DECISION MEMORANDUM

(This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.)

TO: Administrative File: CAG-00060N
Hyperbaric Oxygen Therapy (HBO) in the Treatment of Hypoxic Wounds and Diabetic Wounds of the Lower Extremities

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Subject: Coverage Decision Memorandum for Hyperbaric Oxygen Therapy in the Treatment of Hypoxic Wounds and Diabetic Wounds of the Lower Extremities

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This memorandum serves seven purposes: (1) provides a brief description of hyperbaric oxygen (HBO) therapy; (2) describes wound types covered by the existing Medicare policy on HBO therapy; (3) reviews the history of Medicare's HBO therapy policy as it applies to wounds; (4) analyzes relevant scientific and clinical literature on the use of HBO therapy for the treatment of hypoxic wounds and diabetic wounds of the lower extremities; (5) describes our position concerning physician supervision and physician credentialing; (6) announces our intent to not recognize hypoxic wounds as a distinct category of ulcers; and, (7) announces our intent to issue a positive national

coverage determination for HBO therapy for Wagner grades III and higher diabetic ulcers of the lower extremities that do not heal with standard wound therapy.

I. Clinical Background

Hyperbaric oxygen (HBO) therapy involves the inhalation of 100% oxygen at an elevated (i.e., greater than sea-level) atmospheric pressure. In the treatment of wounds, this is typically between 2 to 2.5 atmospheric absolute (ATA). Originally developed for the treatment of decompression sickness, HBO therapy is used by some physicians in the management of a variety of wound types. The theory is that wounds have a reduced oxygen supply that impairs wound healing. By delivering oxygen to the body under hyperbaric conditions, tissue oxygen levels are raised, and this, some believe, enhances wound healing. Some physicians use transcutaneous oxygen tension (TcPO2) with vascular assessment to help predict the healing potential in patients before they undergo HBO therapy. TcPO2 is a non-invasive quantitative assessment of the amount of oxygen in the tissue.

The delivery system for HBO uses either a monoplace (single person) chamber or multiplace (multiple person) chamber. In monoplace chambers, the entire chamber is pressurized with 100% oxygen to the desired ATA. Multiplace chambers, which can accommodate between 2-12 patients, are pressurized (using compressed air) and the patients breathe 100% oxygen either via mask, head tent, or endotracheal tube. In either setting, the time the patient spends in the chamber under hyperbaric conditions is decided by the attending physician and generally ranges from one to two hours.

Potential risks for patients undergoing treatment with HBO therapy include pressure related traumas (e.g., barotraumatic otitis, pneumothorax) and adverse effects due to oxygen toxicity (e.g., myopia, seizures). Some patients may experience claustrophobia due to the confined space of the chambers. Most adverse events are self-limited and resolve after termination of therapy. Patients with barotraumatic otitis may require the placement of myringotomy tubes.

II. History of Medicare's Coverage of HBO Therapy and Timeline of Recent Activities

Current Coverage Issues Manual (CIM) Policy: The Centers for Medicare & Medicaid Services (CMS) has a long-standing national coverage policy for the use of HBO therapy for certain indications. Section 35-10 of the Coverage Issues Manual (CIM) states that "HBO therapy is a modality in which the entire body is exposed to oxygen under increased atmospheric pressure." The CIM lists 14 covered conditions, nine of which involve wounds. All other indications are not covered.

Benefit Category Determination: CMS has determined that the appropriate benefit categories for HBO therapy are hospital outpatient services set forth in sections 1861(s)(2)(B) of the Social Security Act, physician services set forth in section 1861(q) and 1861(s)(1) of the statute, or incident to physician services under sections

1861(s)(2)(A) of the statute. HBO therapy is not a therapy service as defined in section 1832(a)(2)(C) of the statute.

Timeline of Recent Activities:

- On November 29, 2000, CMS accepted a formal request for a coverage determination on the use of HBO therapy in the treatment of hypoxic wounds that was submitted by the Undersea and Hyperbaric Medical Society (UHMS), the Hyperbaric Oxygen Therapy Association (HOTA), the American College of Hyperbaric Medicine (ACHM), and the International Hyperbaric Medical Association (IHMA).
- On January 17, 2002 CMS received a letter from the HOTA asking that the original request (HBO therapy for hypoxic wounds) be expanded to include HBO therapy of diabetic lower extremity wounds. CMS accepted the HOTA's request.
- On February 11, 2002 CMS decided to also consider physician supervision and physician credentialing of HBO therapy.
- On April 1, 2002, CMS received a letter from the IHMA suggesting the following subpopulation of patients were most appropriate for HBO therapy: (1) infected diabetic foot wounds, or (2) diabetic foot wounds with minimal or no signs of cellulites that are occurring in an extremity with peripheral vascular disease and a hypoxic TcPO2 < 35-40 mmHg on room air.
- On April 12, 2002, CMS received a letter from the UHMS suggesting the diabetic foot wound patient subpopulation they felt were most appropriate for HBO therapy. The UHMS defined these patients as Wagner grade III or greater diabetic foot wound with (1) evidence of persistent or progressive infection, or (2) evidence of dysvascularity as evidenced by abnormal pulse examination, other clinical parameters such as ischemic rubor or distal cyanosis, Doppler study, arteriogram, and TcPO2, or (3) evidence of failure to respond with demonstrable improvement after 8 weeks of appropriate conventional therapy.

III. FDA Status

The Food and Drug Administration (FDA) has granted monoplace and multiplace hyperbaric chambers clearance to market through their 510(k) process. Both monoplace and multiplace chambers were on the market prior to May 28, 1976, the enactment date of the Medical Device Amendments of the Federal Food, Drug and Cosmetic Act, and, therefore, were grandfathered under the statute. Later versions of these chambers were cleared under the 510(k) process, because they were substantially equivalent to the models on the market prior to May 1976.

IV. General Methodological Principles of Clinical Study Design

When making national coverage decisions, we evaluate relevant trials to determine whether or not the data is of sufficient quality to support a finding of clinical effectiveness. It has been our experience that many studies performed to evaluate wound treatments are of poor quality. CMS considers several generally accepted methodological principles when assessing a clinical trial. For example, we evaluate whether or not

general methods of study design have been followed, such as calculating sample size *a priori*, specifying inclusion and exclusion criteria, describing the process for the selection of study participants and the ways in which the consistency of this process was maintained, ensuring comparability of experimental groups at baseline to the extent possible, describing baseline characteristics of the participants, randomizing study subjects, masking of patients and investigators to the therapy administered to the extent feasible, describing co-interventions in detail, and performing appropriate statistical analyses, such as statistical tests of differences in baseline characteristics between the comparison groups. CMS evaluates other study design issues, which, in the case of wound care trials, include, among other things, the following:

- Has an appropriate outcome been used? For example, the optimal outcome to measure is the number and proportion of wounds that reach complete closure. Assessing partial healing provides less assurance of clinical effectiveness, because the clinical benefit of partial healing has not been demonstrated.

- Have appropriate measures of endpoints been selected, identified prior to initiating the trial, and standardized across all study sites? Have clear measurement criteria been provided? Has the process used to measure the selected outcomes and methods in which the study investigators insured the consistency of this process across different study sites been described?

- Was the appropriate patient population studied? For example, was the study performed on patients with the wound type for which coverage is sought?

- Has a single reference wound been selected for each patient? Generally, including multiple wounds on a single patient in the analysis provides limited additional data of value, because individual wounds are not independent.

- Have all subjects, regardless of the protocol arm to which they are assigned (e.g., investigational treatment, control), received good standard care and the same standard care procedures? Have the standard care procedures been described in detail?

- Have variables that may affect results been addressed in the analysis, including surface area, depth, and chronicity of wounds, condition of the subject, age of the subject?

