Decision Memo for Hyperbaric Oxygen (HBO) Therapy (Section C, Topical Oxygen) (CAG-00060R)

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Decision Summary

The Centers for Medicare & Medicaid Services (CMS) received a reconsideration request to remove the coverage exclusion of Continuous Diffusion of Oxygen Therapy (CDO) from NCD Manual 20.29, Section C. This section of the NCD (Topical Application of Oxygen) considers treatment known as CDO as the application of topical oxygen and nationally non-covers this treatment.

After examining the evidence, CMS has decided that no National Coverage Determination is appropriate at this time concerning the use of topical oxygen for the treatment of chronic wounds. We will amend NCD 20.29 by removing Section C, Topical Application of Oxygen and Medicare coverage of topical oxygen for the treatment of chronic wounds will be determined by the local contractors.

See Appendix B for the manual language.

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Decision Memo

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SUBJECT: National Coverage Determination for Hyperbaric Oxygen (HBO) Therapy (Section C, Topical Application of Oxygen)

DATE: April 3, 2017

I. Decision

The Centers for Medicare & Medicaid Services (CMS) received a reconsideration request to remove the coverage exclusion of Continuous Diffusion of Oxygen Therapy (CDO) from NCD Manual 20.29, Section C. This section of the NCD (Topical Application of Oxygen) considers treatment known as CDO as the application of topical oxygen and nationally non-covers this treatment.

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II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology:

ABI – Ankle brachial index
ABS – Absolute pressure
AMWT – Advanced moist wound therapy
ATM – Standard atmospheric pressure AHRQ- Agency for Healthcare and Quality
CCD – Conventional compression dressings
CDO – Continuous diffusion of oxygen
CEAP - Clinical, Etiological, Anatomical and Pathophysiological
CED – Coverage with Evidence Development
CFR – Code of Federal Regulations
CMS - Centers for Medicare & Medicaid Services
CVA – Cerebrovascular accident
DFU – Diabetic foot ulcer
FDA - Food and Drug Administration
HBO – Hyperbaric oxygen
ITT – Intention-to-treat
mbar or mb - Millibar
MWT – Moist wound therapy
NCA - National Coverage Analysis

NCD - National Coverage Determination
RCT – Randomized controlled trial
RoPR - Registry of Patient Registries
SD – Standard deviation
SOC – Standard of care
TCOT- Transdermal continuous oxygen therapy
TOCE – Topical oxygen chamber for extremities
TOT- Topical oxygen therapy
TWO2 – Topical wound oxygen therapy; topical wound oxygen
TWOT – Transdermal wound oxygen therapy; topical wound oxygen therapy
US - United States

In the United States, there are approximately 6.5 million persons affected by chronic wounds (Sen et al., 2009). Chronic wounds are those which have failed to proceed through an orderly and timely reparative process in order to produce anatomic and functional integrity or are those lesions that have proceeded through a repair process but have not established a sustained anatomic and functional result (Järbrink et al., 2016; Sen et al., 2009). There is no specific time frame that defines a chronic wound; it is variably described as a break in the skin that remains unhealed or reoccurs for a period of four (4) to twelve (12) weeks (Järbrink et al., 2016; Markova & Mostow, 2012). Similarly, there is no specific nomenclature for these lesions as chronic wounds are also known as hard-to-heal or difficult-to-heal wounds or ulcers (Järbrink et al., 2016). The most common etiology of these wounds are pressure ulcers, diabetic ulcers, venous ulcers and arterial insufficiency ulcers (Guo & DiPietro, 2010; Markova & Mostow, 2012).

Oxygen plays an important role in the healing of chronic wounds (Brimson and Nigam 2013; Howard, Amiss, Evans, & Mustoe, 2013). Therefore there has been increased interest in oxygen delivery systems in order to improve wound healing. However, the best means to supply oxygen to the wound site remains controversial.

Two methods to deliver oxygen to wounds include hyperbaric oxygen (HBO) and topical oxygen therapy (TOT). As noted in National Coverage Determination (NCD) 20.29, Medicare considers HBO therapy to be a modality in which the entire body is exposed to oxygen under increased atmospheric pressure. HBO therapy is administered in a chamber, where an individual can breathe 100% oxygen at pressures greater than the pressures of air at sea level (e.g. 2-2.4 atmospheres). This systemic therapy is able to increase the plasma oxygen levels in the blood flowing to the wound. Assuming that the wound is adequately vascularized, an increase in the oxygen concentrations of the tissues at the injured site can occur, especially in areas of relative hypoxia. As a result, healing may be improved (Howard et al., 2013; Orsted et al., 2012).

In contrast, CMS considers topical oxygen therapy (TOT) to be a method whereby a local supply of oxygen is applied to a wound (Dissemond, Kroger, Storck, Risse, & Engels, 2015). It is delivered by one of two techniques (Woo, Coutts, & Sibbbald, 2012). In the first, oxygen may be delivered intermittently through an airtight chamber or soft sided 'bag' that is sealed around a wound present on the trunk or limb of the body. The bag or chamber is filled with 100% oxygen at high flow rates (e.g. 10L /min) from an external source to pressures slightly above atmospheric (e.g. 1.004 – 1.013 atm abs) and is delivered to the patient on an intermittent dosaging schedule (Feldmeier et al. 2005; Howard et al., 2013). In the past, this type of oxygen delivery was known by some as topical hyperbaric oxygen therapy, a term that is less commonly used today due to the low pressures delivered (Brimson & Nigam, 2013). Topical oxygen can also be delivered to a wound when applied continuously by a tube supplying pure oxygen at a normobaric pressure and low flow rate (3-12 ml/hour) under an occlusive dressing (Howard et al., 2013). These devices have been variously termed transcutaneous oxygen, transdermal continuous oxygen therapy, low flow oxygen, topical continuous oxygen therapy, continuous topical oxygen and continuous diffusion of oxygen (Dissemond et al., 2015; Howard et al., 2013; Lowell, Nicklas, Weilt,

Johnson, & Lyons, 2009; Orsted et al., 2012; Woo et al., 2012).

Neither intermittent nor continuous provision of topical oxygen is dependent on the systemic circulation reaching the wound, as is the case with HBO. However, because these systems directly apply oxygen to the wound site, it is thought by some that the oxygen can penetrate directly into the injured area and therefore improve healing of cutaneous lesions (Brimson & Nigam, 2013; Howard et al., 2013; Orsted et al. 2012; Woo et al., 2012). Typically, intermittent TOT treatments would be administered four (4) to five (5) days a week for approximately 90 minutes per session (Howard et al., 2013), though there can be other variations of dosaging noted in the clinical protocols. HBO must be provided in medically supervised environments; however, intermittent TOT may be provided in the home setting by a well-trained patient or caregiver. Though infrequent, side effects of HBO can be significant and include the possibility of pneumothorax, ear and sinus barotrauma, pulmonary edema, worsening of congestive heart failure, seizures and retinal damage (Howard et al., 2013). There are also significant concerns among some in the wound care community regarding TOT administered intermittently. For example, some believe that intermittent TOT may impede arterial or capillary circulation, inhibit angiogenesis, and decrease collagen synthesis and fibroblast proliferation; all circumstances which would delay or inhibit healing of a wound (Mutluoglu, Cakkalkurt, Uzun, & Aktas, 2015). TOT may not be appropriate for wounds covered in eschar or those that are deep and penetrating. Moreover, when used on open, exposed wound surfaces, TOT may cause desiccation of the area (Howard et al., 2013).

This national coverage analysis (NCA) will examine the evidence related to the use of both intermittent and continuous flow delivery of oxygen in order to determine if either therapy is reasonable and necessary for the treatment of chronic wounds in the Medicare beneficiary population. This NCA does not examine oxygen containing wound dressings or oxygen diffusion enhancers. In addition, CMS is not reconsidering any other section of the Hyperbaric Oxygen Therapy NCD in 20.29 of the Medicare National Coverage Determination Manual.

III. History of Medicare Coverage

CMS issued a national non-coverage of topical oxygen, asserting that the topical application of oxygen did not meet the definition of HBO therapy as stated in NCD 20.29. Furthermore, the NCD stated that its clinical efficacy had not been established. Therefore, no Medicare reimbursement has been allowed for the application of this procedure.

A. Current Request

CMS received a formal reconsideration request to remove the coverage exclusion of Continuous Diffusion of Oxygen Therapy (CDO) from NCD Manual 20.29, Section C. This section of the NCD (Topical Application of Oxygen) considers treatment known as CDO as the application of topical oxygen and nationally non-covers this treatment. The formal request letter can be viewed via the tracking sheet for this NCA on the CMS website at https://www.cms.gov/medicare-coverage-database/details/nca-details.aspx?NCAId=286&bc.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in the Social Security Act. HBO Therapy may be considered to be within the benefits described under sections:

§1861(s)(2)(A) Incident to a physician's professional Service
§1861(s)(2)(B) Outpatient Hospital Services Incident to a Physician's Service
§1861(s)(1) Physicians' Services

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Date	Action
July 12, 2016	CMS opens an NCA and the Initial 30-day public comment period begins.
August 11, 2016	First public comment period ends. CMS receives 41 comments.
January 12, 2017	Proposed Decision Memorandum posted. 30-day public comment period begins.
February 11, 2017	Second 30-day public comment period closes. Seventeen (17) comments were received.

