HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: INDICATIONS FOR HYPERBARIC OXYGEN THERAPY

DRAFT for HERC meeting materials 11/13/2014

HERC COVERAGE GUIDANCE

Hyperbaric oxygen therapy is recommended for coverage (*strong recommendation*) for diabetic wounds of the lower extremities in patients who meet all of the following criteria:

- Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, and
- Patient has a wound classified as Wagner grade III or higher, and
- Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days.

Hyperbaric oxygen therapy is recommended for coverage for late radiation tissue injury, and gas gangrene (*strong recommendation*).

Hyperbaric oxygen therapy is recommended for coverage for compromised surgical flaps and grafts, and for crush injuries (*weak recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for cerebral palsy, multiple sclerosis or chronic sensorineural hearing loss (*strong recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for the following conditions (*weak recommendation*):

- Venous ulcers,
- Surgical reconstruction without flaps and grafts,
- Refractory osteomyelitis,
- acute traumatic brain injury
- Brain injuries other than acute traumatic brain injury,
- Migraines and cluster headaches,
- Acute sensorineural hearing loss,
- Delayed or non-healing fractures,
- Bell's Palsy,
- Malignant otitis externa,
- Vascular dementia,
- Thermal burns, or
- Acute coronary syndrome.

The following indications are presumed to be appropriate for coverage but are excluded from these coverage guidance recommendations: air or gas embolism, acute carbon monoxide poisoning, decompression illness and cyanide poisoning.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

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RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted Sources

Bennett, M.H., Lehm, J.P., &Jepson, N. (2011).Hyperbaric oxygen therapy for acute coronary syndrome. *Cochrane Database of Systematic Reviews, Issue 8*. Art. No.: CD004818. DOI: 10.1002/14651858.CD004818.pub3. Retrieved from http://summaries.cochrane.org/CD004818/hyperbaric-oxygen-may-reduce-the-risk-of-dying-the-time-to-pain-relief-and-the-chance-of-adverse-heart-events-in-people-with-heart-attack-and-unstable-angina

Bennett, M.H., Stanford, R.E., &Turner, R. (2012a). Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union. *Cochrane Database of Systematic Reviews, Issue 11*. Art. No.: CD004712. DOI: 10.1002/14651858.CD004712.pub4. Retrieved from http://summaries.cochrane.org/CD004712/using-oxygen-at-high-pressure-in-a-compression-chamber-for-the-treatment-of-broken-bones

Bennett, M.H., Trytko, B., & Jonker, B. (2012b). Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. *Cochrane Database of Systematic Reviews, Issue 12*. Art. No.: CD004609. DOI: 10.1002/14651858.CD004609.pub3. Retrieved from http://summaries.cochrane.org/CD004609/does-hyperbaric-oxygen-therapy-improve-the-survival-and-quality-of-life-in-patients-with-traumatic-brain-injury

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Buckley, N.A., Juurlink, D.N., Isbister, G., Bennett, M.H. & Lavonas, E.J. (2011).Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database of Systematic Reviews, Issue 4*. Art. No.: CD002041. DOI: 10.1002/14651858.CD002041.pub3. Retrieved from http://summaries.cochrane.org/CD002041/there-is-insufficient-evidence-to-support-the-use-of-hyperbaric-oxygen-for-treatment-of-patients-with-carbon-monoxide-poisoning

Holland, N.J., Bernstein, J.M., &Hamilton, J.W. (2012).Hyperbaric oxygen therapy for Bell's palsy. *Cochrane Database of Systematic Reviews, Issue 2*. Art. No.: CD007288. DOI: 10.1002/14651858.CD007288.pub2. Retrieved from http://summaries.cochrane.org/CD007288/high-pressure-hyperbaric-oxygen-therapy-for-bells-palsy

Leof, A., Kriz, H., & King, V. (2012).*Hyperbaric oxygen therapy for treatment of gas gangrene.* Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.

National Institute for Health and Clinical Excellence (NICE). (2012). *Diabetic foot problems: Inpatient management of diabetic foot problems. NICE clinical guideline 119*. London: NICE. Retrieved from www.nice.org.uk/guidance/CG119

Phillips, J.S., & Jones, S.E.M. (2013).Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa. *Cochrane Database of Systematic Reviews, Issue 5*. Art. No.: CD004617. DOI: 10.1002/14651858.CD004617.pub3. Retrieved from http://summaries.cochrane.org/CD004617/hyperbaric-oxygen-as-an-additional-treatment-for-malignant-otitis-externa

Washington State Health Care Authority Health Technology Assessment Program (WA HTA). (2013). *Hyperbaric oxygen therapy (HBOT) for tissue damage, including wound care and treatment of central nervous system (CNS) conditions.* Olympia: WA HTA. Retrieved from http://www.hca.wa.gov/hta/Pages/Hyperbaric%20Oxygen%20%28HBO2%29%20Treatment%20for%20Tissue%20Damage.aspx

