂ based its substantial equivalence argument for 510(k) clearance on OxyBox, a traditional TO device that requires a patient to seal the affected extremity in a

chamber infused with oxygen.^{15/} Interestingly, the 510(k) clearance for OxyBox relies on GWR's O₂Boot as a predicate to demonstrate substantial equivalence.

EO2 has attempted to argue that (1) CDO is inherently different from other TO technologies, and (2) no CDO therapies existed on the market in 2002 when CMS issued NCD 20.29. However, the similarities between TO and CDO demonstrated in the FDA device proceedings belie EO2's claims. Not only does FDA consider TO and CDO as two forms of the same technology, but also, FDA regulates both technologies according to identical standards. Further EO2 explicitly based the regulatory clearance of its CDO device on TO technologies, Oxyfast's OxyBox and, by extension, GWR's O₂Boot. Therefore, EO2 cannot now claim that CDO has been significantly distinguished from other TO delivery systems such that CDO devices deserve separate consideration and regulatory treatment with the CMS coverage process. In fact, it is not clear that EO2's device even meets FDA's regulatory definition set forth in 21 C.F.R. § 878.5650, which states that oxygen must be delivered "at a pressure slightly greater than atmospheric pressure," because the indication for TransCu O₂, as well as all of EO2's own literature included in its request to CMS, states that oxygen is delivered at "normospheric" or normal atmospheric pressure. We request that CMS ignore any request to rename the category of TO using the dated and inaccurate phrase THO. We note that UHMS agrees with this specific point.

III. TOPICAL OXYGEN IS SAFE AND EFFECTIVE FOR FDA-CLEARED INDICATIONS

FDA's primary role as a government agency is to ensure that all drugs, biologics, and devices available in U.S. commerce are safe and effective for their intended therapeutic uses. With respect to devices, the manufacturer of a medical device must demonstrate to FDA that the device is safe and effective for its intended use when used in conjunction with general controls alone (Class I) or with general *and* special controls (Class II), otherwise the device will be classified as a Class III.^{16/} Class III is reserved for devices (1) for which insufficient information exists that general *or* special controls will provide reasonable assurance of safety and effectiveness and (2) which are substantially important in preventing impairment of health or which present an unreasonable risk of death.^{17/}

^{15/} OxyBox (510(k) number K023456) was cleared as a Class III device on January 6, 2003 and was manufactured by Oxyfast Corp. The company is no longer an FDA-registered entity, and OxyBox is no longer listed as a device in FDA's databases.

^{16/} 21 U.S.C. § 360c(a)(1)(A)–(B) (2012); *see also* 21 C.F.R. § 860.7(c)(1) ("After considering the nature of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.").

^{17/} 21 U.S.C. § 360c(a)(1)(C); *see also* 21 C.F.R. § 860.7(g)(1) ("It is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III.").

Upon initial consideration of TO devices after the passage of the Medical Device Amendments in 1979, FDA initially proposed classification of such devices into Class II based on the evidence of safety and effectiveness submitted to the General and Plastic Surgery Device Classification Panel.^{18/} However, in the interim between the release of the proposed and final device classification regulations, FDA reconsidered the evidence provided and decided to classify TO devices as Class III due to the lack of sufficient evidence demonstrating safety and effectiveness.^{19/} Then in 2006, FDA issued a proposed rule to reclassify TO devices as Class II, based primarily on the data presented in three, then recent, studies.^{20/21/22/23/} In making its determination, the FDA relied on twenty years of clinical information regarding TO devices, the “agency’s Medical Device Reports,” and comments from the public regarding the clinical information.^{24/} After considering all of the evidence, FDA determined that sufficient evidence had been provided to demonstrate that general and special controls would ensure safe and effective use of TO devices and thus released a final rule formally reclassifying TO devices from Class III to Class II.^{25/}

Importantly, the FDA did not require or specifically rely on randomized clinical trials in reaching its reclassification decision. Rather, FDA concluded that human clinical studies are not required for each new TO device clearance because the safety and effectiveness is well established in existing clinical literature. Furthermore, FDA may only reclassify a currently marketed device if evidence adequately demonstrating safety *and* effectiveness of the device is submitted for consideration. If the evidence on TO devices had not been sufficient to convince FDA of the devices’ effectiveness to treat chronic ulcers, FDA would not have had the authority to determine that the reclassification was warranted.^{26/}

In light of FDA’s regulations, we request that CMS consult with FDA about its process to reclassify TO devices from Class III to Class II, which was finalized in 2011. Specifically, CMS should speak with Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health at FDA, who oversaw the TO device reclassification and who, as Director of the Items

^{18/} Proposed Rule - General and Plastic Surgery Devices; General Provisions and Classification of 54 Devices, 47 Fed. Reg. 2810–2853 (Jan. 19, 1982).

^{19/} Final Rule - General and Plastic Surgery Devices; General Provisions and Classification of 51 Devices, 53 Fed. Reg. 23856, 23869–23870 (June 24, 1988).

^{20/} Proposed Rule: Reclassification of the Topical Oxygen Chamber for Extremities, 71 Fed. Reg. 17390 (Apr. 6, 2006). **ATTACHMENT 4.**

^{21/} Heng, M.C.Y., Harker, J., Bardakjian, V.B., and Ayyazian, H. “Enhanced Healing and Cost-Effectiveness of Low-Press Oxygen Therapy in Healing Necrotic Wounds: A Feasibility Study of Technology Transfer.” *Ostomy Wound Management* 46.3 (2000): 52-60, 62. **ATTACHMENT 26**, Resource 7.

^{22/} Heng, M.C.Y., Harker, J., Csathy, G., Marshall, C., Brazier, J., Sumampong, S., and Paterno Gomez, E. “Angiogenesis in Necrotic Ulcers Treated with Hyperbaric Oxygen.” *Ostomy Wound Management* 46.9 (2000): 18-38, 30-32. **ATTACHMENT 26**, Resource 8.

^{23/} Kalliainen, L.K., Gordillo, G.M., Schlanger, R., and Sen, C.K. “Topical Oxygen as an Adjunct to Wound Healing: A Clinical Case Series.” *Pathophysiology* 9 (2003): 83-87. **ATTACHMENT 26**, Resource 10.