Date	Action
April 3, 2017	Final Decision Memorandum posted.

V. Food and Drug Administration (FDA) Status

In 1988, the Food and Drug Administration issued a final rule classifying the topical oxygen chamber for extremities (TOCE) as a class III device. In 1988, after receiving manufacturing information concerning the safety and effectiveness of TOCE, the General and Plastic Surgery Devices Panel recommended that the TOCE be retained in class III. Based on new information in 2006, the FDA proposed to reclassify the TOCE device from a class III to a class II. This was accomplished with an announcement in the Federal Register, Vol. 76, No. 79 on April 25, 2011.

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM252364.pdf

VI. General Methodological Principles

When making national coverage determinations, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member under section 1862(a)(1)(A) of the Social Security Act. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public comments sometimes cite published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will be redacted or will not be made available to the public. CMS responds in detail to the public comments on a proposed national coverage determination when issuing the final national coverage determination.

VII. Evidence

A. Introduction

Frequently in the wound care arena, wound healing, without complete closure, is used as an outcome measure. However, different measurement techniques result in varying amounts of precision. The accuracy in the determination of wound boundaries can be a major source of error (St-Supery et al., 2011). Time to healing may also be tracked, but may not be precise because it can be dependent on various factors such as the scheduling of follow up assessments dictated by the study design (Gottrup et al., 2010).

Because of the difficulties in obtaining reliable wound measurements, and because CMS believes that wound closure is an important and meaningful goal that will have positive impact upon the beneficiary's life, we agree with the FDA that complete wound closure is the most objective and clinically meaningful endpoint. The FDA defines complete wound closure as skin re-epithelialization without drainage or dressing requirements confirmed at two (2) consecutive study visits, two (2) weeks apart (US Dept. of HHS, FDA, 2006). However, CMS believes that to increase the certainty of a durable closure of a wound and to track reoccurrences, studies must be of sufficient duration so that transient wound coverage can be distinguished from durable wound healing that promotes a subject's return to previous functioning and allows for the adequate monitoring of adverse effects.

We recognize that not all wounds heal completely in a timely manner. Other outcomes, such as a reduction in pain or exudate, served as potential endpoints in various research studies. Surrogate endpoints, such as those that relate to conditions of the wound confirmed by laboratory testing may also be reported in scientific investigations. CMS is most interested in those wound care outcomes that confirm their benefit in a way that enhances patient centered quality of life. Therefore we believe that if wound closure is not to be obtained, the investigational treatment should allow the patient to accomplish a return to previous function and activities (with or without an accompanying change in wound healing trajectory). We believe that this outcome must be durable and if wound "healing", but not closure, is to be correlated with improvement of function, the definition of "healing" must be predefined in the investigational protocol in order to increase the robustness of evidence (Gottrup et al., 2010).

In addition, CMS believes that unless the care applied to all wounds is well described and standardized, variations across providers and institutions may result in meaningless comparisons between study treatments, and diminish the generalizability of a study. Standard of care is a term used to describe the procedural methodology applied both to the investigational and control arms of a wound care trial. The principles of good standard of care include a formal assessment of the wound and surrounding skin at each clinical visit, provision of needed off-loading with a record of compliance and effectiveness, description of the type and frequency of debridement of the wound and its relationship to measurements, selection of appropriate dressings/cleansing routines, usage of an appropriate therapeutic program for infection, evaluation and support of nutritional status, optimal glycemic control, description of bowel and bladder care for those participants with pressure ulcers at risk for contamination, and assessment/treatment of vascular status as necessary (Gottrup et al., 2010; Jeffcoate et al. 2016; US Dept. of HHS, FDA, 2006).

The standard of care chosen should be reported in the investigation with sufficient detail to allow a consistent and uniform application across all study locations and all treating providers. We also believe it is necessary to apply a run-in period within the bounds of the investigation to determine if the wound is truly persistent under appropriate conditions of treatment. The rationale for this is to distinguish those wounds that will heal with compliance to appropriate standard of care from those wounds that require more elaborate interventions to demonstrate improvement or complete healing. If it is not practical to report the elements of the SOC in the journal article, then these details should be referenced for the reviewer elsewhere.

Literature Search Methods

We searched the PUBMED and EMBASE databases, the Cochrane Library, and the National Guidelines Clearinghouse up to November 2016. Search terms included wound, continuous diffusion of oxygen therapy, transdermal continuous oxygen, topical oxygen and oxygen. We identified studies with and without randomized control trial (RCT) design. No meta-analyses and systematic reviews were obtained. Of the references found, we read through the abstracts and titles to find those that met the criteria below. We also reviewed references submitted to us by commenters and performed a hand search of bibliographies to identify other pertinent articles.

For the purpose of this analysis, we reviewed clinical trials performed during the last 10 years (2006-November 2016) with the following inclusion criteria:

- Human adults with wounds from pressure ulcers, diabetic ulcers, venous ulcers and arterial insufficiency ulcers present for at least 4 weeks or otherwise indicated as non-healing (e.g. treated in a hospital setting)
- Investigations that studied wounds of varying types were included if the above etiologies were separated out for analysis
- Studies with ten or more patients
- Prospective trials with well-defined comparators with a primary goal to examine wound healing

We found eight (8) publications representing six (6) research studies that met our inclusion criteria. The details of these investigations are summarized below.

1. Evidence Question(s)

Is the evidence sufficient to determine that Medicare beneficiaries who have chronic non-healing wounds and receive continuous or intermittent topical oxygen therapy to the wound, experience clinically significant health outcomes as indicated by:

a. Complete wound healing;
b. Ability to return to previous function and resumption of normal activities;
c. Reduction in wound size or improvement in healing trajectory, which results in the patient's ability to return to previous function and resumption of normal activities?

We evaluated the evidence related to our analytic questions based on the strength of evidence presented in the reviewed literature, and the overall generalizability of the studies to our beneficiary population.

2. External Technology Assessments

CMS did not request an external technology assessment (TA).

3. Internal Technology Assessment

Azimian J, Nayeri ND, Pourkhaleghi E, Ansari M. Transdermal Wound Oxygen Therapy on Pressure Ulcer Healing: A Single-Blind Multi-Center Randomized Controlled Trial. Iran Red Crescent Med J. 2015; 17(11): e20211. doi:10.5812/ircmj.20211. PMID: 26734476

A convenience sample of 100 hospitalized adult patients from either a medical-surgical intensive care unit or a neurological unit were recruited to this single blinded multi-center study and were randomly assigned to an intervention or control group by coin toss method and block randomization. All subjects were at least 18 years old with a stage II-IV pressure ulcer (University of Texas wound classification system) on the sacral or ischial areas. Excluded from the sample were those individuals with peripheral vascular diseases, including diabetes mellitus.

All patients received the routine care of the study setting. In addition, patients in the intervention group received transdermal wound oxygen therapy (TWOT). TWOT consisted of the direct application of humidified high pressure oxygen via disposable catheter, at a rate of 10 liters per minute, to the wound site for 20 minutes, three times a day for 12 days. After each treatment saline soaked gauzes were applied to the wounds. Dressings were changed once per shift.

Characteristics of the investigational and control groups, both of which consisted of fifty (50) individuals, did not differ significantly in terms of age, gender, previous history of cerebrovascular accident (CVA), level of consciousness, mobility and baseline wound stage ($p > 0.05$). At baseline, the intervention group's mean wound size was 28.74 cm^2 (SD 5.88); the control group's mean wound size was 31.81 cm^2 (SD 3.94) [$p = 0.153$].

After 12 days of treatment, complete wound healing was assessed. Sixteen patients (16/50) in the interventional group and one patient (1/50) in the control group exhibited complete wound healing, as defined by complete epithelialization of the wound without drainage (p 0.001). It was also noted that at the study's end, the total mean wound area in the experimental group (8.52 + 6.36 cm^2) was significantly lower than that of the control group (35.68 + 7.06 cm^2) [p 0.001]).

The authors concluded that transdermal wound oxygen therapy can effectively promote the healing of pressure wounds on the sacral and ischial areas of the body. However, due to the relatively small study sample, they recommended larger studies be pursued.

Blackman E, Moore C, Hyatt J, Railton R, Frye C. Topical Wound Oxygen Therapy in the Treatment of Severe Diabetic Foot Ulcers: A Prospective Controlled Study. Ostomy Wound Manage. 2010; 56(6): 24 -31. PMID: 20567051

The purpose of this controlled, single site study was to perform a prospective comparison of the healing rates of chronic diabetic foot ulcers (DFUs) treated with either topical wound oxygen therapy (TWO_2) or advanced moist wound therapy (AMWT). Furthermore, the investigators wished to study the recurrence rates of these wounds after 24 months in both treatment groups.