- Has the effect of the therapy under investigation on the wound been evaluated? Adverse effects on healing can manifest in several ways, including tissue necrosis requiring more debridement, erythema, and discharge.

- Have adequate follow-up evaluations been performed? Clinical benefits from wound therapies can be short-lived and, therefore, of limited clinical value.

The FDA has also issued guidance that may be useful to investigators.[1] In addition, numerous useful texts have been published on general trial design and evidence-based medicine review of studies.[2]

V. Summary of Evidence

Hypoxic Wounds

The requestors submitted a list of 25 references to support their request for coverage of hypoxic wounds. The bibliographies of each of these references were reviewed to identify additional relevant articles. In addition, CMS also conducted a literature search using the terms "hyperbaric oxygen," "hypoxic wounds," and "hypoxia." The literature search was limited to English language articles involving humans. Review articles were excluded.

To aid CMS in its review, and to address a broader range of questions CMS had regarding HBO therapy, CMS requested a technology assessment (TA) from the Agency for Healthcare Research and Quality (AHRQ) on the use of HBO therapy. AHRQ contracted with the New England Medical Center (NEMC) to perform this TA. A list of questions to be addressed in this TA was created (see below). This TA, received in its final form on November 29, 2001, was reviewed and considered in our decision making process. Questions 4, 5,and 7 of the TA specifically addressed hypoxia in HBO therapy, and the TA's findings in regards to these questions are noted herein. The full list of questions NEMC addressed in this TA was the following:

1) Is there sufficient objective evidence that the use of HBO, as adjunctive therapy to standard wound care, aids in wound healing?
   a) Chronic refractory wounds
   b) Wound conditions covered under current Medicare Policy.
2) At what point in treatment should HBO therapy be introduced?
3) What other treatment modalities must be employed along with HBO therapy in order to maximize therapeutic benefits?
4) Wounds are generally classified based on diagnosis. Could wounds be classified based on a level of "hypoxia" rather than diagnostic specific (such as diabetic)?
5) Are there useful criteria to determine when an individual is likely to benefit from HBO therapy or when an individual will be non-responsive to HBO therapy?

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[1] *FDA Draft Guidance for Industry: Chronic Ulcer and Burn Wounds – Developing Products for Treatment* (June 2000).

[2] For example, Egger M., Smith G.D., Altman DG (eds.), *Systematic Reviews in Health Care: Meta-Analysis in Context*. BMJ Publishing Group, 2001; Gray J.A.M., *Evidence-Based Healthcare: How to Make Health Policy and Management Decisions*. Churchill Livingstone, 1998; Mulrow C., Cook D. (eds.), *Systematic Reviews: Synthesis of Best Evidence for Health Care Decisions*. American College of Physicians, 1998.

6) Are there absolute contraindications when considering HBO therapy in mono-place or multi-place chambers?
7) Which method of measuring tissue oxygen is most reliable and lends itself to standardization?

In the NEMC TA, eight studies were reviewed in addressing questions surrounding HBO therapy and hypoxic wounds (Faglia 1996, Faglia 1998, Zamboni 1997, Mathieu 1990, Wattel 1990, Wattel 1991, Smith 1996 and Schirmaer, 1996). Regarding the above questions, NEMC concluded that there was insufficient evidence to use hypoxia as a criterion for classifying wounds (question #4). Concerning question #5, NEMC noted that several studies considered whether tissue oxygen levels during HBO therapy were predictive of response, however, the TA did not make a conclusion regarding this issue. NEMC noted that question #7 could not be answered adequately by the studies reviewed.

In addition to the articles reviewed in the NEMC TA, the requestors, in a presentation submitted to CMS, identified four articles that they believed supported TcPO2 use in HBO therapy (Burgess 1982, Franzeck 1982, Pecorraro 1991, White 1982). Finally, CMS identified and reviewed four additional articles (Dooley 1996, Padberg 1995, Grolman 2001, Bunt 1996) and the requestors supplied CMS with an article that has been submitted for publication (Fife, submitted for publication).

To answer the question of whether HBO therapy improves net health outcomes in patients with hypoxic wounds, CMS believes that two issues need to be addressed in the literature:

1. are wounds adequately classified primarily on the basis of their tissue oxygen level?
2. are tissue oxygen levels predictive of wound healing following HBO therapy?

No articles were identified, either in the NEMC TA or in CMS's review, in which wounds were primarily identified as hypoxic or classified based on their oxygen level. Indeed, no articles were identified in which tissue oxygen level was used as an inclusion criterion. All of the studies reviewed classified wounds by their disease etiology.

All of the articles the requestor submitted, all of the articles NEMC reviewed, and all of the articles CMS identified, considered, in some manner, the relationship of tissue oxygen level to wound healing. While that does not specifically answer the question of whether wounds can be classified primarily by oxygen level, it could potentially answer the second question posed above. Therefore, these articles were reviewed. The four articles used by the requestor in a presentation to CMS to support the use of TcPO2 in HBO therapy (Burgess 1982, Franzeck 1982, Pecorraro 1991, White 1982) did not address TcPO2 measurements in the course of treating wounds with HBO. As such, their findings were not felt to be applicable to the question of HBO use in hypoxic wounds, and they will not be further addressed in this decision memorandum. Four of the articles (Bunt 1996, Faglia 1996, Faglia 1998, Wattel 1991) measured TcPO2 at some point in their study, but provided no discussion of the ability of TcPO2 to predict healing with

HBO therapy. Therefore, they were not useful in drawing conclusions about the role of TcPO2 in HBO therapy. Eight studies (Bouchour 1996, Dooley 1996, Fife submitted, Grolman 2001, Mathieu 1990, Padberg 1995, Smith 1996, Wattel 1990) did provide some discussion on the use of TcPO2 in predicting response to HBO therapy for wounds of various etiologies. The relevant findings of these eight studies are summarized below.

Of these eight studies, Bouchour et al (1996) was the only randomized controlled clinical trial (RCT). Thirty-six patients with crush limb injuries were randomized to either HBO or non-HBO therapy within 24 hours of initial evaluation and initial surgical procedure. Patients in the HBO arm received therapy at 2.5 ATA twice daily (90 minutes each session) for 6 days. Non-HBO patients were placed in an HBO chamber and breathed room air via facemask at 1.1 ATA for the same time, frequency, and duration. Thus, they served as a placebo-control. The study's primary endpoints included wound healing without tissue necrosis, need for new surgical procedures, time to heal, and length of hospitalization. Prediction of outcome based on initial TcPO2 was not a primary endpoint. Nonetheless, the authors stated that when they looked at completely healed limbs and compared the TcPO2 in the injured limbs to the TcPO2 in the contralateral non-injured limb, the ratio was constantly greater than 0.9.

The remaining seven articles were either prospective or retrospective case series. In six of these articles, the authors concluded that some aspect of TcPO2 was predictive of the wounds' outcome with HBO therapy. However, as the following review of the articles discusses, there were no typical TcPO2 values or indices consistently used to predict outcome.

Grolman (2001) followed 36 patients with non-healing ulcers to investigate the hypothesis that a difference in TcPO2 measured near the lesion while breathing room air, and then while breathing 100% O2 at normobaric pressure, was predictive of wound healing. The authors concluded that patients whose TcPO2 increased by more than 10mmHg on 100% had a 70% chance of healing while those patients whose TcPO2 changed by less than 10 mmHg had only an 11% chance of healing.