^{24/} Proposed Rule: Reclassification of the Topical Oxygen Chamber for Extremities, 71 Fed. Reg. 17390 (Apr. 6, 2006). **ATTACHMENT 4.**

^{25/} Final Rule: Reclassification of the Topical Oxygen Chamber for Extremities, 76 Fed. Reg. 22805 (Apr. 25, 2011). **ATTACHMENT 5.**

^{26/} Please refer to the timeline in Section II of this Comment which includes all FDA actions relevant to TO devices.

and Devices, Coverage and Analysis Group at CMS, was also directly involved in the 2002 NCD currently under reconsideration.^{27/}

IV. TOPICAL OXYGEN REGULATORY AND COVERAGE HISTORY

TO has a complex regulatory and coverage history; one that demonstrates inconsistency among Federal regulatory agencies. As we will discuss, there has been a significant amount of clinical evidence regarding TO developed since CMS's original consideration of NCD 20.29.^{28/} In addition to the clinical evidence, FDA's reclassification of TO devices from Class III to Class II is a significant step regarding recognized safety and effectiveness that also has occurred in the time period since the original consideration. This reclassification, on its own, satisfies the threshold criteria for reconsideration. Because of these developments, we agree that it is appropriate for CMS to be undertaking a reconsideration of the NCD. We are particularly interested in using this reconsideration process as an opportunity to finally align CMS and FDA processes, definitions, and clinical experience. Here, we outline topical oxygen's regulatory and coverage history.

- January 19, 1982** FDA issued notice of proposed rule for General and Plastic Surgery Devices published in Federal Register; 47 Fed. Reg. 2810-2853 (Jan. 19, 1982). Topical oxygen chamber for extremities proposed as Class II device.
- June 24, 1988** FDA proposed change of topical oxygen chamber classification to Class III based on lack of scientific evidence; FDA responded to comments recommending classification as Class I (relevant excerpt at **ATTACHMENT 8**).
- January 1, 1996** HCPCS code A4575 Topical hyperbaric chamber; disposable became effective. "A" codes represent transportation, medical and surgical supplies, miscellaneous, and experimental.
- August 11, 1997** CMS clarified that coverage for hyperbaric oxygen treatment is limited to conditions listed under §35-10.A. (TN 102; CMS transmittals prior to 2000 are not available electronically.)
- August 1997** Two manufacturers submitted to FDA additional safety and effectiveness information related to topical oxygen chambers to the General and Plastic Surgery Devices ("GPS") Panel and recommended reclassification as Class II.
- November 7, 1997** GWR O₂Boot cleared as Class III device (**ATTACHMENT 9**). FDA-approved indications for use are:

^{27/} Coverage Decision Memorandum for Hyperbaric Oxygen Therapy in the Treatment of Hypoxic Wounds and Diabetic Wounds of the Lower Extremities, Aug. 30, 2002. (CAG-00060N). **ATTACHMENT 6**.

^{28/} **ATTACHMENT 7** provides a visual timeline demonstrating the significant amount of clinical evidence amassed since 2006.

- Skin ulcerations due to diabetes, venous stasis, post-surgical infections and gangrenous lesions
- Decubitus ulcers
- Amputations/infected stumps
- Skin grafts
- Burns
- Frostbite

November 17, 1998 GPS Panel recommended at a public meeting that topical oxygen devices retain Class III classification. **ATTACHMENT 10** includes the minutes from this meeting; discussion regarding topical oxygen begins on bottom page 7.

May 1, 1999 CMS clarified the conditions for which hyperbaric oxygen is covered and the requirement for physician supervision. (TN 112; CMS transmittals prior to 2000 are not available electronically.)

January 1, 2000 HCPCS codes C1300 Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval; and E1390 Oxygen Concentrator, single delivery port, capable of delivering 85 percent or greater oxygen concentration at the prescribed flow rate, became effective. “C” codes represent temporary hospital OPPS and “E” codes represent durable medical equipment.

NOTE: According to the OIG report analyzing HBO between 1995 and 1998, HBO generally involved a facility charge and often a charge by a physician for supervision. “Procedure code 99183 is billed for physician supervision and revenue center 413 includes facility charges for HBO. Facility reimbursement is typically included as part of the prospective payment’s DRG payment if provided during an inpatient hospital stay or cost-based if provided by an outpatient department.

February 29, 2000 GWR TO devices added to the Federal Supply Schedule (“FSS”).

October 2000 OIG Report, Hyperbaric Oxygen Therapy: Its Use and Appropriateness; recommended, among other things, that CMS initiate its national coverage decision process for HBO. **ATTACHMENT 11.**

October 19, 2000 First NCD issued for HBO. Includes the following paragraph, “D. Topical Application of Oxygen. This method of administering oxygen does not meet the definition of HBO as stated above. Also, its clinical efficacy has not been established. Therefore, no Medicare reimbursement may be made for the topical application of oxygen.” This NCD was in effect through April 1, 2003. **ATTACHMENT 12.**

GWR Medical, Inc.
August 11, 2016

November 29, 2000 Formal request for NCD accepted by CMS. Requested by: The Undersea & Hyperbaric Medical Society (“UHMS”), American College of Hyperbaric Medicine, and International Hyperbaric Medical Association

February 15, 2001 CMS referred questions related to the NCD request to the Agency for Healthcare Research and Quality (“AHRQ”) for a Technology Assessment (“TA”).

November 29, 2001 CMS received final TA from AHRQ. The TA states that “CMS also requested an evaluation of the use of topical hyperbaric oxygen (THO) therapy in the treatment of hypoxic wounds of the extremities and torso. Topical hyperbaric oxygen systems deliver oxygen at high pressures directly to the site of the wound, typically 50 mm Hg intermittent pressure for hypoxic wounds of the extremities and 22 mm Hg for the treatment of hypoxic wounds to the torso. At present, Medicare has a *Non-Coverage* policy for THO.” See **ATTACHMENT 3**.

However, the Original Reconsideration Tracking Sheet does not make any reference to topical oxygen or acknowledge that CMS made the request to analyze topical oxygen in the scope of the TA. **ATTACHMENT 13**.

January 15, 2002 CMS received a letter from the requestors asking to expand the original request for HBO of hypoxic wounds, to include, more specifically, treatment of diabetic wounds of the lower extremities. CMS accepted amendment to the original request.

February 11, 2002 It was reported to CMS that the HBO service provided included physician supervision. The OIG found that lack of physician attendance is strongly correlated with lower quality of care and inappropriate billing. In addition, training could add to the quality of care. CMS believed it important to evaluate the need for physician supervision and/or physician credentialing and decided to assess the issue in a public comment period.

April 29, 2002 On April 15, 2002, the requestors of the original consideration provided additional information on the subpopulations of patients with diabetic ulcers of the lower extremities for which HBO would be an appropriate treatment. CMS met with requestors on April 29, 2002 to discuss this new information.

August 30, 2002 NCD Decision Memo released. The Decision Memo does not address TO treatment. See **ATTACHMENT 6**.

December 27, 2002 CMS expanded coverage for treatment of diabetic wounds of the lower extremities in patients that meet three criteria; effective date April 1, 2003. This version of the NCD was in effect through June 19, 2006. **ATTACHMENT 14**.