Twenty eight patients were included in the trial. Subjects needed to be at least eighteen (18) years old, demonstrate an ankle-brachial index of at least 0.5 in the affected limb, and have a DFU with a grade of 2A or worse per the University of Texas Wound Classification System. Exclusion criteria included a chronic wound of non-diabetic origin, deep vein thrombosis, pregnancy or lactation, the receipt of palliative care, known noncompliance with therapy, or an HbA1C level above 10%.

The manufacturer of the TWO_2 devices supported the study by providing the medical devices and oxygen used in the study. During the investigation, four (4) TWO_2 devices were available for use. If a TWO_2 device was available after initial assessment, the patient was asked to be in the TWO_2 arm of the study. If all such devices were occupied on the day of the first visit of a study participant, or the patient refused daily TWO_2 treatments, the patient was assigned to the control group and provided an AMWT using a silver based dressing.

The TWO_2 device used in the study delivered humidified medical grade oxygen into an extremity chamber. The device worked in a cyclic manner to pressurize the chamber to 50mb before venting the oxygen out of the chamber to reduce the pressure towards ambient levels (5mb) before re-pressurizing again. Treatment was performed for sixty (60) minutes, Monday through Friday. Saline soaked gauze was applied after treatment and remained in place until the next scheduled oxygen therapy session.

Dressing changes for the control group were performed in the study center per physician recommendation at a minimum of twice per week. Debridement was carried out weekly as needed in each participant. All wounds were offloaded. The primary study outcome, wound closure, was defined as complete epithelialization of the wound with the absence of drainage. Patients were followed for 90 days in the active treatment phase of the investigation until the wound healed; all patients were then monitored monthly for 24 months for reoccurrence. Data from all patients was analyzed.

The TWO_2 (n = 17) and AMWT (n = 11) groups were similar with respect to age, gender, HbA1c and ankle brachial index (ABI). Baseline wound area was larger in the TWO_2 group than in the control group (mean 4.1 cm^2 [SD 4.3] vs. 1.4 cm^2 [SD 0.6]; p = 0.02). Wound duration was longer in the TWO_2 group than the control, but the difference was not statistically significant (6.1 months [SD 5.8] vs. 3.2 months [SD 0.4]). All patients had plantar wounds and peripheral neuropathy; no toe or heel ulcers were noted. Except for one midfoot ulcer in the TWO_2 group, all ulcers were on the first, third and fifth metatarsals.

Fourteen (14) of seventeen (17) wounds healed in the TWO_2 group (82.4%) and five (5) of eleven (11) wounds closed in the control group (45.5%) [p = 0.04]. Median time to closure was 56 days (interquartile range 39-81 days) in the TWO2 group and 93 days (interquartile range 62 -127) in the control group. In the follow up period of up to 24 months, no reoccurrences of ulcers occurred in either group. Furthermore, there were no treatment related adverse events in either group.

The authors concluded that the wounds of study patients treated with TWO_2 were significantly more likely to heal and in a shorter period of time than those treated with AMWT. They also stated that well designed randomized controlled trials to confirm the efficacy of TWO_2 were needed.

Driver VR, Yao M, Kantarci A, Gu G. Park N, 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 Manage. 2013; 59(11): 19-26. PMID: 24201169

The goal of this prospective, randomized study was to evaluate the efficacy of the use of transdermal continuous oxygen therapy (TCOT) in patients with nonhealing diabetic foot wounds by following wound healing and biological markers of tissue response. Consecutive patients, with either Wagner grade 1 or 2 wounds and a wound size ranging from 0.5 cm^2 - 15 cm^2 in area, were enrolled in the study. Eligible patients were randomized either to the intervention group (n = 9) or control group (n=8) by a block randomization scheme. The ulcers had been present for an average of 20.7 ± 21.1 months in the intervention group and 14.3 ± 26.8 months in the control group. Wound volume was 1.3 ± 0.7 cm^3 in the intervention group and 1.5 cm^3 ± 0.6 in the control group. There were no significant differences (p>0.05) in subject age, gender, race, ulcer age, body weight, ankle brachial index, pain score, ulcer volume, Wagner grade and history of infection or amputation between the two (2) groups. All study participants received standard of care (weekly debridement, boot offloading, and moisture); in addition, those in the intervention group were also provided TCOT. TCOT provided a continuous delivery of 99.8% pure oxygen by cannula at a rate of 3 mL/hour directly to the wound site. Each single use unit provided oxygen twenty four (24) hours per day, for up to fifteen (15) days, before being discarded and replaced. The wound site and cannula tip were covered with a transparent film dressing.

Following screening, all individuals underwent a one week washout period during which they received standard of care (SOC) alone. Wound dressings were usually changed every three (3) to seven (7) days per care plan. The study was conducted for four (4) weeks. This study was supported by the manufacturer of the TCOT device. Wounds were measured by ruler for length (L), width (W) and depth (D). Volume was calculated as L x W x D at the screening visit (week 0), treatment visits (weeks 1 through 4) and at the post-treatment follow up visit (week 5). Biological samples were collected once weekly during the active study.

The authors concluded that the clinical efficacy of TCOT was established as there was a significant difference in percent volume reduction in wound size for the TCOT group compared to the control group at week 5 (21.8% ± 20.0% of week 1 versus 49.2% ± 52.3% of week 1 respectively, p 0.05). Additionally, based on biological measurements, the authors stated that their findings supported that TCOT resolves inflammation in the nonhealing DFU and helps to restore tissue turnover. No wounds completely healed during the study.

Niederauer MQ, Michalek JE, Armstrong DG. Interim results for a prospective, randomized, double-blind multicenter study comparing continuous diffusion of oxygen therapy to standard moist wound therapy in the treatment of diabetic foot ulcers. Wound Med. 2015: 8; 19–23. http://dx.doi.org/10.1016/j.wndm.2015.03.005.

This study was a planned interim analysis of a randomized, balanced, double blind, sham controlled, parallel group clinical trial performed to evaluate use of a device providing the continuous diffusion of oxygen (CDO) to diabetic foot ulcers (DFU) compared to treatment of the ulcers with standard moist wound therapy (MWT). The full sample size of the study is anticipated to be 84 subjects; this analysis reports the results of the first 50% of subjects who completed a twelve (12) week course of treatment (n=42). The primary outcome of the investigation is complete wound closure defined as complete reepitheliazation with no drainage.

The CDO device delivered pure oxygen to the wound at a flow rate of 3-10 ml/hour through tubing placed under dressings. Patients eligible for the trial were 30-90 years of age with a non-healing, full-thickness, University of Texas Classification of Diabetic Foot Ulcers Class IA diabetic foot ulcer at or below the malleoli for a duration of at least 4 weeks, but not greater than a year at the time of screening. Furthermore, the index ulcer was required to measure between 1 and 10 cm^2 in area by plainimetric analysis. Among the patients excluded from the investigation were those whose ulcer decreased in area by > 30% between the screening and randomization periods. All enrolled patients received standard wound therapy that included wound cleansing, moist wound care, offloading, and as appropriate, aggressive debridement. Wounds were surgically debrided to a bleeding base as necessary.

After enrollment, patients were randomized to the treatment/active group or the control/sham group. Subjects in the active arm received CDO in addition to standard of care moist wound therapy (MWT). Those in the sham group received no oxygen to the wound, but did receive standard of care MWT. Patients were followed for twelve (12) weeks or until wound closure, whichever came first. Dressing change frequency depended on rate of exudate and varied from 2-12 times per week.

Upon analysis of the data, the investigators excluded[1] from their evaluation subjects who experienced: (1) wounds that closed more than 50% in the first two weeks (from screen to visit 1), or (2) wounds that closed more than 30% in the first week for those subjects who were randomized on the same day as the screen visit (screen/enroll same day) and such subjects were referred to as those who experienced fast closure between Screen and Visit 1. Data was also analyzed by wound size in 0.25 cm^2 segments from all wounds greater than 1.0 cm^2 up to the median wound size of 2.28 cm^2.

As the study progressed, the authors found it necessary to have regular conference calls with investigators to provide emphasis on the proper principles of moist wound therapy, such as debridement, keeping the wound moist, and the number of dressing changes. As a surrogate for training, the authors stratified by calendar period to before and after the median visit date, which was calculated to be July 18, 2013.

Subjects who withdrew from the study for any reason were excluded from the statistical analysis. This study reported on the first 42 subjects (active group: n = 21; sham group, n= 21) to complete the study per protocol. The authors noted that at baseline, the two (2) treatment groups were similar with regard to age, ethnicity, sex and wound size. Enrollment wound area size was 2.6 ± 1.5 cm^2 in the active group and 3.4 ± 2.2 cm^2 in the sham group.