Fife's study (submitted) was a retrospective record review of 1006 patients with diabetic ulcers treated with HBO. Fife et al concluded that TcPO2 levels recorded on room air, or on oxygen but at sea level were not predictive of outcome. However, TcPO2 measurements taken when the patients were breathing oxygen under hyperbaric conditions reliably predicted the outcome in 74% of patients and was associated with a positive predictive value of 58%. Fife noted the tissue oxygen level threshold most associated with a positive outcome was 200 mm Hg.

Mathieu's study (1990) was a case series involving 23 patients with post-traumatic limb wounds. TcPO2 measurements were performed in the normal and traumatized limbs and the ratio of values was compared. The authors found that if the ratio was less than 0.4 the TcPO2 sensitivity in predicting outcome was 100% and the specificity was 94%.

The case series by Padberg (1996) reported on 112 patients with ischemic lower extremity wounds due to diabetes or chronic renal failure. Patients were evaluated using TcPO2, arterial segmental pressure (ASP) and arterial segmental indices (ASI) to determine which readings provided objective risk stratification for healing of these wounds. The TcPO2 values which predicted healing varied from 10 to 40 mm Hg. Baseline values of TcPO2 were not discussed. Using multivariate regression analysis, TcPO2 was superior to both ASP and ASI in predicting healing, however, on univariate analysis ASP and ASI were as predictive of healing as TcPO2.

Smith et al (1996) reported a case series of 26 patients with chronic leg wounds and noted that patients with a TcPO2 of >800 torr at 2.4 ATA had a greater improvement in wound score as compared to patients with a TcPO2 measurement <800 torr.

Wattel et al (1990) reported a case series of 20 patients with either arterial or diabetic lower extremity wounds and noted that TcPO2 measurements distal to the wound were a reliable predictor of outcome. All patients with TcPO2 < 100 mm Hg distal to the wound failed to improve while all patients with TcPO2 > 100 mm Hg distal to the wound healed.

Not all of the studies, however, noted a strong predictive role for TcPO2. Dooley et al (1996) investigated 60 patients with chronic lower extremity wounds and performed TcPO2 before and after a regimen of HBO therapy. They noted that while HBO therapy reduced periwound edema, they were not able to identify a single TcPO2 measurement that was predictive of changes in periwound edema or overall wound severity.

Finally, CMS did not receive any public comment, other than from the requestors, either supportive or not supportive of HBO therapy's use in treating hypoxic wounds.

Diabetic Wounds of the Lower Extremities

The requestors provided CMS with a list of 129 references they believed supported the use of HBO therapy in treating lower extremity diabetic wounds. Each of these references was reviewed. The majority were either non-human studies, reviews in textbooks, review articles, or did not specifically address HBO treatment of diabetic wounds. Eleven articles directly investigated the use of HBO therapy in treating diabetic lower extremity wounds (Abidia 2001, Baroni 1987, Davis 1987, Doctor 1992, Faglia 1996, Kalani 2002, Oriani 1990, Oriani 1992, Stone 1995, Wattel 1991, Zamboni 1997). The bibliographies of these eleven articles were reviewed in an attempt to identify additional studies. Also, a literature search was performed using the search terms "diabetes," "diabetic," "wound," "leg," "foot," "hyperbaric oxygen," and "HBO." This additional search was limited to English language articles that involved human subjects (either clinical trials or case series). CMS identified one additional article (Ciaravino 1996) through these other search methods.

The NEMC TA, discussed earlier under hypoxic wounds, also contained information on chronic non-healing wounds, which included diabetic ulcers, and was

considered in this assessment of HBO therapy in diabetic lower extremity wounds. Two additional technology assessments (Blue Cross Blue Shield 1999 and Australian Medicare Service Advisory Committee (MSAC) 2000) discussed diabetic ulcers and were reviewed. Finally, a 1999 consensus statement on diabetic foot care written by the American Diabetes Association (ADA) was considered in our assessment.

Two of the twelve clinical articles CMS reviewed were RCTs (Doctor 1992, Faglia 1996), one was a combination of a randomized and non-randomized trial (Kalani 2002), seven were case series articles with or without a comparison group (Baroni 1987, Ciaravino 1996, Davis 1987, Oriani 1990, Oriani 1992, Wattel 1991, Zamboni 1997), and two were abstracts (Abidia 2001, Stone 1995).

Doctor et al (1992) was a RCT designed to study the effect of HBO therapy in treating chronic diabetic foot lesions and to assess the effect of HBO therapy on wound culture results. Thirty diabetic patients with chronic foot ulcers were enrolled. The authors did not define "chronic foot ulcer," and did not provide information on the length these wounds had been present or what the patients' past wound care had been. Patients were randomized to receive either HBO treatment plus standard wound care or standard wound care alone. Regular debridement and drainage of abscesses was done in all patients. Patients received four HBO sessions over a 2-week period. HBO therapy was administered at 3 ATA for 45 minutes each session. All patients received a baseline wound culture and then a wound culture at the end of the two-week study. The baseline wound sizes or vascular status was not reported, and it is not clear if follow-up exams or the decision to amputate were performed in a masked fashion.

In the HBO group, 2/15 (13%) of patients had a major amputation (i.e., amputations of more than the forefoot resulting in the patient's inability to ambulate on the extremity without a prosthesis) as compared to 7/15 (47%) of patients in the standard care only group. This difference was statistically significant ($p<0.05$). The number of positive wound cultures also decreased with HBO treatment. In the HBO group 19 positive cultures were noted pre-study (some patients had more than one bacteria grow out on a culture and this resulted in the number of positive cultures being greater than the number of patients) while at the end of two weeks the number in the HBO group was only three. Conversely, there were 16 positive cultures in the standard wound care group pre-study and 12 post-study. This difference was significant with a p value of <0.05. The control of wound bacteria growth was most notable for Pseudomonas and E. Coli.

The 1996 study by Faglia et al was a RCT designed to evaluate the effectiveness of HBO therapy in decreasing major amputations in diabetics hospitalized for severe foot ulcers. Seventy consecutive diabetics patient who were admitted to the authors' institution for treatment of a foot ulcer during a defined two-year period were enrolled. Patients were randomized to receive either HBO therapy plus standard wound care or standard wound care alone. One patient randomized to HBO refused treatment and one patient randomized to the non-HBO group died within the first week of treatment. Both of these patients were excluded from the data analysis. The remaining 35 HBO-treated patients and 33 standard wound care only group were included in the data analysis.

After randomization there were no significant differences between the HBO and non-HBO treatment groups in baseline characteristics. All patients underwent an initial, aggressive debridement followed by twice daily dressing changes as long as necrosis or exudates were present. As the wounds healed, the frequency of dressing changes was decreased, and debridements were done periodically whenever necrotic tissue was present. All patients were treated with systemic antibiotics, had their blood sugars optimized, and were off-loaded. Patients in the HBO group underwent daily 90-minute treatments at 2.5 ATA. A necessary sample size of 34 patients in each group was calculated in order to detect a one-third decrease in major amputation rate with an alpha error of 0.05 and a power of 0.80.

Patients in the HBO group underwent an average of 38$\pm$8 sessions. The only reported complications associated with HBO therapy reported were two cases of barotraumatic otitis (2/35 or 6%). This otitis did not cause an interruption in these two patients' HBO therapy.

Faglia et al grouped the wounds in their study by Wagner grade. Wagner grades are a commonly used classification system and include five grades (Wagner 1981, Cianci 1997). The five grades are defined as follows: grade 0 = no open lesion; grade 1 = superficial ulcer without penetration to deeper layers; grade 2 = ulcer penetrates to tendon, bone, or joint; grade 3 = lesion has penetrated deeper than grade 2 and there is abscess, osteomyelitis, pyarthrosis, plantar space abscess, or infection of the tendon and tendon sheaths; grade 4= wet or dry gangrene in the toes or forefoot; grade 5 = gangrene involves the whole foot or such a percentage that no local procedures are possible and amputation (at least at the below the knee level) is indicated.