GWR Medical, Inc.
August 11, 2016

- February 24, 2003** Oxyfast Corp. OxyBox cleared as Class III device. GWR O2Boot cited as predicate device. **ATTACHMENT 15.**
- 2005** UHMS Position Statement regarding TO treatment.^{29/} **ATTACHMENT 16.**
- March 2006** CMS made technical corrections to the NCD Manual. Effective date is 06/19/2006. **ATTACHMENT 17.**
- April 6, 2006** FDA proposed reclassification of topical oxygen devices to Class II based on three studies reporting safe use and adequate healing of wounds using topical oxygen and on 20+ years of clinical experience with such devices and reviews of reported MDRs. FDA concluded that there was sufficient information to support mitigation of risks through special controls. 71 Fed. Reg. 17390 (Apr. 6, 2006). *See* **ATTACHMENT 4.**
- March 2008** New York State (“NYS”) Department of Health (“DOH”) added GWR’s TO (known in NYS as “Topical Oxygen Wound Therapy” or “TOWT”) products to the list of benefits approved for coverage as part of NY’s Medicaid FFS program. [Note: Medicaid Managed Care plans are required to provide coverage for all benefits available under FFS, therefore, TOWT is also covered for members of NY’s Medicaid Managed Care plans.] **ATTACHMENT 18.**
- August 12, 2009** EO2 Concepts TransCu O2 cleared as Class III device (noted FDA proposal to reclassify as Class II. 71 Fed. Reg. 17390 (Aug. 12, 2009). **ATTACHMENT 19.**
- January 1, 2011** HCPCS code E0446 Topical Oxygen Delivery System, not otherwise specified, includes all supplies and accessories, became effective. “E” codes represent durable medical equipment.
- April 25, 2011** Final rule reclassifying topical oxygen devices published in Federal Register. 76 Fed. Reg. 22805 (Apr. 25, 2011). *See* **ATTACHMENT 5.**
- December 31, 2014** HCPCS code C1300 was terminated.
- January 1, 2015** HCPCS code G0277 Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval became effective. “G” codes represent temporary procedures and professional services.
- March 15, 2015** EO2 submitted to CMS a request for reconsideration of Section C, NCD 20.29. *See* **ATTACHMENT 1.**

^{29/} It is unclear what prompted the UHMS to release this position statement in 2005. However, as argued below, we disagree with the UHMS’s position statement.

V. GWR TECHNOLOGY

GWR is a provider of TO for the healing of open wounds. Our device delivers oxygen directly to the wound surface utilizing GWR's FDA approved O₂Boot[®] or O₂Sacral[®] devices. TO is an adjunct therapy in chronic wound management and treatment. Increasing the oxygen concentration at the wound site for chronic open wounds with the use of this TO device, may promote the rate of healing and suppress bacterial growth.

The O₂Boot and O₂Sacral are TO chambers for extremities and the torso. The devices are composed of a flexible plastic film shaped into a large boot (O₂Boot) or triangular pouch (O₂Sacral). At the open end of the device there is a layer of white fabric impregnated with an acrylic adhesive which is used to secure the O₂Boot and O₂Sacral to the patient being treated and to create a seal around the wound during the treatment session. The device is connected to a portable oxygen source through tubing. The device is inflated with oxygen up to a flow rate of 10L per minute to ensure that the device remains full and taut during the treatment. The device is also fit with a pressure relief valve to ensure that the pressure within the device does not exceed 1.03 atmospheres.

The weekly treatment regimen is a home-use-90-minute session on four consecutive days, followed by three days without treatment. The weekly treatments are continued as directed by the healthcare provider. The device is disposable and is used for a single 90-minute use on a single patient. Our TO device therapy is suitable for all healthcare environments but is most often prescribed for in-home treatment and administered by the patient. This eliminates the need for costly ambulatory care, patient transportation, or home nursing visits.

The intended population for the O₂Boot and O₂Sacral devices is patients with open chronic wounds such as: skin ulcerations due to diabetes, venous stasis ulcers, post-surgical infections, gangrenous lesions, decubitus ulcers, amputations/infected stumps, skin grafts, burns, and frostbite.^{30/}

GWR's TO devices are currently covered items under the New York Medicaid Program, which has approved the TO devices for 1) Stage IV Pressure Ulcers, 2) Neuropathic (for example, diabetic) ulcers, 3) Venous insufficiency ulcers, 4) non-healing surgically created or traumatic wounds and 4) a chronic ulcer of mixed etiology.^{31/}

Nationwide, groups that cover the use of our TO devices include the Department of Veterans Affairs, Department of Defense, private managed care organizations, third party administrators, and all NY Medicaid managed care plans, including Affinity, Amerigroup, Amida Care, Archcare, Centerlight, Centers Plan for Healthy Living, Elderplan, Elderserve, Empire BCBS, Fidelis, Guildnet, HealthFirst, HealthNow, HealthPlus, HIP, Homefirst, Hudson Health, Independent Care Systems, MetroPlus, MVP Health Plan, Neighborhood Health Providers, Senior Health Partners, Senior Whole Health, United HealthCare, Village Senior Max, VNS, Wellcare. In addition, State Workers' compensation programs that cover the use of our TO devices include: California, Delaware, Florida, Georgia, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Michigan, Mississippi, Nevada, New Jersey, North Carolina, Ohio, Pennsylvania, Texas, Utah, West Virginia.

^{30/} See ATTACHMENT 9.

^{31/} See ATTACHMENT 18.

The applicable reimbursement codes for GWR's TO devices are:

- A4575 – Topical hyperbaric chamber; disposable; and
- E1390 – Oxygen concentrator, single delivery port, capable of delivering 85 percent or greater oxygen concentration at the prescribed flow rate.

These codes are obviously different from the codes used for HBO (HCPCS G0277 – Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval and CPT 99183 – Physician attendance and supervision of hyperbaric oxygen therapy, per session).^{32/}

Since 2000, GWR has collected, with appropriate patient consent, digital wound images to demonstrate outcomes for wounds treated with TO. GWR's image registry consists of more than 13,000 digital wound images for patients prescribed TO and contains comparative digitally measured wounds for nearly 3,000 patients.

The wound images are managed in HIPAA-compliant software (WoundMatrix) that is FDA-listed and 21 C.F.R. Part 11-compliant. The software measurement process was validated in a clinical study published by Johns Hopkins in 2007. It uses planimetry to derive precise surface area measurements. Of particular note, CMS requires surface area measurements for wound care products and modalities to qualify for beneficiary services and reimbursement. The digital imaging software is able to provide more objective and precise measurements of wound surface area than manual wound measurements that estimate area by a simple length by width calculation.