The authors reported that they found no significant and beneficial treatment effect in the active arm of the study. However, in a series of subsequent exploratory analyses, the authors found that among subjects with wound size of at least 1.5 cm^2 and who experienced wound closure and excluding subjects who experienced fast closure between Screen and Visit 1 (Active n=9; Sham n=3), the average number of days to closure was significantly lower among the active group than the sham group (mean difference 20 ± 7.9, 95% CI 2.4 – 37.5, p = 0.03). Furthermore, among subjects with wound size of at least 1.5 cm^2, excluding subjects who experienced fast closure between Screen and Visit 1, wound closure was not significantly increased in the active group. However, after stratification at the median randomization date, wound closure was found to be significantly increased in those individuals in the active group seen after the median randomization date (Active 77.8%, n=9; Sham 12.5%, n=8; p = 0.02).

The authors concluded that this interim analysis suggested improved healing with CDO versus MWT for slower to close, larger chronic wounds.

Niederauer M, Michalek J, Armstrong D. A Prospective, Randomized, Double-Blind Multicenter Study Comparing Continuous Diffusion of Oxygen Therapy to Sham Therapy in the Treatment of Diabetic Foot Ulcers. *J Diabetes Sci Technol*. 2017; 1-9.

The study is a continuation of the planned interim report that was published in *Wound Medicine* (see above for additional details). The authors note that on the basis of these earlier results, the protocol was amended to change the minimum baseline wound size and run-in rate of wound closure inclusion/exclusion criteria. Subjects

that failed these criteria were removed from the study.

Therefore individuals eligible for this study demonstrated a DFU present for 30 days, but not more than one (1) year, with wound sizes ranging from 1.5 cm^2 to 10 cm^2 as measured by plainimetric analysis from photographs taken after wound debridement. Also, because the closure rate during the run-in period had an effect on the sensitivity analysis in the interim study , subjects were excluded who during the run-in period experienced either: 1) wounds that closed more than 30% in either week of the first two weeks, or 2) wounds that closed more than 50% in the first two weeks. The authors referred to this as a run-in wound closure rate of 30%/50% PWAR (percentage wound area reduction).

The first fifty (50) subjects with DFUs to complete the study per protocol in each arm were included (79% male, aged 58.3+ 12.1 years). Therefore fifty (50) subjects were in the Active arm and fifty (50) were in the Sham arm. As in the interim study, the primary outcome was complete wound closure at twelve (12) weeks, defined as complete reepithelialization with no drainage as assessed by the treating clinician. This state was confirmed by a blinded observer. Subjects who failed to meet eligibility criteria, withdrew for any reason, or who completed but were not among the first 50% to complete in each arm were excluded.

Forty-six (46) of 146 subjects were dropped from the study after randomization, including twelve (12) from the Active group and fourteen (14) from the Sham group due to adverse events. Twenty other subjects were excluded if they withdrew consent, demonstrated noncompliance, were lost to follow-up, died, or were not in the first fifty (50) in each arm of the study to complete the protocol.

The resulting two treatment arms of 50 each were reported to be similar with regard to age, ethnicity, gender, wound area (cm^2), HbA1C, ABI and the demonstration of no pain.

To evaluate whether there was an effect of wound size on the primary outcome of wound closure, the effect on the primary outcome was reported by wound size in 0.5 cm^2 segments from all wounds greater than 1.5 cm^2 up to a minimum wound size of 4.0 cm^2. Higher minimum wound sizes were not reported as the sample sizes became too small ($n<30$).

To evaluate whether there was an effect of run-in wound closure rate on the primary outcome of wound closure, results were reported by excluding subjects at two lower rates of PWAR. Therefore, the analysis eliminated wounds that experienced more than 25% PWAR in either week of the first two weeks or 40% PWAR in the first two weeks (referred to as a run-in wound closure rate of 25%/40% PWAR), as well as 20% PWAR in either week of the first two weeks or 30% PWAR in the first two weeks (referred to as a run-in wound closure rate of 20%/30% PWAR). Relative performance was defined by the authors as the ratio of the proportion of subjects in the Active arm reaching full closure divided by the proportion of subjects in the Sham arm reaching full closure, expressed as a percentage.

The primary outcome of complete wound closure at 12 weeks was significantly associated with treatment per protocol [Active 23/50 (46.0%), Sham 11/50 (22.0%), RR 0.69 (95% CI 0.52, 0.93), p=0.02].

The authors reported that days to closure increased with wound closure in both arms and the average days to closure was less among patients in the Active arm relative to those in the Sham arm. The treatment effect was significant (p = .026) and the wound closure effect was significant (p < .001). The relative reduction in time to reach 50%, 75% or 100% wound closure was higher initially and decreased as the wounds progressed to full closure. The effect of run-in wound closure rate on the primary outcome showed a linear decrease in the Sham arm with essentially no change in the Active arm as the run-in wound closure rate decreased. There were significant beneficial effects of the Active arm at 25%/40% PWAR (P = .01) and 20%/30% PWAR (P = .006). The Active arm was relatively insensitive to reducing the run-in wound closure rate (values ranged from 46.0% to 42.5% full wound closure), whereas the Sham arm experienced a significant drop from 22.0% full wound closure to 13.5% full wound closure, corresponding to a 39% reduction in efficacy as the wounds become more chronic. This resulted in an overall increase in relative performance of the Active versus Sham from 209% to 315% as the wounds become more difficult to heal.

The effect of baseline minimum wound size on full wound closure showed a decrease in both arms as the wound size increased. The relative performance showed an increasing trend as the minimum wound size increased.

The authors stated that the results of this study suggest that CDO over a wound leads to significantly higher rates of closure and faster time to closure compared to similarly treated patients receiving standard therapy provided along with a sham device. Furthermore, the authors stated that the relative efficacy appears to improve the more the therapy may be needed (more chronic and larger wounds).

Tawfick WA, Sultan S. Does Topical Wound Oxygen (TWO_2Offer an Improved Outcome Over Conventional Compression Dressings (CCD) in the Management of Refractory Venous Ulcers (RVU)? A Parallel Observational Comparative Study. Eur J Vasc Endovasc Surg. 2009 Jul; 38(1):125-32. doi: 10.1016/j.ejvs.2009.03.027. Epub 2009 May 22. PMID: 19464933.

The goal of this parallel group observational comparative study was to examine the safety and efficacy of topical wound oxygen (TWO_2) versus conventional compression dressings (CCD) in the management of refractory nonhealing venous ulcers. Patient preference determined group allocation. Pertinent endpoints of the investigation included proportion of ulcers healed at twelve (12) weeks, time to complete healing, and reoccurrence rates.

Inclusion criteria for the study were: age of at least 18 years, a venous ulcer of more than two (2) years duration which over the past one year had shown no signs of improvement despite adequate compliance with appropriate treatment provided by community based leg ulcer clinics, normal ankle–brachial index (≥0.9) and digital pressures (≥0.7) and Clinical, Etiological, Anatomical and Pathophysiological (CEAP) classification of C6s (active

venous ulcer with symptoms). Excluded from the study were bedridden patients as well as patients with ischemic or diabetic ulcers, osteomyelitis, gangrene or deep vein thrombosis.

TWO_2 was delivered in an inpatient setting. The affected limbs of the intervention group were placed in the TWO_2 device for 180 minutes twice a day under a pressure of 50 mbars; oxygen was supplied at 10 l /min with continuous humidification. The wounds were left exposed until the next session; no dressings or compression were applied. If a patient desired to leave the hospital or ward between sessions, the ulcer was temporarily covered with a non-adherent dressing and gauze. Wounds were cleaned, debrided and re-measured twice per week.

The limbs in the control group were managed in an outpatient clinic. The wounds underwent compression using a multilayer compression bandage system with an underlying nonadherent wound contact layer dressing. Dressings were changed one to three times per week depending on exudate production, after the wound had been cleaned, debrided and re-measured.

Once complete healing occurred, the subjects in both groups were fitted with class II elastic stockings. Those who did not reach healing by twelve (12) weeks in either arm were considered treatment failures. According to the authors, all patients were managed on an intention to treat basis.

Forty-six limbs with 46 ulcers (19 with MRSA) received TWO_2, while 37 limbs with 37 ulcers (17 with MRSA) were treated with compressive dressings. There were no significant differences between groups in the anatomic distribution of the ulcers or their size or duration. After 12 weeks, 80% (37/46) of the ulcers treated with TWO_2 and 35% (13/37) of the ulcers treated with compression were completely healed (p0.0001). The mean reduction in ulcer surface area was 96% in the group receiving TWO_2 compared to 61% in the compressive dressing group. The median time to full closure in the TWO_2 group was 45 days (95% CI, 39-51) compared to 182 days in the compression therapy group (95% CI, 162-203, p0.0001). The ulcer healing time among wounds treated with TWO_2 was shorter regardless of the duration or size of the ulcer. Three patients treated by TWO_2 had been referred to the investigators for primary amputation after failure of other treatments; these three (3) ulcers healed completely, allowing amputation to be avoided. During twelve (12) months follow up, none of the 37 healed TWO_2 ulcers showed signs of reoccurrence, while five (5) of the thirteen (13) healed ulcers by compression did.

The authors concluded that TWO_2 produced superior outcomes to compression therapy in the treatment of refractory venous ulcers by achieving shorter healing times and reducing recurrence rates. They also noted that a randomized controlled trial was underway to further study the benefits of TWO_2.