Xiao, Y., Wang, J., Jiang, S., & Luo, H. (2012). Hyperbaric oxygen therapy for vascular dementia. *Cochrane Database of Systematic Reviews, Issue 7*. Art. No.: CD009425. DOI: 10.1002/14651858.CD009425.pub2. Retrieved from http://summaries.cochrane.org/CD009425/hyperbaric-oxygen-therapy-for-vascular-dementia

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Additional Sources Provided by Expert

Murad, M.H., Altayar, O., Bennett, M., Wei, J.C., Claus, P.L., Asi, N., et al. (2013). Using GRADE for evaluating the quality of evidence in hyperbaric oxygen therapy clarifies evidence limitations. *Journal of Clinical Epidemiology, 67*(1), 65-72. doi: 10.1016/j.jclinepi.2013.08.004. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24189086

Undersea and Hyperbaric Medical Society (UHMS). (2014). *Hyperbaric oxygen therapy indications* (13th ed.). L.K. Weaver (Ed.). Durham, NC: UHMS. Retrieved from http://membership.uhms.org/

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

The following clinical background summary is extracted from the WA HTA report (2013, p. 2-3).

> Hyperbaric oxygen therapy (HBOT) involves the systemic administration of 100% oxygen while the patient is inside a treatment chamber under pressures > 1 atmosphere absolute (ATA). Hyperbaric oxygen was introduced as a medical treatment more than 200 years ago and has been advocated as a treatment for a wide variety of conditions over the years. Despite a large body of published literature, it remains unclear as to the indications for which HBOT is most effective and safe. Among the indications for which questions still remain are diabetic non-healing wounds, including foot ulcers; other non-healing wounds, including skin and tissue grafts, thermal burns, and surgical wounds; refractory osteomyelitis; late radiation tissue injury (LRTI); brain injury; cerebral palsy; headache and migraine; multiple sclerosis; and sensorineural hearing loss.
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> Foot wounds are one of the most common complications of diabetes and are responsible for substantial morbidity. At any given time, lower extremity ulcers affect approximately 1 million diabetics. HBOT is used along with traditional systemic and topical therapies to promote diabetic wound healing. It is purported to reverse anaerobic infection, improve blood supply, and reduce ischemic nerve damage.
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> Chronic wounds other than those related to diabetes include venous and pressure sores, with causes that are related to venous insufficiency, pressure, trauma, vascular disease, and immobilization. Although the causes of chronic

wounds vary, in all cases, at least one of the phases of wound healing is compromised.

Surgical wounds present a medical problem if they are large in size, especially if bones and tendons are exposed and therefore are not amenable to primary closure. By increasing the oxygen tension in hypoxic wounds, HBOT is thought to restore the level of oxygenation required for compromised tissue to function efficiently. HBOT is also proposed as a means of preparing a base for skin grafts and flaps or preserving compromised grafts and flaps.

Thermal burns are the third largest cause of accidental death, with 300,000 serious burns and 6000 fatalities occurring annually in the United States. HBOT for thermal burns is directed at enhancing host defenses, preserving marginally viable tissue, protecting the microvasculature, augmenting neovascularization, and promoting wound closure.

Chronic osteomyelitis can develop when bacterial or fungal infection within bone deprives the bone of its blood supply, and the resulting ischemia causes bone tissue necrosis. It has been hypothesized that the additional oxygen delivered during HBOT may promote collagen synthesis and angiogenesis in patients with hypoxic osteomyelitic wounds.

More than 1.4 million Americans are diagnosed with cancer each year, and approximately half of these patients receive radiation therapy as part of their management. Radiation side effects can be categorized as either acute or delayed (chronic) complications; the latter may develop months or years after radiation treatment and collectively are known as late radiation tissue injury (LRTI) or late radiation side effects. Although any tissue may be affected, late radiation tissue injury occurs most commonly in the head and neck, chest wall, breast, and pelvis, reflecting the anatomical areas most commonly irradiated. Chronic radiation damage is called *osteoradionecrosis (ORN)* when bone is damaged and *soft tissue radionecrosis* when muscle, skin, or internal organs have been damaged. Evidence continues to emerge as to the effectiveness of HBOT for the treatment of LRTI, including ORN.

The use of HBOT for brain injuries is based on a theory that oxygen availability to these cells stimulates the cells to function normally, reactivating them metabolically or electrically. Traumatic brain injury (TBI), accounts for more than 1.3 million emergency room visits, approximately 275,000 hospitalizations, and 52,000 deaths annually.

Cerebral palsy is a neuromuscular disorder that arises in children due to damage of the developing brain. This disorder occurs in 0.1% to 0.5% of live births and is

characterized by impairments of muscle control, the senses, and perception. There is no known cure for cerebral palsy; the usefulness of HBOT for the treatment of cerebral palsy relates to the possibility of restoring function in portions of the brain that have suffered damage due to lack of oxygenation or other trauma.