Other organizations that use this software include the Department of Veteran's Affairs, Home Telehealth division, since 2010, clinical research organizations, home health groups, and recently, the National Health System (NHS) in the United Kingdom has tested and is preparing to implement the software. GWR has also expanded its image and measurement data collection via FDA-registered software that provides caregivers and patients with a free downloadable app to securely send images from any smartphone for immediate observation, measurement and documentation purposes. Caregivers can acquire images and record data immediately at the point-of-care (e.g., inpatient, outpatient, homecare, etc.) or patients can easily capture an image at home and securely send to their caregiver for remote monitoring of their wound progress, outcome observation and better compliance.

With recent advances in mobile technology and FDA's final rule for Medical Device Data Systems (MDDS), GWR has expanded its image and measurement data collection via FDA-registered software that provides caregivers and patients with a free downloadable app to securely send images from any smartphone or tablet for immediate observation, measurement and documentation purposes. *See ATTACHMENT 20.*

In fact, since 2004, GWR has registered over 9,300 wounds in our database. Of those wounds, 4,278 were wounds on patients covered by Medicare. However, approximately 1,300 of those Medicare patients did not receive treatment because of Medicare's non-coverage policy. The remaining Medicare patients were treated and some were covered by other insurance. GWR can provide CMS with a significant volume of evidence-based outcomes for TO over a 15 year

^{32/} Even though NCDs do not include a determination of what code, if any, is assigned to a particular item or service, this stark difference in coding is further evidence that TO is not HBO and should not be included in the same NCD.

period from patient-specific experience that are digitally measured and visually verifiable in the WoundMatrix software registry.

VI. SUFFICIENT CLINICAL INFORMATION EXISTS FOR CMS TO PROVIDE COVERAGE FOR TOPICAL OXYGEN

a. Statutory Framework

Medicare coverage is limited to items and services that are reasonable and necessary for the diagnosis or treatment of an illness or injury and that are within the scope of a Medicare benefit category. The statutory and policy framework within which NCDs are made is set out in Title XVIII of the Social Security Act (“the Act”), and in Medicare regulations and guidance documents. The relevant excerpts include:

Section 1869(f)(1)(B) of the Act:

Definition of national coverage determination.—For purposes of this section, the term “national coverage determination” means a determination by the Secretary with respect to whether or not a particular item or service is covered nationally under this title, but does not include a determination of what code, if any, is assigned to a particular item or service covered under this title or a determination with respect to the amount of payment made for a particular item or service so covered.^{33/}

42. C.F.R. § 405.1060 Applicability of national coverage determinations (NCDs).

(a) General rule.

- (1) An NCD is a determination by the Secretary of whether a particular item or service is covered nationally under Medicare.
- (2) An NCD does not include a determination of what code, if any, is assigned to a particular item or service covered under Medicare or a determination of the amount of payment made for a particular item or service.
- (3) NCDs are made under section 1862(a)(1) of the Act as well as under other applicable provisions of the Act.
- (4) An NCD is binding on fiscal intermediaries, carriers, QIOs, QICs, ALJs, and the MAC.

Sections 1862(a)(1)(A) and 1862(a)(1)(E) of the Act:

- (a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
 - (1)(A) which, except for items and services described in a succeeding subparagraph or additional preventive services (as described in section 1395x(ddd)(1) of this title), are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member...^{34/}

^{33/} Codified at 42 U.S.C. § 1395ff(f).

^{34/} Codified at 42 U.S.C. § 1395y(a).

CMS has broad authority to determine whether Medicare should provide coverage for a health care service or item. The Supreme Court has recognized that “[t]he Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, as clearly discretionary decisions.”^{35/} But in general, NCDs are made through an evidence-based process, with opportunities for public participation.^{36/}

CMS explained in its August 7, 2013 Federal Register notice regarding the Revised Process for Making National Coverage Determinations that it is interested in public comments that provide new evidence that it has not reviewed in past considerations of the NCD. To this end, we are providing a summary of the relevant new literature and clinical information that demonstrates that TO is a reasonable and necessary treatment of an illness or injury and should be covered under Medicare. In fact, the clinical effectiveness of TO is supported by both (i) published scientific evidence that increased oxygen in a chronic wound stimulates a resumption of the wound healing cascade and (ii) unpublished clinical experience data.

b. Scientific Evidence – Clinical Studies

Wound healing is a complex process involving a complex series of biologic responses to stimulate cell migration leading to tissue repair and wound closure. This sequence (known as the wound healing cascade) consists of removal of debris, control of infection, clearance of inflammation, angiogenesis, deposition of granulation tissue, contraction, remodeling of the connective tissue matrix, and maturation. If wounds fail to undergo this sequence, chronic wounds may result.

As noted in the references discussed here, one of the major issues in chronic wounds is the lack of oxygen to support the healing process. This condition, known as hypoxia, may be the result of vascular insufficiency which reduces blood flow to the wound site and increased oxygen demand due to the open wound. We are including references from a variety of clinical experiences including randomized clinical trials, cohort studies and clinical case series. These various studies document that TO can support complete wound closure, help reduce the size of the wound to allow resumption of standard wound care, may help reduce pain, and support important and clinically meaningful changes to the local wound environment (such as increased growth factors expression, reduced inflammation, antimicrobial effect and angiogenesis).

For example, in a recent randomized clinical trial (Driver, 2013), 17 patients were randomized to either TO (treatment group) or to standard wound care (control). The study evaluated the amount of wound reduction at 4 weeks and included assessment of weekly wound biopsies and wound fluid to monitor inflammation. At week 4, average wound size reduction was 87% (range 55.7% to 100%) in the treatment group compared to 46% (15% to 99%) in the control group (P <0.05). Changes in cytokine levels (IL-6, IL-8) and proteinases (MMP-1,-2,-9, TIMP-1) at weeks 2 to 4 in wound fluid correlated with clinical findings. CD68+ macrophage counts showed statistically significant reduction in response to TO compared to the control group (P <0.01).^{37/}

^{35/} *Heckler v. Ringer*, 46 U.S. 602, 617 (1984). [Quoted in 78 Fed. Reg. 48161 (Aug. 7, 2013).]

^{36/} 8 Fed. Reg. 48161 (Aug. 7, 2013).

^{37/} Driver, V.R., Yao, M., Kantarci, A., Gu, G., Park, N., and Hasturk, H. “A Prospective, Randomized Clinical Study Evaluating the Effect of Transdermal Continuous Oxygen Therapy on Biological Processes and Foot Ulcer Healing in Persons with Diabetes Mellitus.” *Ostomy Wound Management* 59.11 (2013): 19-26.
ATTACHMENT 26, Resource 3.