Tawfick WA 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. 2013:47 (1); 30-37. DOI: 10.1177/1538574412467684. PMID 23223182.

(Note: This research study is a continuation of the earlier study immediately above).[2]

The goal of this parallel group observational comparative study was to examine the efficacy of topical wound oxygen (TWO_2) versus conventional compression dressings (CCD) in the management of refractory nonhealing venous ulcers by observing both the proportion of ulcers healed at 12 weeks and the reoccurrence rate of these wounds at 36 weeks. Choice of treatment was patient preference. According to the authors, all patients were managed in an intention to treat basis.

Inclusion criteria for the study were: an age of at least 18 years, a venous ulcer more than two (2) years without improvement for at least one (1) year despite treatment in a dedicated veins unit, Clinical, Etiological, Anatomical and Pathophysiological (CEAP) classification of C6s, and a normal ankle brachial index with normal digital pressure. Excluded from the study were bedridden patients as well as patients with ischemic ulcers, malignant ulcers or osteomyelitis in the treated limb.

The limbs in the intervention group were placed in the TWO_2 device for 180 minutes twice a day under a pressure of 50 mbars; oxygen was supplied at 10L/min with continuous humidification. The pressure was cycled from atmospheric to 50 mbars and back to atmospheric in one (1) minute cycles. The wounds were washed and left exposed until the next session; no dressings or compression were applied. Wounds were cleaned and then debrided twice per week. The limbs in the control group underwent compression using a multilayer compression bandage system with an underlying nonadherent wound contact layer dressing. Dressings were changed one to three times per week depending on exudate production.

Once complete healing occurred, the subjects in both groups were fitted with class 3, closed toe, below knee elastic stockings during the day and were advised to use tap water soakings, as well as baby or olive oil to prevent itching and scratching. Those who did not reach healing by twelve (12) weeks in either arm were considered failures of treatment. They were then managed with compressive dressings and seen weekly. Patients were followed up every three (3) months following cessation of therapy. Sixty-seven limbs with 67 ulcers (24 MRSA positive) were managed with TWO_2; 65 limbs with 65 ulcers (19 MRSA positive) were managed with CCD. Treatment continued until complete ulcer healing or for twelve (12) weeks, whichever time point came sooner. The two patient groups were similar in age with the TWO_2 group mean being 69.34 years (range 46-85), and the CCD group mean being 67.78 years (range 44-88)]. The groups were not significantly different in risk factors (diabetes, smoking, hypertension, MRSA, referral for amputation), or anatomic distribution, size or duration of ulcers. Furthermore there was no difference between the two groups when prior surgical or medical management of the ulcer was compared.

At the end of twelve weeks, 76% (51/67) of the TWO_2 treated ulcers versus 46% (30/65) of the compression treated ulcers healed completely (p 0.0001). The median time to full healing in the TWO_2 group was 57 days as compared to 107 days in the compression group (p 0.0001). The TWO_2 treated ulcers had a shorter healing time compared to the CCD ulcers no matter the duration (p 0.0001) or size of the ulcer (p 0.0001). Notably, the three (3) patients within the TWO_2 group who were referred for primary amputation following failure of other treatment modalities fully healed. Using the pain numerical ranking scale, the pain score in the TWO_2 group

decreased from eight (8) to three (3) in thirteen (13) days. Furthermore, 11/24 MRSA ulcers in the TWO_2 group were MRSA negative after five (5) weeks of treatment regardless of the closure of the ulcer; none of the 19 MRSA positive ulcers in the control group were negative by this same time point. (p .001). No local or systemic complications were demonstrated by either group.

Patients were followed for a median of 36 months. During the follow up period, three (3) TWO_2 treated ulcers that had healed, showed signs of recurrence. Fourteen (14) of the thirty (30) fully healed ulcers treated with compression dressings, showed signs of recurrence. The authors concluded that TWO_2 significantly reduces the time needed for the healing of refractory venous ulcers and reduces pain and MRSA infection. The authors also noted that a randomized controlled trial was underway to further explore the benefits of TWO2 therapy.

Yu J, Lu S, McLaren A, Perry JA, Cross KM. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. Wound Repair Regen. 2016. doi: 10.1111/wrr.12490. PMID: 27733020.

The aim of this pilot randomized controlled trial was to compare a continuous topical oxygen delivery system to standard best practice in patients with nonhealing DFUs. Patients were randomized into either a group which received topical oxygen as well as SOC (n=10) or into a nonplacebo control group which received SOC alone (n = 10). The SOC consisted of iodine-based dressings, sharp debridement of wounds, and off-loading by total contact cast for hindfootand midfoot ulcers and removable cast walkers for forefoot ulcers. Subjects were randomized by placing a piece of paper with the study ID numbers into a bag and blindly choosing subjects for each group in the trial.

Subjects were greater than eighteen (18) years of age, demonstrated a DFU which had been treated for more than four (4) weeks, and for whom there were no plans for surgical interventions or to treat peripheral arterial disease. Exclusions included the presence of invasive infection requiring intravenous antibiotics, a hard eschar covering more than 10% of the surface area of the wound on presentation as well as a pure neuropathic ulcer without arterial insufficiency (unless the wound failed to heal within twelve (12) weeks of optimum management).

Furthermore, the wounds were assessed by the University of Texas criteria. Both the intervention group and the control group contained ulcers of Grade Ia (clean superficial wound not involving tendon, capsule or bone) to Grade IIId (ischemic, infected wounds penetrating bone or joint) at baseline.

In the treatment group wounds were dressed with the new oxygen delivery pad applied weekly. However, in the first two weeks of treatment with topical oxygen, there was a clinically significant increase in exudate. During this period, foam dressings were used. Also for those individuals in total contact casting, the device tubing was protected in a foam dressing to prevent the risk of pressure necrosis. In the control group, subjects received the standard prescribed wound dressings.

The study was performed for eight (8) weeks. One subject in the continuous topical oxygen group dropped out; the results of one subject in the control group were discarded as an outlier in the analysis, due to the large size of the wound. The two groups demonstrated similar mean ages, HbA1c values, and ankle brachial indexes. At baseline, the ulcers of the oxygen treated group demonstrated a surface area of 1.37 cm^2 ± 0.95 versus 1.68 cm^2 ± 1.31 in the control group (p> 0.5). The mean duration of the wounds was 47.4 weeks ± 23.4 in the oxygen treated group versus 46.2 weeks ± 17.9 in the control group (p 0.18).

Grade I ulcers in both groups all healed completely (defined as a wound surface area of 0 cm^2) during the eight (8) week study. None of the Grade II ulcers in the control group healed in that time period, while 100% of the Grade II oxygen treated wounds healed completely. Of the Grade III wounds in the study, 50% healed completely with topical oxygen; none healed in the control group.

The authors concluded that though this study was underpowered, it demonstrated that topical oxygen applied continuously to a chronic wound, can have a powerful effect on healing.

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened on this issue.

5. Evidence-Based Guidelines

CMS did not find any relevant evidence-based guidelines.

6. Professional Society Recommendations / Consensus Statements / Other Expert Opinion

An internet search failed to locate any professional society position statements exclusively concerning topical oxygen. CMS received one professional society statement and several other comments from providers and experts on the proposed decision supporting topical oxygen for chronic wounds.

7. Public Comment

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=286&ExpandComments=n&bc.

Initial Comment Period: 07/12/2016 – 08/11/2016
During the initial 30-day comment period, CMS received 41 comments. The majority of comments support coverage of topical oxygen for chronic non-healing wounds while three comments specifically expressed that topical oxygen is not hyperbaric oxygen and its clinical efficacy is not adequately supported by scientific data. The majority of comments were from physicians (11/41), nurses (10/41) and podiatrists (6/41). Three comments were from manufacturing companies; one being the requestor, all of whom supported the removal of Section C 'Topical Application of Oxygen' from NCD 20.29 Hyperbaric Oxygen Therapy. The remaining comments were from patients (4/41), wound care/medical centers (3/41), and individuals who did not identify an associated organization or profession (7/41). We reviewed the comments in their entirety, including all referenced literature submitted.

Second Comment Period: 01/12/17 – 02/11/17
During the second comment period, 17 comments were received. Comments were received from five (5) patients, three (3) nurses, three (3) manufacturers; one being the requestor, two (2) podiatrists, two (2) research fellows, one (1) physician and (1) professional society. No commenters opposed our proposal to remove topical application of oxygen from subsection C of the Hyperbaric Oxygen NCD in section 20.29. Most commenters also supported our proposed decision to remove the existing national non-coverage determination. A few commenters were opposed to our decision to allow Medicare contractors to make the coverage determination under 1862(a)(1)(A). We reviewed the comments in their entirety.

Coverage

Comment: Most commenters made favorable statements concerning the use of topical oxygen based on personal experience or observations of the treatment on particular patients and generally support the removal of the national non-coverage of topical oxygen for the treatment of chronic wounds. One commenter applauded CMS for conducting a very complete and thoughtful review of the different types of topical oxygen devices available in the marketplace and the published clinical evidence related to their respective efficacy.