More than 45 million individuals in the United States suffer from chronic, recurring headaches. Approximately 90% of headaches are primary headaches, which do not arise from an underlying medical condition. Cluster headaches are quite rare and occur in only 0.1% of the population. Migraine headache affects more than 28 million individuals in the United States and more than 300 million individuals worldwide. The theory is that HBOT might favorably influence vascular headache resistant to conventional drug therapy.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that afflicts an estimated 400,000 individuals in the United States and more than 2.5 million worldwide. The use of HBOT as a treatment for MS was originally based on the demonstrated ability of HBOT to produce vasoconstriction with increased oxygen delivery and some anecdotal evidence of efficacy. For several years, there was a flurry of investigation into its effectiveness for the treatment of MS, which produced a number of randomized studies in the UK, U.S., and Europe.

Sudden sensorineural hearing loss (SSHL), or sudden deafness, is a rapid loss of hearing with onset over a period of less than 72 hours. The estimated incidence of SSHL ranges from 5 to 20 per 100,000 persons per year but may be as high as 300 per 100,000 persons per year. HBOT has been proposed for the treatment of SSHL, the rationale being that the hearing loss appears to be caused by a hypoxic event in the cochlear apparatus; therefore, HBOT may potentially reverse the oxygen deficit, increase oxygen pressures in the cochlea, and improve microcirculation. Proving the effectiveness of HBOT for SSHL is complicated given the fact that up to two thirds of SSHL cases resolve spontaneously.

Bell's palsy is an acute unilateral facial weakness without an identifiable cause. It is often associated with ear discomfort, noise sensitivity and decreased tear production. It is estimated that it affects one person in 60 during their lifetime. Corticosteroids improve rates of recovery, while antiviral agents do not. It is hypothesized that in Bell's palsy, hypoxic degeneration of the facial nerve can be reduced and functional recovery can be improved with use of HBOT.

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Fractures of bone are common and typically heal within three to six months (Bennett, 2012a). However, the fracture healing process may be impaired leading to delayed or non-union of the fractured bone. Non-union is considered present when there has been no evidence of healing after six months. Rates vary widely, but range from 5% to 10% of fractures. In cases where there is a strong possibility of a delayed or non-union, extra interventions to promote healing are often appropriate. HBOT has been proposed as one of those interventions.

Malignant otitis externa is a potentially fatal infection of the external ear canal and surrounding soft tissue and bone (Phillips, 2013). It may be complicated by involvement of cranial nerves, principally the facial nerves and the contents of the jugular foramen. It is an uncommon condition mainly found in the elderly or in diabetics. Traditionally the mainstay of treatment has been prolonged antibiotic therapy, repeated debridement of necrotic tissue and sometimes aggressive surgical management. Hyperbaric oxygen has been proposed as a beneficial adjunctive therapy.

Carbon monoxide is a gas generated from incomplete combustion, and poisoning with CO is an important cause of injury worldwide (Buckley, 2011). In the United States alone, there are an estimated 50,000 annual incidences of CO poisoning. There are two syndromes that can occur after acute CO poisoning, persistent and delayed neurologic sequelae. Standard treatment for CO poisoning includes removal from the site of exposure, administration of supplemental oxygen, and general supportive care. The elimination of carboxyhemoglobin is shortened significantly by the administration of 100% oxygen at atmospheric pressure. The administration of HBOT further hastens this process.

Dementia is a condition characterized by loss of memory, confusion, problems with speech and comprehension, and changes in personality (Xiao, 2012). The number of dementia cases is projected to reach 81 million by the year 2040. Vascular dementia, the second most common form of dementia, is not a single disease but a group of syndromes based on a variety of vascular conditions. There are no current effective treatments, and possible benefits of HBOT have been proposed.

Cardiovascular disease (CVD) is the leading cause of death in the world (Bennett, 2011). Acute coronary syndrome (ACS) is defined as unstable or persistent angina with or without myocardial infarction (MI). A significant number of patients with acute MI will suffer major morbidity or mortality, despite interventions such as thrombolysis or angioplasty. Hyperbaric oxygen therapy has been proposed to improve outcomes following ACS.

Gas gangrene is a bacterial infection usually caused by Clostridium perfringens bacteria (Leof, 2012). Infection of this type is a medical emergency and can cause myonecrosis,

gas production and sepsis and, without immediate treatment, may progress to toxemia, shock and death. Treatment usually consists of wound debridement and excision and can frequently require amputation. HBOT therapy has also been frequently used.

Technology Description

The technology description is extracted from the WA HTA report (2013, p. 3-4).

> HBOT involves the therapeutic administration of 100% oxygen at environmental pressures > 1 ATA, the atmospheric pressure at sea level. Administering oxygen at pressures greater than 1 ATA requires compression. This is achieved by placing the patient in an airtight chamber. The pressure is increased inside the chamber, and 100% oxygen is given for respiration, which delivers a greatly increased pressure of oxygen to the lungs, blood, and tissues.
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> There are 2 types of chambers used for administering HBOT: a monoplace chamber for a single patient; or a multiplace chamber used for multiple patients and medical personnel. No standard protocol has been identified for administering HBOT.