In another randomized clinical trial (Heng, 2000), 40 patients (with 79 ulcers) were treated with either TO or standard of care. The study measured the percentage of wound healing in each group and measured the capillary density of wound tissues during the healing process. The results showed that 90% of the wounds healed in the TO group compared to 22% in the standard wound care controls. The study also reported that the size of ulcers (at 4 weeks) was significantly smaller with TO treated wounds, but larger with standard of care treated wounds. The study also found that capillary density of tissue evaluated under high power microscopy was significantly higher in TO wounds than in standard wound care wounds ($P < 0.001$).^{38/}

In a recently reported cohort study of non-healing venous ulcers (Tawfick, 2012), a parallel observation of 65 patients treated with TO and 65 patients treated with conventional compression dressings was completed. The primary study endpoint was defined as the proportion of ulcers healed at 12 weeks. Mean reduction in wound size was also measured at 12 weeks. The study also evaluated the degree of wound pain as measured by a standardized pain score. At 12 weeks, 76% of the TO-managed ulcers had completely healed, compared to 46% of the compression dressing-managed ulcers ($P < .0001$). Mean reduction in ulcer surface area at 12 weeks was 96% in patients managed with TO and 61% in patients managed with compression therapy. The pain score threshold in TO-managed patients improved from 8 to 3 by day 13.^{39/}

Another study (Rao, 2016) examined the effect of TO on the hind limb wounds of rats under ischemic conditions. Here, researchers compare twelve injured rats treated with TO to twelve injured control rats. The results demonstrated that TO improved ischemic healing: wound healing time was shorter in the TO group than the control group; wound healing rate and granulation tissue formation in the TO group showing significant improvement on days 3, 7, and 14; the accumulation of collagen fiber in the TO group improved when compared to the control group on day 7; and, many more new vessels were found in the TO group than the control group on day 7.^{40/}

A case series of 9 patients with chronic lower extremity wounds (Woo, 2012) also showed a positive effect of TO on wound healing as well as reduction of wound infection. After 4 weeks of treatment, mean wound surface area and wound infection checklist scores were significantly reduced. Signs of bacterial damage were also reduced. Findings from this study provide additional evidence that TO may be beneficial in promoting chronic wound healing.^{41/}

A retrospective review of case studies (Kalliainen, 2003) demonstrated that TO (GWR's device) had no detrimental effects on wounds and showed beneficial indications in promoting wound healing. Researchers analyzed the results of TO by collecting data from seven surgeons

^{38/} Heng, M.C.Y., Harker, J., Csathy, G., Marshall, C., Brazier, J., Sumampong, S., and Paterno Gomez, E. "Angiogenesis in Necrotic Ulcers Treated with Hyperbaric Oxygen." *Ostomy Wound Management* 46.9 (2000): 18-38, 30-32. **ATTACHMENT 26**, Resource 8.

^{39/} Tawfick, W.A. and Sultan, S. "Technical and Clinical Outcome of Topical Wound Oxygen in Comparison to Conventional Compression Dressings in the Management of Refractory Nonhealing Venous Ulcers." *Vascular and Endovascular Surgery* 47.1 (2012): 30-37. **ATTACHMENT 26**, Resource 16.

^{40/} Rao, C., Xiao, L., Liu, H., Li, S., Lu, J., Li, J., and Gu, S. "Effects of Topical Oxygen Therapy on Ischemic Wound Healing." *The Journal of Physical Therapy Science* 28.1 (2016): 118-123. **ATTACHMENT 26**, Resource 13.

^{41/} Woo, K.Y., Coutts, P.M., and Sibbald, R.G. "Continuous Topical Oxygen for the Treatment of Chronic Wounds: A Pilot Study." *Advances in Skin and Wound Care* 25 (2012): 543-547. **ATTACHMENT 26**, Resource 17.

who treated 58 wounds in 32 patients, with TO with follow-up ranging from 1 to 8 months, over the course of 9 months. Researchers noted that upper extremity and trunk wounds were most responsive to TO.^{42/}

Similarly, in a cohort study comparing TO to HBO (Gordillo, 2008), wound healing was evaluated at 12 weeks. Overall, HBO did not result in statistically significant improvements in wound size in the given population over the time monitored in this study. However, TO did significantly improve wound size. Furthermore, among three oxygen-edge tissue biopsies, TO treatment was associated with higher vascular endothelial growth factor (VEGF) expression in healing wounds.^{43/}

c. Scientific Evidence – Systematic Literature Reviews

In addition to the emerging clinical evidence for the use of TO in the treatment of chronic wounds, recent publications highlight the importance of oxygen in the wound healing process. For example, in a recent review article (Brimson, 2012), the author reports that for wounds to heal, meaning the growth of new cells and tissues, it is essential that the wound bed is adequately supplied with oxygen. The need for oxygen to be present early on in wound repair has long been established, not simply as a requisite in cellular metabolism, but also for other vital healing processes, such as neovascularization and collagen synthesis. Often due to compromised oxygen delivery, chronic wounds are resistant to conventional treatment, and healing progresses very slowly, if at all. Therapeutically, oxygen can be used as an aid to healing this type of wound.^{44/}

In another review article (Eisenbud, 2012) on the role of oxygen in wound healing, the author indicates that there are important roles of oxygen in wound healing. These roles include:

- Energy source to fuel biochemical reactions and cellular function
- Nutrient essential to the synthesis and crosslinking of collagen
- Cofactor that is manufactured into signaling molecules such as nitric oxide and hydrogen peroxide
- Substrate for generation of reactive oxygen species (ROS) that combat wound colonization and infection
- Essential signaling component that turns on and off genes that encode proteins critical to the healing cascade
- Deliberate hyperoxygenation recruits endothelial progenitor cells to the wound, increases (VEGF), and promotes angiogenesis^{45/}

^{42/} Kalliainen, L.K., Gordillo, G.M., Schlanger, R., and Sen, C.K. “Topical Oxygen as an Adjunct to Wound Healing: A Clinical Case Series.” *Pathophysiology* 9 (2003): 83-87. **ATTACHMENT 26**, Resource 10.

^{43/} Gordillo, G.M., Roy, S., Khanna, S., Schlanger, R., Khandelwal, S., Phillips, G., and Sen, C.K. “Topical Oxygen Therapy Induces Vascular Endothelial Growth Factor Expression and Improves Closure of Clinically Presented Chronic Wounds.” *Clinical and Experimental Pharmacology and Physiology* 35.8 (2008): 957-964. **ATTACHMENT 26**, Resource 5.

^{44/} Brimson, C.H. and Nigam, Y. “The Role of Oxygen-Associated Therapies for the Healing of Chronic Wounds, Particularly in Patients with Diabetes.” *Journal of the European Academy of Dermatology and Venereology* 27 (2012): 411-418. **ATTACHMENT 26**, Resource 1.

^{45/} Eisenbud, D.E. “Oxygen in Wound Healing: Nutrient, Antibiotic, Signaling Molecule, and Therapeutic Agent.” *Clinics in Plastic Surgery* 39 (2012): 293-310. **ATTACHMENT 26**, Resource 4.