CMS Response: CMS appreciates the supportive comments.

Comment: Many commenters expressed support for the removal of Section C, Topical Application of Oxygen from NCD 20.29 (Hyperbaric Oxygen Therapy).

CMS Response: CMS appreciates the supportive comments.

Comment: We received several patient and provider comments discussing personal experiences with topical oxygen used as a treatment for a chronic wound.

CMS Response: While we acknowledge that some individuals are sincerely conveying their personal experiences with topical oxygen, we must point out that anecdotal personal experiences may be subject to biases. Moreover, we may not always hear from patients or practitioners if those individuals have not obtained positive results. The evidence we draw from formal clinical studies is more persuasive to produce confident conclusions about the impact of medical technologies than are anecdotal experiences. However we do appreciate the importance of these events to our stakeholders.

Comment: One commenter expressed support for the Hyperbaric Oxygen Chamber.

CMS Response: While we appreciate the comment, it is outside the scope of this NCA. The focus of this NCA was topical application of oxygen only.

Comment: Several commenters believed that CMS should provide national coverage for topical oxygen based on the evidence discussed in the proposed decision and have also noted that some devices have been found to be safe and effective by the FDA.

CMS Response: We do not agree that a positive national coverage determination is warranted based on the existing evidence in the record at this time. While the evidence is sufficient to remove the existing national non-

coverage determination, the evidence does not support a positive national coverage determination because there is not adequate evidence that topical oxygen is reasonable and necessary for the treatment of chronic wounds. In National Coverage Determinations (NCDs) under 1862(a)(1)(A), CMS assesses the quality, strength and totality of published evidence in making a determination on whether or not an item or service is reasonable and necessary to diagnose or treat an illness or injury or to improve the functioning of a malformed body member. Overall, since the evidence on chronic wound healing from topical oxygen therapies has increased over the past few years, CMS believes a national non-coverage decision is no longer appropriate. However, given the inability to identify the characteristics of chronic wounds (such as etiology, size, depth and chronicity) that best respond to topical oxygen therapy and the type of patients best suited to use this therapy, we are not able to define a national patient population that would benefit from topical oxygen therapy at the present time.

As we have explained in other publications, (78 Fed. Reg. 48164, 48165 (August 7, 2013)), a Medicare coverage determination is based on different statutory authority and serves a different purpose from an FDA determination that a device is safe and effective for its intended use by consumers. FDA approval or clearance alone does not entitle that technology to Medicare coverage.

Scientific Literature

Comment: One commenter stated that the literature search method for this NCA was insufficient as it did not consider evidence from 2002 (when CMS last addressed this issue) and did not refer to scientific articles that the commenter had previously submitted that were stated to positively demonstrate the physiology of wound healing and the effectiveness of topical oxygen. The commenter also suggests that CMS did not consider animal studies or investigations that were completed before 2006.

CMS Response:
We disagree that our literature search method was insufficient to identify the relevant clinical and scientific evidence related to topical oxygen. CMS considers the scientific literature (including original research articles, systematic reviews, meta-analyses and guidelines) most relevant to the questions posed in the national coverage determination. In general, CMS does not consider animal studies, in vitro studies, preclinical data, studies older than ten (10) years and studies on physiology since these studies do not provide relevant and/or current evidence on health outcomes in the Medicare population. The timeframe for the literature is focused on current, applicable evidence on topical oxygen for chronic wounds. For this analysis, we limited the search to the time period of 2006 to present and believe this captures all relevant studies on the current technology. In this specific case, the literature search methodology, including inclusion (and therefore exclusion) criteria, was determined prior to the initiation of our proposed decision memo. Furthermore, the breadth of the scientific literature to be examined was determined *a priori* to consider those germane outcomes which would characterize whether or not topical oxygen was reasonable and necessary to accomplish the healing of chronic wounds and the subsequent return to function of the affected individual. As stated in the NCA, we reviewed the references presented to us by the commenters to determine which of these articles met our inclusion criteria.

Comment: A few commenters provided references for our review.

CMS Response: We thank those commenters who supplied scientific literature to us. We have considered all suggested references and, if relevant as described above, included them in the evidence section of this NCD. One study by Niederauer (2017) was added to the evidence. The remainder of articles submitted by commenters were general in nature or were animal studies, preclinical data or studies concerning physiology that did not meet inclusion/exclusion criteria or were outside the scope of this analysis.

Coverage with Evidence Development (CED)

Comment: One commenter requested that coverage with evidence development (CED) be offered in this national coverage determination, rather than local contractor discretion, in order to stimulate additional high quality studies of topical oxygen therapies and to determine which therapies provide meaningful benefits to Medicare beneficiaries.

CMS Response: We appreciate the comment. CMS has decided not to move forward with a national coverage determination, but will allow the section 1862(a)(1)(A) coverage determination for topical oxygen in the treatment of chronic wounds to be determined by local contractors. We did not find sufficient evidence to issue either a National Coverage Determination or Coverage with Evidence Development decision. Given the inability to identify the characteristics of chronic wounds that best respond to topical oxygen and the type of patients best suited to this type of therapy, we are not able to define a national patient population that would benefit from topical oxygen therapy at the present time. Ongoing research in the US and Europe and pending publications may provide additional evidence that may support a request to reconsider a national determination in the future.

Other

Comment: Several commenters request that the definition of topical oxygen be changed.

CMS Response: We are not adopting this suggestion. A number of commenters suggested further refinement of the definition of topical oxygen but each commenter who suggested a definition provided different language. We believe it is in the best interest of the field to provide a generally accepted, standard definition of topical oxygen that does not inadvertently limit potential advancement in the wound care arena.

Comment: Several commenters requested that topical oxygen be made available to beneficiaries with unrestricted wound types.

CMS Response: We appreciate the comment. We have removed the national non-coverage with this national coverage determination to allow the Medicare Administrative Contractors to decide if the application of topical oxygen is reasonable and necessary for the healing of any type of chronic wound.

Comment: Several commenters stated that the use of topical oxygen would reduce costs.

CMS Response: While we appreciate the comment, CMS does not consider cost in evaluating evidence in making NCDs.

VIII. CMS Analysis

A. Introduction

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. See § 1862(a)(1)(A) of the Social Security Act).

In our analysis we addressed the questions below:

Is the evidence sufficient to determine that Medicare beneficiaries who have chronic non-healing wounds and receive continuous or intermittent topical oxygen therapy to the wound, experience clinically significant health outcomes as indicated by:

a. Complete wound healing;
b. Ability to return to previous function and resumption of normal activities;
c. Reduction in wound size or improvement in healing trajectory, which results in the patient's ability to return to previous function and resumption of normal activities?

We evaluated the evidence related to our analytic questions based on the quality and strength of evidence presented in the reviewed literature, and the overall generalizability of the studies to our beneficiary population.

B. Discussion

A total of 6 research studies (4 randomized trials and 2 observational studies) were reviewed. All reported some positive findings; however, significant issues were present in each study which reduced the overall quality and strength of evidence. A number of researchers have reported the challenges that are involved in the conduct of wound care research and the methodological difficulties that may lessen the strength of conclusions (Bolton, 2016; Brölmann et al., 2013; Eskes et al., 2012; Gottrup, Apelqvist, Price, 2010; Gottrup, Apelqvist, Price, 2012; Jeffcoate et al., 2016; Price, Gottrup, Abel, 2014). The articles summarized in the Evidence section of this NCA provide examples of many of the problems encountered in this scientific arena.

Our analysis indicates that the reviewed studies have flaws that prevent us from understanding the true effectiveness of topical oxygen in the Medicare population. These flaws include:

- Lack of randomization, for at least one category of topical oxygen;
- Lack of effective blinding of patients, practitioners, and assessors, suggesting the potential for differential treatment of the intervention group versus the control group;
- Dependence on use of incomplete wound healing as the only outcome measured; Potential lack of systematic wound measurement;
- Lack of evidence for improvement in function among patients with chronic wounds; Limited evidence for durability of wound healing;
- Uncertainty about the standard of care being used in the reviewed studies; Lack of a defined run in period to help eliminate fast healing wounds;
- Small sample sizes; and
- Inappropriate statistical analyses

Below we analyze several characteristics of the studies reviewed that weaken the strength of evidence presented.

Outcome Measures: Though all of the reviewed studies had, at a minimum, the goal of wound healing, only the two observational studies by Blackman et al. (2010) and Tawfick & Sultan, (2009 and a publication of follow-up results in 2013) provided information about the extended durability of wound closure (recurrence). Unfortunately, the design and methodological weaknesses described below in these studies limit the utility of this information.

None of the investigations reviewed reported on patient functional abilities in relationship to the wounds which did or did not heal during the study period. Furthermore, we also note that except for the study by Yu et al., 2016 in which photographs were taken at weekly clinic visits, and the study by Niederauer et al., 2017, in which complete wound closure was confirmed by a blinded observer, none of the investigations gathered independent verification of the state of either the healed or unhealed wounds after treatment, a step we believe would have increased the validity of the outcomes.