Table 1 details the major amputation rate in the HBO and non-HBO groups as well as the major amputation rate by Wagner grade. The authors noted that the rate of major amputations was significantly greater in the non-HBO patients. When analyzed by Wagner grade, the group that demonstrated the greatest benefit from HBO was those with Wagner grade IV wounds.

Table 1

	HBO	Non-HBO	P value
Maj. Amputations (all Wagner grades)	3/35 (9%)	11/33 (3%)	0.016
Maj. Amputations- Wagner grad II	0/4	0/5	n/a
Maj. Amputations- Wagner grade III	1/4(25%)	0/8	0.33
Maj. Amputations- Wagner grade IV	2/22 (9%)	11/20 (55%)	0.002

Faglia et al performed a multivariate analysis on the variables they found to be associated with major amputation in the univariate analysis. The authors stated that this multivariate analysis showed a protective role of HBO with an odds ratio of 0.084 (p=0.033 and 95% CI 0.008-0.821).

Kalani et al (2002) was a combination of a randomized and non-randomized clinical trial. These authors investigated the use of HBO therapy in treating chronic diabetic foot ulcers. While the authors did not state what the Wagner grade of the investigated wounds was, they did state that none of the wounds had deep infection or were gangrenous, and, as such, most likely were Wagner grade II or lower. Thirty-eight patients were included in their study – 17 received HBO therapy and 21 were treated with standard wound care. The first 14 patients enrolled in the study were randomly allocated to HBO or standard care, and this produced 7 patients in each group. For two years the study was interrupted because of lack of availability of HBO therapy. When the study was restarted, the remaining patients were allocated to treatment groups in a non-randomized method depending on HBO availability. Each patient was followed-up for at least three years. The authors reported that there was no difference between the HBO and non-HBO treated patients in terms of baseline blood pressure, hemoglobin A1c (HgA1c) levels, diabetes duration or peri-wound tissue oxygen level. There was a statistically significant difference between the number of patients with insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) in the two groups. Of the HBO patients 65% (11/17) had IDDM as compared to 43% (9/12) in the non-HBO group ($p<0.05$). All of the patients had a baseline vascular work-up that included angiography and evaluation by a vascular surgeon. None of the patients enrolled were eligible for surgery. All patients received the same standard wound care including off-loading, diabetic control, blood pressure control, and nutritional assessment. The patients in the HBO group underwent 90-minute sessions five times a week and received between 40-60 sessions.

Kalani et al reported that at the three-year follow-up point, 76%(13/17) of the HBO-treated patients were healed as compared to 48% (10/21) of the standard-care group. No information on statistical significance was presented. Amputations were necessary in 2/17 (12%) of the HBO-treated group as compared to 7/21 (33%) of the standard care-only group (no statistical data presented on this difference). Finally, of those wounds that healed, the mean time to healing was 15 ± 7 months in the HBO group and 15 ± 4 months in the standard care group ($p=0.8$).

The case series by Baroni (1987) reported on 28 diabetic leg ulcer patients referred to their clinic during a two-year period. Gangrene was noted in 23 of the patients while the authors noted that five patients had "perforating ulcers." They stated that their preliminary observations convinced them that HBO therapy was beneficial in diabetic patients, and, accordingly, they decided to use this treatment on all of their patients. Ten of the 28 patients, however, refused HBO therapy (due to claustrophobia or fear of earache). These ten patients received standard wound care leaving 18 patients in the HBO group. The authors stated that all patients received daily debridement of necrotic tissue, however, further discussion of the wound care received by the groups was not provided. The two groups were not statistically different in terms of baseline lesion size, presence of infection, or diabetic control as defined by HgA1c or mean blood glucose levels. The authors stated that patients were evaluated for lower extremity vascular disease but did not provide information on how this assessment was done or what the results were. Although baseline ulcer size was reported, the Wagner grade was not.

The outcome reported was the number of ulcers healed. The authors, however, did not define what constituted complete healing. Also, it is unclear if those who assessed the healing status of these wounds were masked to the treatment group. Of those patients who underwent HBO therapy, 16/18 (98%) had their ulcers heal within 62±30 days and after 34±22 sessions. Conversely, one of the ten (10%) patients in the standard wound care group had their ulcer heal. The authors did not state how long it took for this patient's ulcer to heal. This difference of 98% versus 10% healing between the groups was statistically significant (p=0.001).

The two articles by Oriani et al (1990 and 1992) were also performed at the Milan center where the Baroni and Faglia (1996) studies were conducted. Indeed, Oriani was an author in all of these studies. The 1990 and 1992 Oriani studies were case series articles, and their dates of patient enrollment overlapped with each other and with the Baroni study. It is unclear if the patients represented in each of these studies constituted a separate group or if some of them had been reported in past studies. The Faglia et al 1996 study enrollment dates did not overlap with any of these three other studies.

Oriani et al (1990) stated that beginning in 1982 they recommended HBO therapy to all diabetic patients with necrotic leg ulcers. In their study they provided information on 80 diabetic foot ulcer patients - 62 were treated with HBO and 18 patients received standard wound care only. These 18 patients served as a comparison group after refusing HBO therapy. The authors stated there was no difference between the two groups of patients in terms of vascular disease. However, the manner by which patients' vascular status was evaluated, and the degree of vascular disease noted, were not discussed. Oriani noted that the ulcers in both groups were curettaged each day although there was no further description of wound care provided to either group. HBO treatments were administered at 2.8 ATA (length not stated) six days a week until granulation tissue formed and then five days a week until healed.

The authors assessed two outcomes – number of ulcers healed and the number of patients who required amputation. A definition of when healing occurred was not provided, and it is not stated if the amputations reported were only major ones (i.e., beyond the forefoot). Amongst the HBO-treated group, 59/62 (95%) ulcers healed versus 12/18 (67%) in the group that did not receive HBO (p value not stated). In regards to the number of amputations, 3/62 (5%) HBO patients as opposed to 6/18 (33%) of the non-HBO patients underwent an amputation ($p<0.001$).

In Oriani et al's 1992 study, they reported their experience using HBO therapy over a 10-year period. Since this would have started in 1982, the same time that their 1990 study began enrolling patients, it is highly likely that patients reported in this 1992 study were also reported in their earlier article. The authors, however, did not address this.

Oriani et al reported on 172 diabetic patients with 192 lower extremity lesions. It is unclear how long the wounds had been present prior to beginning HBO therapy. Forty-

one patients were excluded from their analysis. In describing why these patients were excluded, the authors stated that it was "because they were given only 12 HBO sessions (or due to general complications, subjective reasons, or poor cooperation with the attending physician)."[3] Exactly how many were excluded for each reason was not specified. The requirement that patients have at least 12 HBO sessions was the result of the authors' observation that patients with fewer than 12 sessions did not show a benefit. Unlike their 1990 study, the 1992 study was without a comparison group. They did not present baseline data on wound size or severity of vascular disease. They did define a positive outcome from HBO therapy as occurring in one of three scenarios, (1) wound either completely healed or minimal skin lesions destined to heal, (2) demolitive surgery that was less than expected prior to HBO therapy, or (3) no major amputation required. It is unclear if the provider who assessed the wounds or who made the decisions regarding surgery was masked to the fact that patients were undergoing HBO therapy.

The authors stated that the average number of HBO sessions in this cohort was 40 (range 12-186). Of the 151 lesions that remained in their analysis following the aforementioned exclusions, 130 (86%) had a positive outcome. Oriani also stated that the number of HBO sessions correlated to the size of the lesion but not to the duration of disease. No data or r-values were given to support this.