The antimicrobial effects of oxygen are also noted in the article by Gordillo (Gordillo, 2009). The author cites evidence that oxygen is a rate-limiting substrate for the production of reactive oxygen species (ROS) that serve as a disinfectant and as intracellular signaling molecules that orchestrate the wound healing response. In particular, at the wound-site, ROS are generated from oxygen by almost all wound-related cells. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) is the enzyme that generates ROS for signal transduction necessary to promote healing. In phagocytic cells at the wound site, the ROS produced by NADPH oxidase are used to kill bacteria.^{46/}

A review article (Howard, 2013) provides points of comparison and distinction among HBO, TO, and CDO treatments.^{47/} The authors point out that a large amount of clinical data supports HBO effectiveness for a wide range of wounds and other conditions (e.g., CO poisoning and necrotizing fasciitis) but also note that many side effects, such as exacerbation of tension pneumothorax, barotrauma, and oxygen toxicity, as well as some risk of fire and explosion. Howard et al. then present TO as an alternative to HBO having fewer risks but also a narrower range of therapeutic uses. The authors cite a number of studies, including Fries 2005, Gordillo 2008, Tawfick & Sultan 2009, and Blackman 2010, as providing significant evidence of the effectiveness of TO over conventional standard of care treatments and cite the following positive effects of TO:

- Oxygen delivery to the tissue during therapy;
- Increased VEGF expression and angiogenesis;
- Improved wound healing;
- Improved wound closure rate;
- Reduction in MRSA infection;
- Pain reduction; and
- Reduced venous stasis ulcer recurrence.^{48/}

The subsequent review of CDO technology raises a number of comparisons to traditional TO: both treatments deliver pure oxygen directly to the wound site within an enclosed, sealed space, and both are classified as the same type of device by FDA. The authors then discuss only minor distinctions between CDO and traditional TO: CDO offers greater mobility, extended therapy time, low oxygen flow rate, and compatibility with the existing wound dressing. The article goes on to provide a review of the limited clinical evidence supporting CDO but offers no evidence that CDO is essentially different from or more effective than traditional TO.

Another scientific publication reviews the positive effects of oxygen on the wound healing process and provides an overview of the benefits of HBO and TO (Sen 2009). The article

^{46/} Gordillo, G.M. and Sen, C.K. "Evidence-Based Recommendations for the Use of Topical Oxygen Therapy in the Treatment of Lower Extremity Wounds." *The International Journal of Lower Extremity Wounds* 8.2 (2009): 105-111. **ATTACHMENT 26**, Resource 6.

^{47/} We noted that Dr. Howard also submitted a comment in response to this NCA. We believe that his article findings support the use of HBO, TO, and CDO; and not only CDO.

^{48/} Howard, M.A., Asmis, R., Evans, K.K., and Mustoe, T.A. "Oxygen and Wound Care: A Review of Current Therapeutic Modalities and Future Direction." *Wound Repair and Regeneration* 21 (2013): 503-511. **ATTACHMENT 26**, Resource 9.

provides a relatively comprehensive overview of the oxygen-dependent pathways involved in wound healing, as well as a review of the supporting scientific literature. The author also includes a brief comparison of HBO and TO, concluding that TO is preferred when the “goal is to correct hypoxia of the superficial tissue” rather than increase “supraphysiological levels of tissue pO₂.”^{49/}

A separate review of TO technology was conducted in 2012 by a Canadian independent advisory group in an attempt to establish clinical standards by which physicians and policymakers could determine the appropriateness of implementing TO in clinical settings (Orsted 2012). The article reviews data from various clinical studies, including treatment applications, patient populations, expected outcomes, and safety precautions, and concludes that “[c]urrent studies show the efficacy of [TO] therapy in [diabetic foot ulcers] and venous leg ulcers.”^{50/} The authors also state that as of 2012 TO is approved for use at all U.S. Veterans Affairs Medical Centers and under Medicaid in five states, with three additional states considering approval.

The body of evidence supporting the safety and effectiveness of TO for treating wounds has grown substantially in the fifteen years since CMS commissioned the TA for NCD 20.29. This expansion of evidence is amply demonstrated in our literature list in **ATTACHMENTS 26 and 27**. As we have discussed, this NCD’s TA was completed in 2001, ten years before FDA investigated the evidence of safety and effectiveness supporting the reclassification of TO device. Therefore, CMS has not yet taken an opportunity to examine the same evidence reviewed by FDA, as well as the scientific literature released since 2011, to determine whether sufficient support exists to show that TO should be covered under Medicare. Because of this, we urge CMS to review the literature attached here in its reconsideration of NCD 20.29.

Among the scientists and clinicians who have been studying the advantages of TO as a treatment for wounds, Dr. Chandan Sen has been one of the most prolific.^{51/} Dr. Sen is the John H. & Mildred C. Lumley Professor of Surgery at The Ohio State University, Executive Director of The Ohio State University Comprehensive Wound Center, and Director of The Ohio State University’s Center for Regenerative Medicine and Cell-Based Therapies. Since 2002, Dr. Sen has participated in over 100 studies related to TO, as shown in the list of TO publications in **ATTACHMENT 28**, and has contributed a significant amount to the growing evidence supporting TO. In fact, Dr. Sen is the principal investigator in a clinical study entitled “Topical Oxygen Therapy for Diabetic Foot Ulcers (TOFU)” which is entirely supported by Medicaid funds from the Ohio Department of Medicaid and a matching grant from CMS for state Medicaid TAs.^{52/} Recruitment for the clinical study is currently underway, but the funding structure means that participation in the study is restricted to beneficiaries receiving primary coverage from Medicaid, which essentially excludes all Medicare beneficiaries.

^{49/} Sen, C.K. “Wound Healing Essentials: Let There Be Oxygen.” *Wound Repair and Regeneration* 17.1 (2009): 1-18. **ATTACHMENT 26**, Resource 14.

^{50/} Orsted, H.L. and Poulson, R. “Evidence-Based Practice Standards for the Use of Topical Pressurised Oxygen Therapy.” *International Wound Journal* 9.3 (2012): 271-284. **ATTACHMENT 26**, Resource 11.

^{51/} As an example of Dr. Sen’s expertise in this area, **ATTACHMENT 28** includes a Google Scholar search demonstrating the numerous articles that Dr. Sen has written or collaborated on since 2002, the Original Consideration of NCD 20.29.

^{52/} See **ATTACHMENT 21** for information regarding this clinical protocol.

If sufficient funds were made available from CMS, in general, the OSU clinical study team has clinicians, home health workers, and customer support personnel who are trained in managing patients using TO, and this study team can support a much larger clinical study population including Medicare beneficiaries. While sufficient evidence already exists to support separate coverage of TO, an expanded version the OSU study would provide additional clinical evidence of the significant advantage TO offers compared to standard of care treatments. GWR and the OSU research team would welcome the opportunity to discuss option for Coverage with Evidence Development (“CED”) using the strength of the OSU clinical design.