Costs for HBOT were reported in the WA HTA report for three different populations, public employees, Medicaid and labor and industry. Costs, average treatment days and the range of days of treatment are presented in the table below:

Population	Public Employee	Medicaid	Labor and Industry
Average allowed amount per patient	$27,710	$46,774	$9,526
Average days of treatment	29	23	20
Range of days of treatment	1-101	1-93	1-120

Evidence Review

Effectiveness of HBOT

The majority of the evidence presented in this document that pertains to HBOT comes from the trusted sources listed at the beginning of this document. However, for several conditions, evidence was determined by HTAS to be insufficient for the committee to recommend policy, therefore they requested that additional evidence provided by the assigned expert be incorporated into this document. Two such evidence sources were utilized. One was the book, Hyperbaric Oxygen Therapy Indications, published by the Undersea and Hyperbaric Medical Society (UHMS) in 2014. The other, Murad 2013, is a systematic review of the literature on HBOT for all outcomes. The authors included 17

systematic reviews that included 44 RCTs and 131 observational studies, plus an additional 5 RCTs published after the dates of the SRs. The authors (three of whom are members of the GRADE working group) then rated the quality of the evidence using GRADE for all indications for which there was sufficient information, and compared that rating to an assessment using the American Heart Association (AHA) criteria that relies primarily on study type. This AHA evidence quality grading system is used by the UHMS, and in this framework, level A evidence is derived from multiple RCTs or meta-analyses, level B is derived from a single RCT or non-randomized studies, and level C is derived from expert opinion or case studies. When the evidence is from one of these two sources, it will be identified as such by *italics.*

Diabetic Nonhealing Wounds, Including Foot Ulcers

Moderate-quality evidence from three systematic reviews (1437 participants), including 16 peer-reviewed studies reporting on the effectiveness of HBOT for the treatment of diabetic foot ulcers, suggests that the addition of HBOT to standard wound care promotes wound healing and limb salvage in the short term (WA HTA, 2013). The results are clinically meaningful, with pooled data from three studies suggesting that eight patients would need to be treated with HBOT as an adjunct to standard wound care for an additional one person to have complete wound healing. In addition, the findings from two studies (one good quality, one fair quality) provide moderate quality evidence that the effectiveness of HBOT to heal remains significant at one-year follow-up. Incidence of healing and wound size reduction are clinically synonymous but are often measured as separate research outcomes. There was insufficient evidence to determine the effectiveness of HBOT to reduce wound size but given that the evidence supports HBOT for improved incidence of healing, it is reasonable to assume that further study into the effectiveness of HBOT to reduce wound size would find similar benefits. There is low-quality evidence suggesting no benefit from HBOT on quality of life (QOL) measures.

A NICE guideline on inpatient management of diabetic foot problems recommends that HBOT not be offered as a treatment unless part of a clinical trial (NICE, 2012). However, the evidence review that supports the guideline included six RCTs, and allowed authors to conclude that there was moderate evidence that HBOT resulted in fewer surgical interventions and low evidence that it resulted in fewer major amputations. On the other hand, there was moderate evidence that HBOT did not reduce the number of minor amputations, or improve complete wound healing at 4 to 6 weeks, and low evidence that it does not reduce ulcer surface area. A cost-effectiveness evaluation found that an incremental cost-effectiveness ratio of around £25,000.

Other Nonhealing Wounds, Including Skin and Tissue Grafts, Thermal Burns and Surgical Wounds

Overall, there is limited low-quality evidence from 12 peer-reviewed studies, suggesting that HBOT may improve healing when employed as an adjunct treatment for venous ulcers, flaps and grafts, and surgical reconstruction (without grafts or flaps) (WA HTA, 2013). There is low confidence in the reported estimate of effects for these conditions and the reported benefits should be interpreted with caution.

Venous Ulcers

The evidence for venous wounds includes two small RCTs (total N=46) and one case series (n=35). One of the RCTs found a significant reduction in wound area after 6 weeks but no difference at 18 weeks, while the other found a 59% reduction in wound area in the HBOT group compared to a 26% increase in the control group after 30 days.

UHMS 2014 notes the existence of one RCT evaluating HBOT for treatment of leg ulcers of undefined etiology, but go on to state:

> *"HBOT treatment is not indicated in the primary management of venous stasis ulcers of the lower extremities."*

Murad 2013 states that for venous ulcers, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of the proportion of ulcers healed, the relative effect size is 5.00 (95% CI 0.28 to 90.18), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias and imprecision, and upgraded for a large treatment effect.