The remaining four case series articles were conducted at different centers by different groups of investigators. The article by Davis (1987) was a retrospective case series that reported on 168 patients with diabetic foot ulcers who underwent HBO treatment. There was no information provided on how patients were selected or what their baseline characteristics were. Davis reported that patients received HBO daily for 30-60 days and that 30% failed to respond to treatment and required major amputation.

The prospective case series by Wattel et al (1991) enrolled every diabetic foot ulcer patient who was referred to their unit for HBO treatment during a two-year period. Fifty-nine patients were treated with HBO at 2.5 ATA for 90 minutes twice daily five days a week. There was no comparison group. The presence and severity of vascular disease, and the wound size/stage at baseline, was not stated. The authors measured TcPO2 levels near the wound under three conditions: room air, 100% normobaric oxygen, and 100% oxygen at 2.5 ATA. The mean treatment duration was 3 ± 2 weeks and the mean number of HBO sessions was 29 ± 19. In the abstract of the article, the authors stated that 52/59 (88%) ulcers healed, but in the body of the paper it stated that 48/59 (81%) ulcers healed. In addition, in the abstract it stated that 7/59 (12%) patients required amputation, but in the body of the paper the number of amputations was reported as 11/59 (19%). These discrepancies were not discussed and p values for these differences were not provided. Information on the comparability of the vascular status of the healed and failed groups was not provided.

Zamboni et al (1997) prospectively evaluated the effect of HBO therapy on the healing of diabetic lower extremity wounds in 10 consecutive patients with chronic foot wounds. Five of the patients refused HBO (two due to claustrophobia and three because

[3] Oriani 1992, page 217.

they lived too far to travel to the center for daily treatments) and served as a comparison group. Three of the control patients and four of the HBO-treated patients had evidence of osteomyelitis. The authors stated that there were no significant differences in characteristics such as baseline wound size (p values were not provided). The article also noted that all patients underwent a prior evaluation by a vascular surgeon. Two patients in the control group had prior lower extremity bypass surgery and "all other patients were without significant macrovascular disease amenable to surgical intervention."[4] The actual manner by which patients' vascular status was evaluated, however, was not provided. In addition, baseline Wagner grades were not reported.

HBO sessions were done five days a week at 2.0 ATA for 120 minutes each. All patients underwent an initial debridement and a standardized wound care regimen of twice daily dressing changes. A nurse masked to the treatment group measured the wounds weekly. Patients underwent a total of 30 sessions. After the course of HBO, each patient was followed for four to six months.

Zamboni defined the study's endpoint as complete healing of the wound or need for major amputation. During the course of the study there was a greater reduction in wound area in the HBO group as compared to the non-HBO patients ($p<0.05$). Likewise, after the four-six month follow-up, only 1/5 (20%) of the HBO patients as compared to 4/5 (80%) of the non-HBO patients had persistent, non-healing wounds ($p=0.0578$).

In the retrospective case series by Ciaravino et al (1996) the 54 patients reviewed had either peripheral vascular disease or diabetes as their underlying disease. The authors stated that in reviewing these patients' charts, 17 patients had their wounds classified as diabetic although many of the other 37 patients whose wounds were classified as due to peripheral vascular disease also had diabetes. Thus, the etiology of the wounds was not clear. In addition, the method by which patients were selected for HBO treatment and the underlying disease severity in these patients was not stated. Overall, the authors noted that 43/54 (80%) of the patients showed no improvement with an average of 30 (range 5-81) HBO sessions.

Although the flaws in this study's methodology make it difficult to use it to draw conclusions regarding the efficacy of HBO therapy, what was notable was the high number of HBO-related complications reported. In all of the other studies reviewed in this decision memorandum, only minor problems, such as barotraumatic otitis (sometimes requiring myringotomy tubes) or claustrophobia were reported, and then occurring in less than one percent of patients. Ciaravino et al, however, reported that 42% (23/54) of their patients had barotraumatic otitis and 17 of these (74%) required myringotomy tubes. Also, 4/54 (7%) patients had a cardiac arrhythmia while in the chamber, one patient (2%) had a seizure, and one (2%) had a stroke while under hyperbaric treatment. The authors did not address the high rate of complications reported in their patients as compared to the complication rates reported in other studies.

[4] Zamboni 1997, p.176.

CMS identified two abstracts that reported on the use of HBO therapy in treating diabetic foot wounds. Abidia (2001) studied 18 patients with non-healing leg ulcers who were randomized in a placebo-controlled study. Patients received either HBO treatment with 100% oxygen at 2.4 ATA or room air at 2.4 ATA. Each group received 30 treatments, each for 90 minutes. The authors reported that at 12-weeks, 13/19 (68%) HBO ulcers had healed versus 4/14 (29%) control ulcers (no p value given). They also reported that there was no difference in the major amputation rate between the groups.

Stone et al provided a retrospective review of 469 consecutive patients with diabetes treated at a referral wound care center over a 33-month period. Eighty-seven of the patients received HBO therapy while 382 received standard care only. The authors stated that the patients in the HBO group had more and larger wounds than the standard care group. The limb salvage rate was 72% in the HBO group versus 53% in the standard care group ($p<0.002$). Both of these abstracts provided limited information on their methodology, patient selection, inclusion criteria, baseline characteristics, and results.

Finally, CMS received one public comment from a physician who uses HBO therapy to treat diabetic lower extremity wounds. This practitioner was supportive of HBO's use in these patients. The practitioner did not offer any additional scientific evidence.

Summary of the Technology Assessments and American Diabetic Association (ADA) Consensus Statement

The NEMC TA included a section that reviewed articles on chronic non-healing wounds - both diabetic and non-diabetic ulcers. NEMC identified two randomized clinical trials (Doctor 1992, Faglia 1996) and four case series articles (Baroni 1987, Faglia 1998, Oriani 1990, Zamboni 1997). With the exception of the 1998 Faglia study, these articles were also considered by CMS in our review. The Faglia 1998 article was not considered relevant to our decision memorandum because it investigated the role of angiography as a prognostic indicator for amputation in diabetic foot ulcers and did not investigate the use of HBO to treat such ulcers. NEMC concluded that HBO aids in the healing of chronic non-healing wounds. However, they also stated that direct evidence on non-diabetic chronic non-healing wounds was not sufficient, thus it appears that their conclusions of HBO's use in chronic non-healing wounds was primarily directed at diabetic wounds. NEMC had not been asked to nor did it address in which subpopulation of patients with chronic non-healing diabetic ulcers does HBO therapy aid in healing. In addition, the TA did not assess the methodology used by the studies that were reviewed.

The two other TAs reviewed (Blue Cross Blue Shield 1999, Australian Medicare Service Advisory Committee 2000) considered the same articles reviewed by NEMC and considered by CMS in this decision memorandum. These two TAs concluded that there was sufficient evidence to support the use of HBO therapy in chronic non-healing wounds (Blue Cross Blue Shield) and diabetic wounds (MSAC). The Blue Cross Blue Shield assessment reviewed the finding of the articles but did not assess the methodology

of these studies. The MSAC assessment did note methodologic flaws with some of the studies - flaws that CMS has noted in this decision memorandum.

The ADA published a consensus statement on diabetic foot wound care in 1999 in the journal *Diabetes Care*. The ADA convened a multidisciplinary 8-member panel that heard presentations from 25 experts on different aspects of diabetic foot wound care. In regards to the effectiveness of HBO therapy for treating diabetic wounds, the ADA consensus statement noted that there were no randomized controlled trials supporting the use of HBO to treat diabetic foot wounds. The consensus statement, however, did not detail what articles they identified and reviewed. It should be noted that this consensus statement was produced in 1999 after the publication date of the 1996 Faglia et al study, which was a RCT. The statement concluded that:

> "There are no randomized controlled trials supporting the use of hyperbaric oxygen therapy to treat neuropathic diabetic foot wounds. Given the limited evidence of positive results in select groups of patients with severe wounds, additional randomized clinical trials are warranted. It is reasonable, however, to use this costly modality to treat severe and limb- or life-threatening wounds that have not responded to other treatments, particularly if ischemia that cannot be corrected by vascular procedures is present."[5]

The authors did not define what was meant by a "select group" of patients.