All of the studies discussed here demonstrate that (1) the clinical effectiveness of TO is supported by results of recent clinical trials, and (2) TO is a beneficial treatment alternative for chronic wounds. The recent publications highlight the scientific evidence that increased oxygen in a chronic wound stimulates a resumption of the multiple factors wound healing cascade. These effects are documented in a number of clinical evaluations and are manifested in as important and clinically meaningful changes to the local wound environment (such as increased growth factors expression, reduced inflammation, anti-microbial effect and angiogenesis).

d. Unpublished Clinical Experience Data

Moreover, the collected information from New York Medicaid patients treated with TO further substantiates the clinical benefit of this treatment.^{53/} Since 2008, GWR has provided TO to New York Medicaid beneficiaries and has recorded information about the demographics and outcomes in its electronic Management Information (MIS) system. The following represents a summary of information for New York Medicaid beneficiaries, who received TO between 2008 and 2014, for a minimum period of two months and a minimum initial wound size of greater than 1 cm²:

- A total of 165 men with 196 wounds and 135 women with 164 wounds for a total of 360 wounds were treated.
- The average age of the men was 61 years and of the women was 69 years.
- Wounds that were less than six months old at the beginning of the treatment had an average healing rate greater than 50% in an average of 19.5 weeks.
- 158 of 360 (43.88 %) wounds were classified as healed.
- 64% of all wounds treated showed a minimum of 50% healing or complete healing.
- These patients represent 22 different cities within the State of New York.
- The largest proportions include 42% of patients from Brooklyn, 22% from the Bronx, 10% from New York, approximately 7% from Jamaica and 5% from Flushing.
- The majority of wounds treated were diabetic ulcers (250.80) followed by venous insufficiency ulcers (459.81).
- There were no adverse events reported for any of the 300 patients.

This New York Medicaid clinical experience does not adjust for or exclude patients unable to complete TO due to circumstances such as hospitalizations, surgery, non-compliance,

^{53/} See ATTACHMENT 22.

or other reasons. Nonetheless, the collected (unpublished) information from New York Medicaid patients treated with TO further substantiates the clinical benefit of this treatment.^{54/} *See also, ATTACHMENT 22* for additional data regarding our experience treating New York Medicaid beneficiaries.

As discussed in Section V above, GWR has significant data regarding the Medicare beneficiary population. While we appreciate the opportunity to comment on the reconsideration request, 30 days is simply not a sufficient amount of time to adequately analyze and present the full scope and depth of our available Medicare beneficiary data. However, we can confirm that 28% of Medicare patients treated by GWR devices were covered and paid for by traditional NYS Medicaid. This represents 830 wounds on Medicare beneficiaries paid for by traditional NYS Medicaid from January 2004 to current, out of 2,927 total wounds on Medicare beneficiaries treated from January 2004 to current. Therefore, the data presented in **ATTACHMENT 22** includes Medicare beneficiaries.

e. Topical Oxygen Therapy is Safer than other Wound Treatment Therapies

In addition, there is strong evidence that there are few if any adverse events reported with the use of TO. The clinical case studies demonstrate that the use of TO is well tolerated and generally does not have adverse effects. From a public health perspective, in the FDA proposed a reclassification of this device from Class III (premarket approval) to Class II (special controls) the FDA identified several potential risks with the use of topical oxygen.^{55/} These potential hazards included infection, fire and explosion, local tissue damage, adverse tissue reaction and electrical shock.

Notwithstanding these possible risks, FDA ultimately reclassified these devices from Class III to Class II concluding that the publically available information supported a lower risk category for TO. This is consistent with our review of the published literature in which none of these harms were reported. Further, a review of the FDA Manufacturer and User Facility Device Experience (MAUDE) database (from 1997 to 2014) identified only one reported case of fire. This was not related to a GWR device, and involved a patient who was smoking during TO. *See ATTACHMENT 24*. Thus, TO has a substantial history of safe use when compare to other commonly used wound therapies such as HBO and negative wound pressure therapy (“NWPT”).

As you are aware, HBO is a treatment modality in which the patient breathes 100% oxygen at a pressure greater than one atmosphere: the pressure of air at sea level. This therapy occurs while the patient is entirely enclosed in a stationary pressure chamber. HBO increases the plasma oxygen levels and is systemic, therefore dependent on adequate blood-flow to the wound. As HBO is systemic and raises the pO₂, there is a risk of high pressure oxygen complications such as seizures, damage to the tympanic membrane of the ear (barotraumas) and damage to the retinal nerve (retinopathy). If patients have diabetes their glucose levels could also be affected by an increased pO₂. Our review of the MAUDE database indicates there were 41 device malfunctions and/or patient injuries reported with the use of hyperbaric oxygen chambers from 1997 to 2014. Malfunctions included chamber explosion, sudden decompression, pressure leaks

^{54/} Even though this data is unpublished, our experience in treating NY Medicaid beneficiaries provides compelling evidence as to the clinical efficacy of TO. Additionally, there are references in CMS guidance documents that note the possibility of considering relevant, non-proprietary but unpublished data in the NCD process. *See ATTACHMENTS 2 and 23*.

^{55/} *See ATTACHMENT 4*.

and higher than specified compression rates. Reported patient injuries included pain, ringing in the ears, visual impairment and auditory seizures.

NWPT applies a localized vacuum to draw the edges of the wound together while providing a moist environment conducive to rapid wound healing. The development of negative pressure techniques for wound healing is based on two theories: (1) the removal of excess interstitial fluid decreases edema and concentrations of inhibitory factors, and increases local blood flow; and (2) stretching and deformation of the tissue by the negative pressure is believed to disturb the extracellular matrix and introduce biochemical responses that promote wound healing. NPWT systems include a vacuum pump, drainage tubing, and a dressing set. The pump may be stationary or portable, may rely on AC or battery power, allows for regulation of the suction strength, has alarms to indicate loss of suction, and has a replaceable collection canister. The dressing sets may contain either foam or gauze dressing to be placed in the wound and an adhesive film drape for sealing the wound.

With regard to the safety of NPWT, a Technology Assessment Report was issued in November 2009 by AHRQ. In that assessment, adverse events were reported in 37 of 40 studies comparing NPWT to other treatments. Of the 37 studies reporting events, seven (19%) studies described NPWT as a safe treatment. Fewer complications were reported in the NPWT-treated patients than in those receiving other wound therapies in 19 (51%) studies and similar complications were reported in 8 (22%) studies. Adverse events reported in 103 case series included pain (n = 12), bleeding (n = 7), infection/bacterial colonization (n = 15), mortality (n = 4), and other complications (n = 18).