Study Design: Two studies (Blackman et al., 2010 and Tawfick & Sultan, 2009 and 2013) that used an observational design provide us with limited guidance on who should be treated because of the biases inherent in unrandomized and unblinded research—selection bias, performance bias, and observer bias. While four trials used a randomized design, each had significant flaws that limit their utility in making coverage policy. Three of the RCTs were open label (Azimian et al., 2015; Driver et al., 2013; and Yu et al., 2016) —patients, providers and investigators were aware of the treatment allocation. In these studies, there may be observer bias, in which the treatment group is scrutinized more carefully than the control group; or there may be performance bias, in which the intervention group is treated differently than the control group. Either bias can result in overestimation of the treatment effect.

There was one double blinded placebo controlled study (Niederauer et al., 2015 and 2017) that demonstrates blinding can be accomplished in studies of topical oxygen. However, the authors' conclusions in the final study, are based on an analysis that effectively disrupted the randomization scheme, as almost 1/3 of the randomized patients were eventually dropped from the study during the final analysis.

Randomization is used in studies to evenly distribute both known and unknown prognostic factors so that differences found in outcomes between the study groups can be attributed to the experimental intervention only, and not confounding factors [Jüni, Altman, & Egger, 2001]. Therefore, in RCTs, before the interventions are applied, but after recruitment and the assessment of eligibility has been made, subjects are randomly assigned to receive one of the treatments being studied (Price et al., 2014).

While randomization is a means to eliminate bias, it is not sufficient in of itself to do so. An important feature of randomization is allocation concealment (Eskes et al., 2012). Allocation concealment implies that the assignment of individuals to the various arms of the study is unpredictable, allowing all subjects an equal chance of receiving the different treatments. Consequently, allocation concealment protects the randomization scheme. Therefore proper randomization implies that both researchers and study participants have no a priori knowledge of the group assignments (Brölmann et al., 2013; Suresh, 2011).

In the RCT studies analyzed, allocation concealment was poorly, if at all, reported. Only Azimian et al., 2015, stated that patients/families were blind to allocation, but not provider/researchers. In the RCTs performed by other investigators, allocation concealment methods were not specifically described, leaving the reader unsure if this design feature was considered. This omission creates a potential layer of selection bias that can tend to overestimate treatment effects (Suresh, 2011).

The analysis of the research by the intention to treat (ITT) principle also serves to protect the randomization process and its goal of obtaining an unbiased estimate of selecting one treatment over another. Under the ITT principle, research subjects are analyzed as members of the treatment group to which they were originally randomized, regardless of whether or not they complied with or received the assigned treatment. Therefore an ITT analysis will maintain the prognostic balance generated from the original randomized distribution of subjects. It avoids over-optimistic estimates of outcomes which can result from the removal of those subjects who do not comply with the assigned treatment as is likely to occur in real world practice (Detry & Lewis, 2014; Eskes et al., 2012; Gupta, 2011).

In the RCT performed by Azimian et al., 2015, there is confusion as to whether this principle was carried out. The article states: One patient from the intervention group and two patients from the control group were excluded. The sample size in this publication was 100, with fifty (50) subjects each in the interventional and control groups. A flow diagram was presented by the authors and indicates that the data may have been analyzed by intent to treat methodology, but does not demonstrate when the three patients were excluded from the study, thereby raising questions.

In the study by Driver et al., 2013, although it is assumed that all study participants were analyzed in the group to which they were originally allocated and that none withdrew or switched treatment protocols, this was not explicitly stated by the authors. In the 20-patient pilot RCT performed by Yu et al., 2016, the data of one subject from both groups was not included in the analysis.

In the RCT by Niederauer et al., 2015 the authors declared at the outset that the study was an interim analysis of a larger planned sample size. After determining that there was no treatment effect in the interim ITT analysis, the author conducted a series of *post hoc* analyses. The authors then provided results to support their hypothesis of a beneficial effect of oxygen that restricted their analysis to only those subjects with certain wounds described by closure rates, training periods and wound size, not originally specified in the analysis methodology. The equality of patient baseline characteristics produced by randomization was not upheld in these *post hoc* analyses.

In the report of the final account of this study (Niederauer et al., 2017), the authors note the above protocol amendments and stated that subjects who failed these criteria were removed from the study. Furthermore, as referred to above, of the 146 subjects randomized to either the Active or Sham groups, 46 were dropped from the final analysis, the majority due to "adverse events" that were not otherwise described. This loss of almost 1/3 of the study subjects jeopardized the strength and quality of the investigators conclusions.

In the two studies that were not randomized (Blackman et al., 2010; Tawfick & Sultan, 2009 and 2013), the investigative groups were determined by equipment availability, and/or patient preference. Thus, treatment allocation was unconcealed and the risk of between group differences affecting the outcome of the study, increased. Even though both studies did perform statistical analyses of selected demographic characteristics at baseline to demonstrate the success of their production of similar groups, unknown factors which were not analyzed, may still have confounded the results of the investigation.

The goal of randomization, that being to evenly distribute both known and unknown prognostic factors so that any differences found in outcomes between the groups studied can be attributed to the intervention only, can be overridden by unequally applied co-interventions (Eskes et al., 2012). For example, if researchers are aware of the assignment of the study participants, they may unintentionally provide one select group of patients with more or less care than that received by the comparator group. Furthermore, if patients are aware of their group intervention, they may be influenced to comply differently with study protocols or withdraw from studies altogether based on their perceptions of the treatment assigned (Bolton, 2016; Eskes et al., 2012; Price et al., 2014).

Such biases can be minimized when study participants, providers and outcome assessors are blinded as to the group to which a study subject belongs (Ryan, Hill, Prictor & McKenzie, 2013). However, the study by Niederauer et al., 2015 and 2017, was the only investigation reviewed in this body of evidence to use a sham (placebo) methodology to keep both providers and participants unaware of their intervention assignment. In all of the other studies reviewed, both patients and providers were aware of group assignments. While we recognize that blinding may be difficult to apply to all aspects of wound care research, we found at least one (1) randomized, double-blinded, parallel group, sham-controlled, multi-center study of topical oxygen applied for ninety (90) minutes, five (5) days per week on ClinicalTrials.gov. This investigation is actively recruiting at the time this analysis is being written (https://clinicaltrials.gov/ct2/show/NCT02326337); accessed 11/08/16). This trial and the study by Niederauer et al., 2015 and 2017, indicate that blinded investigations of topical oxygen therapies applied both continuously and intermittently, are attainable. We therefore believe that the use of this study design should be encouraged to increase the overall strength of evidence in the field.

Moreover, a randomized design can allow for the application of identical clinical management (as nearly as possible) to each group of the investigation and thereby will avoid differences in settings and treatment that, in themselves, may affect the results of the investigation. In this regard, we note that in the observational study by Tawfick & Sultan (2009 and 2013), the patients receiving TOT were inpatients as oppose to the control group who were outpatients. This differential in clinical management in itself, could easily influence the outcome of the investigation.

Sample size: It is important to power a study adequately in order to potentially detect a pre-defined and clinically significant outcome that is important to patients. In the RCT articles reviewed, only Azimian et al., 2015, performed a power calculation to justify the numbers of patients (n=100 hospitalized patients) that drove their conclusions. However, this study conducted its interventional and control treatments in an inpatient setting, lessening the generalizability to the Medicare population receiving treatment for chronic ulcers in an outpatient setting. Furthermore, only Niederauer et al., 2015 and 2017 and Yu et al., 2016, provided an outcome analysis by subgroups that would allow us to evaluate important factors influencing wound healing such as wound size, severity and duration. However, in the interim Niederauer study (n=84), the analyses were performed with post hoc criteria, which weaken any conclusions drawn because initial power calculations do not apply and can potentially unbalance a randomization scheme. The problematic concerns regarding the sample population in the 2017 study are described above. The Yu et al., 2016 study is a pilot of only 20 subjects and as such would be limited, among other reasons, by small total and subgroup sizes, as was the study by Driver et al., 2013 (n=17).

Generalizability: One of the goals of clinical research is to be able to extend trial results from a small sample onto the larger population, in this case, the Medicare population. In order to accomplish this, it is necessary to determine the applicability of the current evidence base to the Medicare beneficiary, not only in relation to the type, size and duration of wounds treated, but also in relation to the defining characteristics of the treatment regimen and the setting in which it is delivered (Juni et al., 2001). Randomization will control important covariates that are likely to affect results. It may also be necessary to make certain the appropriate populations are well represented as the outcomes of wound closure and patient function are studied. Furthermore, "cut points" which are deemed important to the results of the trial (e.g. wound size greater than XX), should also be identified prospectively (US Dept. of HHS, FDA, 2006).

Standard of Care: When evaluating the pertinent body of literature for this review, it was noted that the description of SOC was frequently insufficient to determine if both intervention and control groups were treated equally. For example in the article by Azimian et al., 2015, the authors stated that "…the control group received only the routine care of the study setting. Patients in the experimental group received the routine care of the study setting in addition to [topical wound oxygen therapy]". There was no complete description of the standard care and no run in period was described in this study.