Physician Supervision and Credentialing

In July 1999, CMS proposed changing the national coverage policy on HBO to include physician supervision and credentialing. At the time, the agency received many comments addressing these topics and revision to the existing policy was postponed. We have now been asked by physicians and contractors to provide guidance on the issues of physician supervision and credentialing and CMS has agreed to revisit these issues.

The objective of our review was to acquire information from professional and other technical sources concerning the safety, operations, procedures and technology of hyperbaric medicine in order to gain more knowledge about risks that may be involved in the delivery of HBO therapy. To locate the most credible sources we performed literature searches and contacted experts in the fields of fire safety, hyperbaric technology, certification for hyperbaric physicians, nurses and technicians, and professional associations. On February 11, 2002, we revised the HBO tracking sheet on the CMS website to reflect our renewed interest in these issues. We indicated our intention to evaluate the need for these services as a part of our review and requested public comment.

For information pertaining to the safety of HBO chambers we gathered information from the FDA, the National Fire Protection Association (NFPA), the Clinical

[5] Ibid, page 1359.

Hyperbaric Medicine Department at Brooks Air Force Base, the Undersea and Hyperbaric Medical Society, and the National Board of Diving and Hyperbaric Medical Technology.

The first safety codes for HBO therapy were developed by the NFPA in 1968 and were based on safety guidelines developed for the use of various gases and oxygen in hospital operating rooms. The NFPA has oversight of non-diving HBO facilities designed for medical therapeutic use. No fatalities due to fire have been reported in facilities falling under the jurisdiction of NFPA.

The FDA Enforcement Report, dated August 14, 1996, reported an explosion with fatalities within a monoplace chamber and listed the reason for the mishap to be a failure to follow labeled safety procedures. Letters from the FDA to the manufacturer urged users to review the safety and emergency procedures outlined in the manufacturer's operations manual. In international reports of safety in hyperbaric chambers it has been noted that although hyperbaric chamber fires are rare, they are usually fatal to inside occupants.

At the 2001 UHMS Gulf Coast Chapter meeting James C. Sheffield, BBA, CHT and Paul Sheffield, PhD, CHT reported on 21 years of operation at three wound care and hyperbaric facilities in Texas. They performed a retrospective analysis on data extracted for 166,701 treatments for 8,078 patients. There were 1,382 complications that resulted in removal from the chamber. The three main reasons for removal from treatment were listed as ear barotraumas (44/10,000 exposures), sinus barotraumas (8/10,000 exposures) and claustrophobia/anxiety (7/10,000 exposures). Other complications were attributed to existing medical conditions and included nausea and vomiting, hypoglycemia, abdominal pain and diarrhea, seizures and chest pain. According to the report, none of the listed complications resulted in a fatality. During our review of articles pertaining to hypoxia in wounds and the use of HBO therapy for treatment of diabetic wounds we found generally minor complications, such as ear barotraumas, as described above.

As a result of our review, CMS has been unable to find current statistical evidence pertaining to the safety or the adverse effects precipitated by the administration of HBO therapy in a multiplace or monoplace chamber.

The need for physician supervision is based on considerations for appropriate and safe administration of HBO therapy. Routinely, this treatment is prescribed as an adjunct therapy when standard wound care has failed to produce satisfactory results. In October 2000 the Department of Health and Human Services, Office of Inspector General (OIG) issued a report: "Hyperbaric Oxygen Therapy: Its Use and Appropriateness." The OIG review indicated that physician attendance is strongly correlated with quality of care. The report also suggested that training requirements might provide a means of promoting quality care.

On February 11, 2000, a revision was made to the CMS Coverage Policy web site tracking sheet for HBO therapy in which we asked for public comment on the issues

of physician supervision and credentialing. Nine comments were received from individual practitioners, but they provided no clinical data. All of the comments received by CMS were supportive of the clinical concepts and guidelines put forth by UHMS in a 1999 document:

> *"The physician attending a patient undergoing hyperbaric oxygen treatment must be present during all critical and key portions of the treatment and be immediately available to furnish services during the entire treatment. The responsibility for determining which components of treatment are critical and key portions will vary with each patient and must be determined by the physician attending the patient undergoing hyperbaric treatment based upon the physician's training and experience."*

In reaching our conclusions we have given consideration to all of the comments forwarded to CMS.

VI. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. § 1869(f)(1)(B). 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." § 1862(a)(1)(A).

As previously mentioned in this decision memorandum, HBO therapy for hypoxic wounds or diabetic wounds of the lower extremities falls within a Medicare benefit category. In addition, no statutory provision specifically precludes payment. Finally, we have fully examined the medical and scientific evidence submitted with the request for a national coverage decision as well as additional evidence that we have identified.

Hypoxic Wounds

CMS believes that in order to cover HBO therapy for hypoxic wounds, the literature must demonstrate:

1. that wounds can be primarily classified based on their tissue oxygen level. To this end, the literature must show that response to HBO therapy is coupled to tissue oxygen level irrespective of wound etiology, and
2. that transcutaneous oxygen tension (TcPO2) values are predictive of a wound's response to HBO therapy.

No studies were identified that classified wounds based on their TcPO2, and there

is no evidence that wound care providers classify wounds by tissue oxygen level. In the past, CMS has taken the position that wounds of different etiologies cannot necessarily be considered the same in terms of healing, and we have requested that other wound care treatments be investigated on an etiology-based approach (i.e., diabetic wounds, pressure ulcers, venous ulcers, etc.).[6] CMS believes that in order for coverage of HBO therapy to be extended to hypoxic wounds evidence must be presented that demonstrates wounds of similar tissue oxygen pressure respond in the same manner to HBO irrespective of their disease etiology.

Several studies did report on the predictability of TcPO2 in the healing response to HBO therapy. These studies, as discussed earlier, were inconclusive in this regard. The majority of the studies were case series articles with unclear patient selection criteria, failure to set the predictability of TcPO2 in wound response as a primary outcome, and inconsistency in the methods for measuring TcPO2. The one randomized clinical trial (Bouchour 1996) was well designed and investigated the use of HBO therapy in the treatment of acute, severe crush injuries (an etiology for which CMS already covers HBO therapy). The study's primary endpoints all centered on healing and not on the utility of TcPO2 in predicting the outcome with HBO therapy. In addition, the authors did not give a level of TcPO2 that was predictive of outcome nor did they discuss the sensitivity/specificity of TcPO2 in predicting a wound's response to HBO therapy. Instead, Bouchour provided a ratio of TcPO2 between the injured and non-injured limb that they believe was predictive of outcome. Other studies were also inconsistent in the level of TcPO2 that was predictive of an HBO response or in what TcPO2 indices could be used to predict HBO response. In addition, Fife's report that TcPO2 was 74% reliable in predicting outcome and had a positive predictive value of 58% does not demonstrate confidence in this test's ability to predict the outcome with HBO therapy.

In summary, the evidence is not adequate to conclude that "hypoxic wounds" is a type of wound for purposes of Medicare coverage. The literature does not adequately demonstrate that wounds can be primarily classified based on their tissue oxygen level, nor demonstrate that TcPO2 can reliably predict the wounds' outcome with HBO therapy.