Surgical Reconstruction without Flaps and Grafts

For patients who have undergone surgical reconstruction without flaps or grafts, the evidence is limited to two poor quality prospective cohort studies (N=84). One found improved healing in more HBOT patients (89% vs. 83%), while the other found significantly more patients suffered infection and breakdown in the control group (78% vs. 17%). *This indication is not addressed in the UHMS 2014 book or by Murad 2013.*

Compromised Flaps and Grafts

For graft and flap survival, the evidence includes three RCTs (2 poor quality, 1 unknown quality), four case series and one additional study of unknown design. Total N=425. One of the RCTs found significantly better graft survival at 7 days in the HBOT group, while another found no significant benefit when compared to heparin and dexamethasone. The third RCT found improved healing of compromised skin grafts, while the study of unknown design reported significantly greater delay in wound healing in the control group (55% vs. 11%).

UHMS 2014 reported on a large number of animal studies. With regard to studies in humans, the authors report that there are no fewer than 16 studies supporting the effectiveness of HBOT for threatened grafts, which include a range of study types from RCTs to animal research. The only RCT discussed in detail (Perrins 1967) was included in the WA HTA report and was rated poor quality; it found that grafts survived in 64% of the HBOT arm compared to 17% of control (p<0.01). The authors also reference one retrospective cohort study and 8 case series to support their assessment. They state:

> *"the use of HBOT for the salvage of compromised grafts and flaps should be considered as a class 1b intervention according to the American Heart Association Evidence-based Guidelines as it is both useful and effective based on evidence from a single randomized trial and non-randomized studies with the potential benefit far outweighing the risks."*

Murad 2013 states that for split skin grafting, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of complete graft survival at day 7, the relative effect size is 3.5 (95% CI 1.35 to 9.11), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias, imprecision and indirectness, and upgraded for a large treatment effect.

For flap grafting for limb skin defects, the quality of evidence is listed as class B using the AHA grading system. Murad et al. report that for the outcome of flap survival at day 7, the relative effect size is 1.18 (95% CI 1.02 to 1.35), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias and imprecision.

In addition, there is insufficient evidence from one study to determine the effectiveness of HBOT for crush injuries, insufficient evidence (primarily due to mixed results) from two studies to determine if HBOT is effective for the treatment of thermal burns, and insufficient evidence from one study to determine the effectiveness of HBOT for the treatment of acute traumatic peripheral ischemia.

Crush Injuries

For crush injuries, the evidence is limited to one fair quality RCT of 36 patients, which found significantly more complete healing in the HBOT group, but no difference in time to healing, number of amputations or length of hospital stay.

UHMS 2014 reports approximately 600 clinical cases of using HBOT for crush injuries, and of those, approximately 80% reported positive outcomes. Only one RCT is specifically discussed (Bouachour 1996), which was included as the only RCT in the WA HTA review and rated fair quality. UHMS states that complete wound healing

occurred in 94% of the HBOT group compared to 33% of controls (p<0.01), and that there was a need for additional surgeries in 6% of the HBOT group compared to 33% of controls (p<0.05). The description of this study in the WA HTA report adds additional information:

> *"…significantly more complete healing among the HBOT group (94% complete healing) compared with controls (56% complete healing) (RR, 1.7; 95% CI, 1.11-2.61; NNT, 3), no significant difference with regard to mean time to healing among the HBOT group (50.2 days) versus controls (55.8 days) (MD, 5.6 days; 95% CI, –19 to 7.8), no significant difference with regard to the number of amputations among the HBOT group (0) versus controls (2) (RR, 0.2; 95% CI, 0.01-3.89), and no significant difference in mean length of hospital stay among the HBOT group (22.4 days) versus controls (22.9 days) (MD, –5.0; 95% CI, –9.96 to 8.96)."*

Murad 2013 states that for crush injuries, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of complete wound healing without necrosis requiring excision, the relative effect size is 1.70 (95% CI 1.11 to 2.61), and using GRADE, has low quality evidence; evidence from one RCT was downgraded for increased risk of bias and imprecision.

Thermal Burns

For patients with thermal burns, the evidence includes two fair quality RCTs (N=141). One found no significant difference in hospital length of stay, additional surgeries or mortality, while the other found better time to healing in the HBOT group (20 days vs. 44 days).

Acute Traumatic Peripheral Ischemia

For acute traumatic peripheral ischemia, the evidence is limited to one case series (n=23) that did not provide detailed data.

Refractory Osteomyelitis

Low-quality evidence from 23 primary data studies (one fair quality nonrandomized controlled trial, one poor quality nonrandomized controlled trial, 21 case series) suggests that HBOT may be effective as an adjunct treatment for refractory osteomyelitis but there is low confidence in the reported estimate of effects (WA HTA, 2013). There is some evidence from the one small, fair-quality, nonrandomized trial that HBOT may reduce the rates of relapse infection (0% vs. 33%), but this is contradicted by the other nonrandomized trial, which found no significant difference in relapse rate (14% for HBOT, 7% for control). The latter trial (n=28) also found no benefit from HBOT as an adjunct to surgery and antibiotics with regard to cure (79% cure for HBOT vs.