The article by Blackman et al., 2010, stated that "Both groups received treatment based on current best practice guidelines, as decided in consultation with three participating surgeons. Dressing changes in the control group also were performed in the study center according to the physicians' recommendation at a minimum of twice a week. Each participant's wound was assessed weekly and debrided if necessary." The physician recommended care was not described.

The authors also state that patient adherence to protocol (particularly offloading) in a study of neuropathic DFU is an important factor in healing. All patients in the study were advised to offload. However, the authors state that poor adherence to this recommendation may be partly responsible for the positive findings in the study. In addition, a differential in treatment frequency can influence study outcomes. In this study, the oxygen group had daily treatments (5 times per week) while the control group was seen approximately twice per week. Furthermore, the authors noted debridements were performed, but described these procedures as follows, "All wounds were surgically debrided to a bleeding base; the number of debridements was not limited but usually debridements were performed once a week before treatment commenced". Again, no run-in period was described.

In the Driver et al., 2013 article, the authors noted that standard of care was reported as "...including debridement (once a week), boot offloading and moisture..." Although these investigators did document a formal, one (1) week washout period on SOC (not described in detail) before their subjects returned for the baseline visit and initiation of treatment, there was no *a priori* description of the conditions that would determine if the incident wounds were or were not persistent during this period.

The investigation by Niederauer et al., 2015, stated that, "All enrolled subjects received a standard wound therapy regimen consisting of wound cleansing, moist wound care, off-loading and, as appropriate, aggressive debridement." However the authors also stated that, "As the study progressed, it was found that increased emphasis needed to be placed on proper moist wound therapy principles such as debridement, keeping the wound moist and the number of dressing changes. Multiple initiatives, including regular conference calls ...were initiated to emphasize these points." The study design did have an *a priori* requirement that wounds experiencing more than 30% closure between screening and randomization would be excluded from the study.

The investigation by Niederauer et al., 2017, stated that, "All subjects in the Active arm received CDO therapy in addition to standard of MWT during the Treatment Period and all of those in the Sham arm received sham units (functioning CDO device with no oxygen going to the wound) and standard of care MWT during the Treatment Period." Further, dressings were described as follows, "Between visits, dressings were changed as needed by the subjects themselves or a relative/friend for the vast majority of subjects (>99%)."

In the study by Tawfick & Sultan (two articles 2009 and 2013), a more complete description of the type of wound dressings and the frequency of their changes was provided, but details regarding wound debridement were not. Also, no run in periods were described.

In the investigation of Yu et al., 2015, best practice was defined as iodine based dressings, regular sharp debridement of wounds and offloading using either a total contact cast for hindfoot and midfoot ulcers or a removable cast walker for forefoot ulcers. No run in period was described.

The vagaries of all of the above descriptions of SOC make it difficult to assess whether patients in the control and intervention groups in this body of literature were treated equally during their study experience. Furthermore, the lack of formal run in periods in most of the studies makes it difficult to determine if the wounds under investigation would have closed with the SOC alone or truly required a more elaborate intervention.

C. Health Disparities

A review of the articles discussed above in this decision memorandum reveals no analysis of clinical outcome by racial or ethnic categories. CMS also notes the absence of evidence about benefits or harms related to other population classifiers that have been associated historically with healthcare access or outcome disparities, such as gender, sexual orientation, religion, and age, and encourages additional studies in which such associations might be studied.

This lack of evidence about racial and ethnic factors and the response to TOT represents in our view an evidence gap that we encourage trial designers to consider when proposing clinical trial designs under this NCD. While recognizing that this consideration may complicate the design of appropriate clinical studies, we will nevertheless prefer clinical study proposals in which data on racial and ethnic factors are specifically collected and analyzed.

IX. Summary

Chronic wounds are prevalent in the Medicare population and cause a disproportionate burden on beneficiaries and their families and caretakers. CMS recognizes the need for new therapies that will heal wounds and the standardization of wound care in general. Overall, since the evidence on chronic wound healing from topical oxygen therapies has increased over the past few years, CMS believes a national non-coverage decision is no longer appropriate. CMS received 17 public comments and most of the commenters support this position. However, given the inability to identify the characteristics of chronic wounds that best respond to topical oxygen therapy and the type of patients' best suited to use this therapy, we are not able to define a patient population that would benefit from topical oxygen therapy in a national coverage determination at the present time. Ongoing research in the US and Europe and pending publications may provide additional evidence that may support a national determination in the future. CMS realizes that double blinded RCTs cannot always be used in order to answer questions regarding the outcomes of exposure to various treatment regimens in the wound care space. However we acknowledge that various investigative groups have, and are currently, studying the treatment of chronic wounds by TOT through randomized controlled trials. CMS reviewed a number of articles from commenters, considered all additional information and has determined to finalize the proposed decision.

X. Conclusion

The Centers for Medicare & Medicaid Services (CMS) received a reconsideration request to remove the coverage exclusion of Continuous Diffusion of Oxygen Therapy (CDO) from NCD Manual 20.29, Section C. This section of the NCD (Topical Application of Oxygen) considers treatment known as CDO as the application of topical oxygen and nationally non-covers this treatment.

After examining the evidence, CMS has decided that no National Coverage Determination is appropriate at this time concerning the use of topical oxygen for the treatment of chronic wounds. We will amend NCD 20.29 by removing Section C, Topical Application of Oxygen and Medicare coverage of topical oxygen for the treatment of chronic wounds will be determined by the local contractors.

See Appendix B for the manual language.

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[1] Personal communication from Dr. Mark Niederauer, COO, EO_2

[2] Personal communication from Dr. Mike Griffiths, CEO and President, Advanced Oxygen Therapy Inc. (AOTI Inc.)

APPENDIX A
General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups. Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely
- explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to that group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is to the extent that differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias). Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of that have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials

Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e. g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in that confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well- designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to that the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community

practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

APPENDIX B
Medicare National Coverage
Determinations Manual
Draft
This material represents a preliminary draft of Medicare's national coverage determination (NCD) manual. The information is subject to formal revision and formatting changes prior to the release of the final contractor instructions and publication in the Medicare National Coverage Determinations Manual.
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(Rev.)

20.29 – Hyperbaric Oxygen Therapy
(Rev.xx, Issued: XX-XX-XX; Effective/Implementation Dates: XX-XX-XX) 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.

A. Covered Conditions

Program reimbursement for HBO therapy will be limited to that which is administered in a chamber (including the one man unit) and is limited to the following conditions:

1. Acute carbon monoxide intoxication,
2. Decompression illness,
3. Gas embolism,
4. Gas gangrene,
5. Acute traumatic peripheral ischemia. HBO therapy is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.
6. Crush injuries and suturing of severed limbs. As in the previous conditions, HBO therapy would be an adjunctive treatment when loss of function, limb, or life is threatened.
7. Progressive necrotizing infections (necrotizing fasciitis),
8. Acute peripheral arterial insufficiency,
9. Preparation and preservation of compromised skin grafts (not for primary management of wounds),
10. Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management,
11. Osteoradionecrosis as an adjunct to conventional treatment,
12. Soft tissue radionecrosis as an adjunct to conventional treatment,
13. Cyanide poisoning,
14. Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment,
15. Diabetic wounds of the lower extremities in patients who meet the following three criteria:
    a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
    b. Patient has a wound classified as Wagner grade III or higher; and
    c. Patient has failed an adequate course of standard wound therapy.

The use of HBO therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30 days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present. Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of HBO therapy. Continued treatment with HBO therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.

B. Noncovered Conditions

All other indications not specified under §270.4(A) are not covered under the Medicare program. No program payment may be made for any conditions other than those listed in §270.4(A).

No program payment may be made for HBO in the treatment of the following conditions:

1. Cutaneous, decubitus, and stasis ulcers.
2. Chronic peripheral vascular insufficiency.
3. Anaerobic septicemia and infection other than clostridial.
4. Skin burns (thermal).
5. Senility.
6. Myocardial infarction.
7. Cardiogenic shock.
8. Sickle cell anemia.
9. Acute thermal and chemical pulmonary damage, i.e., smoke inhalation with pulmonary.
10. Acute or chronic cerebral vascular insufficiency.
11. Hepatic necrosis.
12. Aerobic septicemia.
13. Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease).
14. Tetanus.
15. Systemic aerobic infection.
16. Organ transplantation.
17. Organ storage.
18. Pulmonary emphysema.
19. Exceptional blood loss anemia.
20. Multiple Sclerosis.
21. Arthritic Diseases.
22. Acute cerebral edema.

C. Topical Application of Oxygen

Section C-Topical Application of Oxygen has been removed from NCD 20.29. Effective for dates of service on and after (DATE), Medicare Administrative Contractors (MACs) acting within their respective jurisdictions may determine coverage of topical application of oxygen for chronic non-healing wounds.

Cross reference: §270.5 of this manual.

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