Diabetic Wounds of the Lower Extremities

The body of literature consists of two RCTs, one combination randomized/non-randomized trial, seven case series articles, two abstracts, and several TAs. Although the results of TAs are taken into account when CMS makes coverage determinations, we also review all of the evidence on its own merits.

With the exception of the studies by Ciaravino (1996) and Davis (1987), all of the studies reported a benefit in the healing of diabetic leg ulcers using HBO therapy. Ciaravino reported a response to HBO therapy in only 20% of treated patients while Davis reported that 30% of HBO-treated patients failed to respond. Each of these studies,

[6] Decision memorandum for Noncontact Normothermic Wound Therapy. http://www.cms.hhs.gov/coverage/8b3-hhh2.asp

however, had methodologic limitations that make drawing conclusions from their findings problematic. Ciaravino's study was a retrospective case series in which the method of patient selection was not defined, the method of wound assessment not stated, and the baseline disease status of the patients not stated. The Davis article, which did not have a comparison group, provided no information on how patients were recruited nor was there information on baseline characteristics or disease status. In addition, the manner by which outcomes were assessed was not addressed.

Faglia et al (1996) was the best designed and conducted study we reviewed. Patients were randomized to either HBO therapy plus standard wound care or standard wound care only. They reported that HBO therapy significantly decreased the major amputation in patients with Wagner grade IV lesions but not in grade II or III lesions (there were no grade I or grade V patients in this study). The number of patients in this study with grade II or III lesions, however, was small. In addition, whether or not HBO therapy improved other outcomes, such as wound healing, was not assessed. This study was randomized with clear patient selection/inclusion criteria, a defined outcome, adequate power, and a comparable group of patients in the HBO and non-HBO arms. In addition, the authors demonstrated that on multivariate analysis, conducted on variables they found to be associated with major amputation on univariate analysis, HBO showed a protective effect.

The Doctor study was also a RCT and, while it suffered from some methodologic problems, it too showed that patients treated with HBO also had need for fewer amputations as compared to those treated with standard care alone. Doctor et al also demonstrated that patients treated with HBO were more likely to have a reduction in positive wound cultures as compared to patients not treated with HBO. This is important because it implies that HBO can be helpful in fighting serious wound infections, especially those caused by Pseudomonas and E. coli.

The findings by Doctor et al that HBO reduced the amount of positive wound cultures, along with other findings reported in the literature, support a biologic plausibility that HBO may have a beneficial effect in fighting infection. Local hypoxia is known to predispose patients to infection because neutrophil-mediated killing of bacteria by free radicals is decreased.[7] By increasing the tissue oxygen level, many authors note that neutrophil-mediated killing can be increased. In addition, HBO can be directly bactericidal to anaerobic bacteria and bacteriostatic to such bacteria as E. coli and pseudomonas. Doctor et al did not specifically report what the Wagner grade of the lesions in their study were, but the fact that the wounds in their study were infected, and that they had their abscesses drained, made these ulcers at least Wagner grade III. Thus, Doctor et al provide evidence that supports HBO's use in Wagner grade III lesions.

The Kalani et al study (2002) combined patients who were randomized to HBO or standard care alone and patients who were allocated to HBO or standard care alone in a non-random fashion based on HBO availability. This study presented many methodologic flaws that made it difficult to conclude their findings are correct. First was

[7] Tibbles 1996, page 1643.

the issue of treatment allocation. The majority of their patients were assigned to a therapy based on the availability of HBO. This is inherently subject to bias. Also, it is not clear if the wounds that led to amputation were the wounds that led to the patient's enrollment in the study. While they reported statistical significance data for some results, they did not provide statistical significance data for the number of ulcers healed or number of limbs amputated. Finally, in patients that did heal, the time to healing was the approximately the same in each group.

There were five case series that reported benefits in the treatment of diabetic lower extremity ulcers with HBO therapy (Baroni 1987, Oriani 1990, Oriani 1992, Wattel 1991, Zamboni 1997). Three of these studies (Baroni 1987, Oriani 1990, Oriani 1992) were conducted at the same institution by the same group of investigators. The dates of enrollment in these three case series overlapped, such that each successive article may have reported information on patients that were also reported in prior studies. In addition, in the two studies where there was a comparison group (Baroni 1987 and Oriani 1990), the comparison group was comprised of patients who had refused HBO. It is difficult to consider these patients a control group since the reasons they refused treatment may have been related to their outcome. In the Baroni study, the authors stated "preliminary observations (data not included) convinced us of the benefits of HBO in the treatment of diabetic gangrene. Accordingly, we decided to use this treatment (approved by our hospital ethical committee) in all subjects with diabetic foot lesions."[8] Thus, there is a strong suggestion of treatment bias (i.e., having a predetermined idea of the response to treatment).

In Baroni et al, and the two Oriani studies, there was limited information on the vascular disease status of their patients, and no information on the grade of the ulcers in these studies. As such, it is not possible for CMS to conclude that in these two studies (Baroni 1987 and Oriani 1990) the HBO and non-HBO treated patients groups were comparable. The 1992 Oriani study did not provide statistical significance data on their results. In addition, in the 1992 Oriani article one of their positive outcomes was defined as "wound healed completely or destined to evolve positively."[9] The authors did not define what was meant by "destined to heal," and, therefore, the reader must be concerned that this could have biased the way wounds were assessed. Finally, in Oriani's 1992 study 41 patients were excluded from analysis for a variety of reasons such as if they received less than 12 HBO sessions, general complications, subjective reasons, and poor cooperation. The limit of 12 sessions was because the authors noted that patients who received less than 12 sessions were not likely to heal. This patient censoring is problematic, and may have introduced bias in favor of the HBO results.

The patients in Wattel's study also were all referred for HBO – creating the potential for investigator bias in favor of the treatment - and there was no comparison group. The authors did not provide detailed information on baseline characteristics such as wounds size or grade. They did state that there was no significant difference between the treatment successes and failures in terms of micro-angiopathy or large vessel

[8] Baroni 1987, page 82.
[9] Oriani 1992, page 216.

alteration, but they did not say how the vascular status was assessed or what was the level of vascular disease. Also, it is not clear what their results actually were. As detailed earlier, the results reported in the abstract of their paper do not correspond with the results reported in the body of the paper.

Zamboni's study involved a small number of patients – five in each the HBO and non-HBO treatment groups. As with the other case series articles reviewed, patients in Zamboni's study were referred to the investigators for the purpose of receiving HBO therapy. The five patients in the non-HBO group refused HBO, two because they were claustrophobic and three because they lived too far to travel to the center for daily treatments. As mentioned earlier, such a comparison group that is selected by default may have differences that could affect the outcome of therapy. Also concerning is that the three patients who could not travel to the center for daily treatments may also not have received as comparable standard wound care as the HBO patients. This would then be an independent variable that could affect the outcome of their wounds. In addition, there is no information on the baseline vascular status of the patients or on the grade of the lesions.

In summarizing the case series articles, five of the seven reported positive results with HBO treatment of diabetic leg wounds (Baroni 1987, Oriani 1990, Oriani 1992, Wattel 1991, Zamboni 1997). Regarding the two case series that did not report positive results (Ciaravino 1996, Davis 1987), CMS questions the reliability of the investigators' conclusions because the studies contain serious methodologic flaws. The five supportive case series also have methodologic flaws (such as problems in the comparability of patients, problems in comparison groups, possible treatment bias, and censoring of patient data). While these five case series articles, by themselves, would not be enough to conclude that a treatment benefit exists with HBO, they do demonstrate a trend that supports HBO's effectiveness in helping to heal severe diabetic foot wounds. When the reports of these case series articles are combined with two RCTs (Faglia 1996, Doctor 1992) that demonstrated HBO is useful in treating the most severe diabetic foot wounds, CMS feels confident that a benefit does exist.