93% cure for control). Further good-quality studies are necessary to determine the effectiveness of HBOT for the treatment of refractory osteomyelitis.

UHMS 2014 reports that the evidence pertaining to the use of HBOT for refractory osteomyelitis consists of 26 reports, three of which utilized some kind of comparison group, although none were RCTs. The authors recommend the use of HBOT either before or after surgical debridement, depending on location of the infection, rationalizing that:

> *"The overwhelming majority of available studies supported the use of HBOT as a beneficial adjunct in the management of refractory osteomyelitis …. Treatment success rates generally exceeded that found in the literature for "standard of care" therapy using antibiotics and debridement alone…."*

Murad 2013 states that for refractory osteomyelitis, the quality of evidence is listed as class B using the AHA grading system. The authors report that for the outcome of infection cure, the relative effect size is 0.85 (95% CI 0.62 to 1.15), and using GRADE, has very low quality evidence; evidence from one prospective cohort study was downgraded for imprecision.

Late Radiation Tissue Injury

There is moderate-quality evidence from 35 primary data studies suggesting that HBOT improves outcomes of late radiation tissue injury affecting bone and soft tissues (WA HTA, 2013). There is no overall estimate of effect because of the heterogeneity between studies, but the evidence suggests that radiation-induced tissue and bone damage to the head and neck, anus, and rectum show consistent clinical improvement with HBOT. There is also moderate-quality evidence that HBOT reduces the risk of developing ORN following tooth extraction in a previously irradiated area.

Brain Injury

For TBI, moderate quality evidence consisted of seven studies that included 571 people (Bennett, 2012b). The results of two studies indicate use of HBOT results in a statistically significant decrease in the proportion of people with an unfavorable outcome one month after treatment using the Glasgow Outcome Scale (GOS) (RR for unfavorable outcome with HBOT 0.74,95% CI 0.61 to 0.88, P = 0.001). This five-point scale rates the outcome from one (dead) to five (good recovery); an 'unfavorable' outcome was considered as a score of one, two or three. Pooled data from final follow-up showed a significant reduction in the risk of dying when HBOT was used (RR 0.69, 95% CI 0.54 to 0.88, P = 0.003) and suggests we would have to treat seven patients to avoid one extra death (number needed to treat [NNT] 7, 95% CI 4 to 22, moderate quality evidence). The Glasgow Coma Scale (GCS) has a total of15 points, and two small trials reported a significant improvement in GCS for patients treated with HBOT

(mean difference [MD] 2.68 points, 95%CI1.84 to 3.52, P < 0.0001), although these two trials showed considerable heterogeneity (I^2 = 83%).The improvement of 2.68 points in GCS is difficult to interpret. This scale runs from three (deeply comatose and unresponsive) to 15 (fully conscious), and the clinical importance of an improvement of approximately three points will vary dramatically with the starting value (for example an improvement from 12 to 15 would represent an important clinical benefit, but an improvement from three to six would leave the patient with severe and highly dependent impairment). In general, the studies were small and carried a significant risk of bias. None described adequate randomization procedures or allocation concealment, and none of the patients or treating staff were blinded to treatment.

Evidence from six poor or very-poor-quality primary data studies are insufficient to determine if HBOT is effective in improving health outcomes among patients with brain injuries other than TBI (WA HTA, 2013).

Cerebral Palsy

There is insufficient evidence from six studies (two RCTS and four observational studies) to determine the effectiveness of HBOT for the treatment of cerebral palsy (WA HTA, 2013). Inconsistencies in the direction of the results, a paucity of studies, small sample sizes, differences in baseline characteristics, and the number of treatment sessions provided, all contributed to the low-quality grade assigned to motor function, which was considered the major outcome of interest. Fair- to poor-quality observational data suggests an improvement in motor function and other disease-specific subjective outcome measures among children receiving HBOT, but a fair-quality RCT found no additional benefit from HBOT among children receiving HBOT versus those receiving pressurized air.

Multiple Sclerosis

Moderate-quality evidence from nine trials suggests little effect of HBOT on outcomes related to MS (WA HTA, 2013). Two small, good-quality trials found modest benefits, while seven fair-quality trials found no benefit. Furthermore, the statistical benefits observed in the two positive trials are unlikely to translate into clinically significant benefits for the patient. Of note, there were no RCTs found on this topic post 1990, and there appears to be little interest in further investigation into the use of HBOT for MS.

Migraines and Cluster Headaches

Low-quality evidence from three fair-quality RCTs suggest that 40 to 45 minutes of HBOT is effective in significantly relieving an acute migraine attack (WA HTA, 2013). Just two patients need to be treated to obtain significant relief for one additional patient. There is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or reduce the need for rescue medication, based on

two fair quality trials. There is insufficient evidence from two studies to determine the effectiveness of HBOT for preventing, relieving, or terminating cluster headaches.