Moreover, in February 2011, the FDA issued an FDA Safety Communication: Update on serious complications associated with negative pressure wound systems. The FDA issued the alert to make individuals aware of deaths and serious complications, especially bleeding and infection, associated with the use of NPWT systems, and to provide recommendations to reduce the risk. Although rare, these complications can occur wherever NPWT systems are used, including acute and long-term healthcare facilities and at home. Since issuing the 2009 Preliminary Public Health Notification and Advice for Patients, the FDA received reports of an additional six deaths and 97 injuries, for a total of 12 deaths and 174 injury reports since 2007. Bleeding continues to be the cause of the most serious adverse events, and was reported in 12 patients, including three of the additional death reports (FDA, 2011).

As described, TO has a much better safety profile than both HBO and NWPT.

VII. NCD 20.29 IS NOT APPLICABLE TO TOPICAL OXYGEN AND IT WOULD BE MORE APPROPRIATE FOR CMS TO CONSIDER A SEPARATE NCD FOR TOPICAL OXYGEN

It is clear that TO is not HBO, this is even stated in the NCD. But, it is absolute opaque as to why the “Topical Application of Oxygen” is included in NCD 20.29. Without any explanation regarding the reference to TO, the original NCD published on October 19, 2000 included a paragraph regarding “Topical Application of Oxygen.”^{56/} See ATTACHMENT 12.

^{56/} We acknowledge that it is possible there is an explanation regarding the inclusion of topical application of oxygen in the 1997 and 1999 TNs that are not available. However, large gaps exist in explaining the continued exclusion of TO and what, exactly, “topical application of oxygen” refers to.

This NCD was issued shortly before a formal request was submitted for an NCD process (November 29, 2000) and the updated NCD issued at the close of CMS's review contained the same language regarding topical application of oxygen. But, this raises questions as to why CMS included TO in its decision; and, at the time of its review, what CMS considered to be topical application of oxygen.

The only reference to TO that is available in the materials is in AHRQ's TA summary in 2001. As discussed in the timeline in Section IV, that TA summary states, "CMS also requested an evaluation of the use of topical hyperbaric oxygen (THO) therapy in the treatment of hypoxic wounds of the extremities and torso. Topical hyperbaric oxygen systems deliver oxygen at high pressures directly to the site of the wound, typically 50 mm Hg intermittent pressure for hypoxic wounds of the extremities and 22 mm Hg for the treatment of hypoxic wounds to the torso. At present, Medicare has a *Non-Coverage* policy for THO." See **ATTACHMENT 3**. We assume that AHRQ's reference to a "*Non-Coverage* policy for THO" refers to the October 19, 2000 NCD in place during the time of AHRQ's review that also carved out TO as distinct from HBO.

At the same time, the NCD's Original Reconsideration Tracking Sheet does not make any reference to TO or acknowledge that CMS requested AHRQ to analyze TO in questions referred for the TA. Moreover, the NCD Decision Memo does not address TO. So, how did TO get included with HBO in NCD 20.29?

The 2001 TA does include a review of studies regarding "topical hyperbaric oxygen," but states that it is "difficult to draw conclusions from th[e] collection of heterogeneous studies about whether THO is beneficial for any of the conditions studies. The quality and relevance of these studies are also questionable as seven of these reports were case series and of the studies were published over 20 years ago." But again, there is no evidence that CMS considered this information from the 2001 TA in its decision to include paragraph C in NCD 20.29. Furthermore, as we discussed earlier in Section II, in light of the multitude of terms used for TO, a limited TA review focused on the term "topical hyperbaric oxygen" could reasonably exclude applicable studies. Even if there were not enough studies in 2001, numerous studies regarding the efficacy of TO have been published since the 2001 TA. As we presented earlier, and in the attachments submitted with these comments, there exists a substantial body of literature available today that supports coverage of TO.

One possible explanation of the continued non-coverage of TO without any additional information is the level of involvement of the UHMS and the other requesters during the original consideration of the NCD. We know that the NCD request process strives to be transparent and collaborative, and CMS works closely with the requesters; which is demonstrated in the Original Consideration Tracking Sheet.^{57/} We think that the UHMS may have tried to carve out Medicare coverage for HBO only.

GWR received a letter directly from UHMS Executive Director, Leon Greenbaum in 1999. See **ATTACHMENT 25**. In this letter, Mr. Greenbaum takes issue with the term topical hyperbaric oxygen and concludes with the less than professional statement of, "I think that until people using Topox [topical oxygen] units come up with acceptable clinical data that is publishable in peer reviewed journals, the use of Topox [topical oxygen] units will hopefully diminish and eventually be relegated to one of the museum cabinets at the FDA complex."

^{57/} **ATTACHMENT 13.**

But, the fact remains that we agree with the UHMS, Mr. Greenbaum in 1999, and the present comments submitted by Dr. Caroline Fife to this current reconsideration request: HBO is a separate and distinct treatment from TO. We certainly understand how the term “topical hyperbaric oxygen” may have been confused or overlooked among the many other descriptors, but we want to reiterate now, that HBO and TO have been incorrectly included in the same NCD for too long, and we implore CMS to take this opportunity to establish a separate NCD providing for coverage of TO.

Further bolstering support for a separate NCD is the fact that TO should be covered under different beneficiary categories than those included in NCD 20.29. With the caveat that this list may not be exhaustive, NCD 20.29 provides coverage for HBO under the benefit categories of: (1) Incident to a Physician's Professional Service; (2) Outpatient Hospital Services Incident to a Physician's Service; and (3) Physicians' Services. TO should be covered under the category of Durable Medical Equipment, in line with the HCPCS used for its reimbursement (A4575 and E1390) and the NYS Medicaid reimbursement guidelines.^{58/}

One other major difference between HBO and TO is the treatment setting. HBO requires the patient to travel to a facility with a hyperbaric chamber. On the other hand, after an initial treatment in a hospital or healthcare facility, TO can be continued in the home setting. This ultimately has a great impact on the patient's quality of life. Imagine a patient who has long been battling a chronic wound that will not heal and who would be able to receive effective treatment in his or her home without risking additional infection on a trip, or multiple trips, to a health care facility. We believe that this is a truly beneficial and patient-centered treatment alternative, with little risk, and potential for significant improvement in outcomes and quality of life.

VIII. CONCLUSION

We again thank you for your time and attention to this important information. We urge CMS to use this opportunity to evaluate the substantial body of new evidence since its last consideration of TO and align its analyses with FDA's. As we have discussed we believe that GWR's TO device is safe and effective for FDA-cleared indications; that there is sufficient clinical evidence to support Medicare coverage of TO as an effective wound treatment modality; that TO is, in fact, safer than other wound treatment therapies; and finally, that many patients would experience an improved quality of life by being able to receive successful wound treatment in their homes. We will make ourselves available to discuss any questions related to these comments.

^{58/} See §1861(s)(6) and of the Act and **ATTACHMENT 18**.