The two abstracts (Abidia 2001, Stone 1995) both reported a benefit from HBO therapy – Stone's abstract was a retrospective case series and Abidia's abstract was a RCT. The manner of patient selection, detailed information on baseline characteristics, and complete information on the results and statistical analyses was not presented. As such, these abstracts provided limited information from which CMS could critically review the studies. The Abidia abstract did report that their study was a RCT and CMS encourages that the full text of this study be published.

CMS reviewed three TAs as part of this decision memorandum. The NEMC TA was commissioned by CMS to assess the use of HBO therapy in hypoxic wounds. The review of chronic non-healing wounds was not its primary purpose. The TA concluded that HBO therapy aids in the healing of chronic non-healing wounds, however, it appears that this determination was based on studies that investigated diabetic wounds. Likewise the Blue Cross Blue Shield TA also addressed a wide range of HBO indications of which

HBO's use in treating chronic non-healing wounds was only one part. Their review of chronic non-healing wounds included a RCT by Hammarlund (1994). This RCT excluded diabetic foot wounds, and, as such, was not felt to be applicable by CMS for this decision memorandum. Thus, the Blue Cross Blue Shield assessment conclusion that HBO aids in chronic non-healing wounds was not a conclusion that singled out HBO effectiveness in diabetic wounds. Finally, the MSAC was focused on the use of HBO in treating diabetic lower extremity wounds and did conclude that HBO was effective in treating these wounds. This TA noted the methodologic limitations of the studies reviewed (all of which were also reviewed by CMS).

Finally, the American Diabetic Association's consensus statement on diabetic foot wound care was reviewed. The ADA found that it is reasonable to use HBO therapy as a treatment of last resort for patients with severe limb- or life-threatening wounds that have not responded to other treatments, but thought that additional randomized clinical trials are warranted.

Physician Supervision and Credentialing

Physician Supervision: Two perspectives on the meaning of "attendance" are prominent in the hyperbaric community: (1) the physician is physically present during the entirety of the treatment and uses that time to manage the patient's overall care; and (2) the physician remains available to manage rare emergency situations. There are differing opinions within the medical community as to whether a physician can supervise a treatment without being in constant attendance. Some argue that the administration of HBO therapy for wound care is routine and relatively risk free and therefore requires a physician only in cases of emergency or when a patient demands specialized care for a particular condition. In a letter to CMS from the American College of Surgery (ACS) addressing HBO therapy and on the topic of physician supervision the ACS stated:

> *"A physician should be present and in constant attendance, carefully monitoring the patient should a complication occur, during treatment of a critically ill patient. Other patients need to have a physician available should a complication occur."*

CMS has determined the benefit category for HBO therapy is hospital outpatient services, physician services, or incident to physician services. To be covered as incident to physician services, the services and supplies must be furnished as an integral, although incidental, part of the physician's professional service in the course of diagnosis or treatment of an illness or injury. CMS believes that the level of physician supervision for HBO therapy should not exceed that required for all "incident to" treatments (i.e., direct supervision). CMS is not imposing any new requirements when it states that HBO therapy must be provided under "direct supervision." The "direct supervision" requirement for "services and supplies incident to physician services" has been clearly defined and specified by CMS in regulations (42 CFR. § 410.26 and 42 CFR § 410.27). Additional descriptions of what constitutes "direct supervision" are contained in the

Medicare Intermediary Manual (MIM § 3112.4) and the Medicare Carrier Manual (MCM § 2050).

Physician Credentialing: Certification in hyperbaric technology (CHT) is an added qualification for licensed health care and related professionals. The certification is open to several disciplines in allied health, including therapists, technologists, chamber technicians, physician's assistants, diving medical technicians, corpsmen, physiologists, emergency medical technicians, paramedics, life support technicians, researchers and physicians. Registered nurses and licensed nurses may also take the CHT examination, although there is a separate certification process and examination for nurses.

CMS recognizes the need for specialized skills to administer hyperbaric oxygen technology and encourages members of the medical community directly involved with administering HBO therapy to patients who are members of the Medicare population to take advantage of the training offered by credible professional organizations as well as training in advanced cardiac life support.

Summary of CMS Analysis

In summary, the medical literature does not support a finding that HBO therapy warrants coverage for hypoxic wounds. The evidence is not adequate to conclude that wounds can be primarily classified as hypoxic, nor that tissue oxygen levels are predictive of the healing outcome of wounds with HBO therapy.

There are several studies that report a benefit with HBO treatment for diabetic lower extremity wounds. In general, these studies looked at the use of HBO therapy in cases where the limb was in immediate jeopardy of amputation. While many of the reviewed studies had serious methodologic flaws, two studies were reasonably well designed clinical trials (Faglia 1996, Doctor 1992) and demonstrated a lower rate of major amputation following HBO therapy. In Faglia et al the reduction was noted in patients with Wagner grade IV ulcers that received HBO therapy. This same study found no statistically significant benefit, in terms of major amputation rate, in patients with less severe ulcers (i.e., Wagner grade II or III) although the number of patients with these less severe wounds was small and other outcomes, such as wound healing, were not assessed. The study by Doctor et al also demonstrated that HBO therapy reduced the number of infected wounds (i.e., Wagner grade III). As such, CMS believes that the evidence supports the use of HBO therapy in the treatment of lower extremity diabetic wounds that are limb-threatening andare Wagner grade III or greater. The literature reviewed used HBO as an adjunctive therapy in patients who had not responded to conventional therapy. Consistent with our other national coverage policies on wound care, failure to respond to a minimum of 30-days of conventional diabetic wound care will be required before patients are otherwise eligible for CMS coverage of HBO therapy.

DECISION:

Hypoxic Wounds: The evidence is not adequate to conclude that hypoxic wounds are a distinct wound type for purposes of Medicare coverage, and, thus, Medicare has decided not to expand coverage.

Diabetic Wounds of the Lower Extremities: The evidence is adequate to conclude that HBO therapy is clinically effective and, thus, reasonable and necessary in the treatment of certain patients with limb-threatening diabetic wounds of the lower extremity. Accordingly, Medicare has decided to announce its intention to issue a national coverage determination for HBO therapy in the treatment of diabetic wounds of the lower extremities in patients who meet each of the following three criteria:

1. patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
2. patient has a wound classified as Wagner grade III or higher; and
3. patient has failed an adequate course of standard wound therapy (defined below).

The use of HBO therapy will be 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. CMS has used 30 days as the cut-off for determining whether or not a particular wound treatment, such as standard wound therapy, has produced measurable signs of healing in an individual patient in previous national coverage determinations (e.g., Coverage Issues Manual 60-19 Air-Fluidized Beds decision). Measurable signs of improved healing include a decrease in wound size either in surface area or volume, decrease in amount of exudates and decrease in amount of necrotic tissue. 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, such as systemic antibiotics and surgical debridement. 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.

Medicare intends to retain its non-coverage of HBO therapy in the treatment of diabetic wounds of the lower extremities in all other subgroups. Medicare will also retain its non-coverage policy for use of HBO therapy as an initial treatment for diabetic ulcers of the lower extremities. We encourage interested parties to undertake well-designed clinical trials to assess the clinical effectiveness of HBO therapy in other subgroups of diabetic lower extremity ulcers.

Physician Supervision and Credentialing: CMS concludes that special supervision and credentialing requirements should not be imposed on physicians who perform HBO therapy. Contractors may not impose a higher level of supervision than direct supervision as is required for all "incident to" therapies. CMS encourages physicians who perform HBO therapy to obtain adequate training in the use of HBO and in advanced cardiac life support.

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