Sensorineural Hearing Loss

Low-quality evidence (due to mixed results) from eight RCTs is inconclusive as to whether there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase (WA HTA, 2013). A large systematic review suggests that HBOT is beneficial among patients who present within two weeks of onset of the disease; however, there is no evidence that the statistical benefit observed translates into a functional benefit, and the results from a recent RCT do not suggest benefit from HBOT. Moderate-quality evidence suggests that HBOT provides no added benefit to patients presenting with chronic sensorineural hearing loss.

Murad 2013 reports that for chronic idiopathic sudden sensorineural hearing loss (> 2 weeks after presentation), the quality of evidence is listed as class A using the AHA grading system. The authors report that for the outcome of any improvement in hearing, the relative effect size is 0.64 (95% CI 0.30 to 1.33), and using GRADE, has very low quality evidence; evidence from one RCT was downgraded for increased risk of bias, imprecision and indirectness.

Delayed or Non-healing Fractures

No studies met the inclusion criteria of the review that addressed this indication (Bennett, 2012a). Authors identified three ongoing RCTs. Three excluded RCTs either did not report fracture healing outcomes or had been abandoned.

Bell's Palsy

No RCTs met the inclusion criteria of the review that addressed this indication (Holland, 2012). One small RCT (n=79) that did not meet criteria because the outcome assessor was not blinded reported that patients treated with HBOT had facial function recovery more often than those treated with prednisone (RR 1.26, 95% CI 1.04 to 1.53).

Malignant Otitis Externa

No RCTs met the inclusion criteria of the review that addressed this indication (Phillips, 2013).

Carbon Monoxide Poisoning

Seven RCTs of varying quality were identified; one was excluded because it did not evaluate clinical outcomes (Buckley, 2011). Of the six remaining trials involving 1361 participants, two found a beneficial effect of HBOT for the reduction of neurologic sequelae at one month, while four others did not. One of these is an incomplete publication (an abstract of an interim analysis). Although pooled random effects meta-analysis does not suggest a significant benefit from HBOT (OR for neurological deficits 0.78, 95%CI 0.54 to 1.12), significant methodologic and statistical heterogeneity was

apparent among the trials, and this result should be interpreted cautiously. Moreover, design or analysis flaws were evident in all trials. Importantly, the conclusions of one positive trial may have been influenced by failure to adjust for multiple hypothesis testing, while interpretation of the other positive trial is hampered by a high risk of bias introduced during the analysis including an apparent change in the primary outcome. Both were also stopped early 'for benefit', which is likely to have inflated the observed effect. In contrast three negative trials had low power to detect a benefit of HBOT due to exclusion of severely poisoned patients in two and very poor follow-up in the other. One trial that was said to be finished around eight years ago has not reported the final analysis in any forum. (Strength of evidence: very low)

Murad 2013 reports that for carbon monoxide poisoning, the quality of evidence is listed as class A using the AHA grading system. The authors report that for the outcome of resolution of signs and symptoms at 4-6 weeks, the relative effect size is 0.78 (95% CI 0.54 to 1.12), and using GRADE, has very low quality evidence. Evidence from multiple RCTs was downgraded for increased risk of bias, inconsistency and imprecision.

Vascular Dementia

One study involving 64 patients was included in the review (Xiao, 2012). It compared HBOT as an adjuvant to donepezil with donepezil alone. This one study was judged to be of poor methodological quality. Patients receiving HBOT plus donepezil had significantly better cognitive function than the donepezil only group after 12 weeks of treatment, measured by the Mini-Mental State Examination (MMSE) (WMD 3.50; 95% CI 0.91 to 6.09) or by Hasegawa's Dementia Rating Scale (HDS) (WMD 3.10; 95% CI 1.16 to 5.04). There were no deaths or withdrawals, and the study did not mention safety assessment at all. Global function, behavioral disturbance and activities of daily living were not investigated in the study. (Strength of evidence: very low)

Acute Coronary Syndrome

Six trials with 665 participants contributed to this review (Bennett, 2011). There was a significant decrease in the risk of death with HBOT (RR 0.58, 95% CI 0.36 to 0.92, P = 0.02). The extent of heart muscle damage was lower following HBOT, as shown by a lesser rise in muscle enzyme in the blood (mean difference (MD) 493 IU, P = 0.005) and a better LV ejection fraction (MD 5.5%, P = 0.001). There was evidence from individual trials of reductions in the risk of major adverse coronary events (MACE) (RR 0.12, P = 0.03); re-infarction (RR 0.28, P = 0.04) and dysrhythmias following HBOT (RR 0.59, P = 0.01), and the time to relief of pain was reduced with HBOT (MD 353 minutes shorter, P < 0.00001). One trial suggested a significant incidence of claustrophobia in single occupancy chambers of 15% (RR of claustrophobia with HBOT 31.6, P = 0.02). The authors conclude:

> For people with ACS, there is some evidence from small trials to suggest that HBOT is associated with a reduction in the risk of death, the volume of damaged muscle, the risk of MACE and time to relief from ischemic pain. In view of the modest number of patients, methodological shortcomings and poor reporting, this result should be interpreted cautiously. The routine application of HBOT to these patients cannot be justified from this review. (p. 4)
> (Strength of evidence for risk of death: low)

Gas Gangrene

Evidence pertaining to the use of HBOT for this indication is limited to four retrospective comparison studies and 13 case series (Leof, 2012). All four of the retrospective comparison studies compared mortality rates between patients treated with HBOT and those receiving standard wound care. All four studies found that HBOT improved survival rates. One of the cohort studies included reported that amputation rates among survivors were lower for HBOT patients (18%) than for controls (75%). The significance of these findings was not reported. (Strength of evidence: low)

Optimal Dose, Frequency and Duration of HBOT

The available data from 13 studies provides insufficient evidence to determine the optimal treatment frequency, duration or dose for HBOT (WA HTA, 2013). No studies reported on the optimal duration of treatment sessions; there were mixed results from subgroup analysis involving 8 studies looking at frequency; and significant heterogeneity means that there is low confidence in the available results from five studies that looked at dose.

Harms of HBOT

There is moderate evidence suggesting that harms associated with HBOT are generally mild and self-limiting (WA HTA, 2013). The majority of reported harms include barotrauma, temporary visual disturbances, and, more rarely, oxygen toxicity. Occasional reports of seizures represent the most serious side effects. The Medical Services Advisory Committee (MSAC) of Australia reported an overall harms incidence rate of 6.3%; 17% incidence of general pain or discomfort during decompression; 4.8% incidence of ear pain; 1.5% incidence of tympanostomy tube placements; 0.9% incidence of persistent ocular changes; 0.6% incidence of ear barotrauma; 0.34% incidence of abdominal pain; and 0.1% incidence of claustrophobia.

Notable indication-specific harms found in the literature include the following:

- Among patients with late radiation tissue injury, there were reports of ear pain (16% in a trial of 150 patients), transient myopia (3% in one study 8% in another), and confinement anxiety (1.7%).

- Pooled data from two trials reported severe pulmonary complications (defined as either, rising oxygen requirements and infiltrates in chest x-ray or cyanosis and hyperpnoea so severe as to imply “impending hyperoxic pneumonia”) among 13% of TBI patients receiving HBOT compared with none in the control groups (RR, 15.57; 95% CI, 2.11-114.72).
- One study reported ear problems among 47% of children with cerebral palsy receiving HBOT versus 22% among controls (P significant but value not reported). Another study reported a 12% seizure rate and found that 35% of patients reported ear problems. Another reported that 8% of 50 children stopped treatment due to adverse events, including seizures, and one other study reported 1 seizure in an observational study of 230 patients.
- Among patients with MS, a 2011 Cochrane Collaboration review reported 77 patients (55%), across 4 trials, suffered temporary deterioration in visual acuity in the HBOT group versus 3 patients (2.3%) in the sham group (OR, 24.87; 95% CI, 1.44-428.5; NNT, 1; 95% CI, 1-2).
- Six of the case series evaluating HBOT for gas gangrene reported on harms (total N= 337). Two deaths were attributed to HBOT treatment, and seizures occurred in 7% of patients.
- Among patients with TBI, two studies reported an incidence of 13% for significant pulmonary impairment in the HBOT group versus 0% in the non-HBOT group (P = 0.007).

Differential Efficacy or Safety

The evidence is insufficient to determine the differential effectiveness and safety of HBOT according to sex, race, ethnicity, disability, wound duration, or treatment setting (WA HTA, 2013). There is evidence of very low quality suggesting that younger TBI patients may recover faster with HBOT than older patients. There is low quality evidence suggesting that radiation dose influences the effectiveness of HBOT to prevent ORN among head and neck cancer survivors. There is low quality evidence that transcutaneous oxygen measurement (TCOM) is a good predictor of response to HBOT when measured under hyperbaric conditions, and there is mixed evidence as the whether TCOM can predict response to HBOT by first measuring the response of a wound to normal air or to 100% oxygen breathed at sea level. There is insufficient evidence from poor-quality studies to determine the differential safety of HBOT across populations.

Costs of HBOT

HBOT may be cost-effective under very specific assumptions of effectiveness and costs (WA HTA, 2013). All included cost analyses found HBOT to be cost-effective or cost saving. However, the available economic evaluations were severely limited by sparse cost data and unreliable efficacy and cost estimates used to make model assumptions. Only one model was found to be robust during sensitivity analysis, making most estimates very unreliable. Overall, there is low-quality evidence to suggest that HBOT may be a cost-effective treatment under certain conditions, for certain populations and indications.

Evidence Summary

Moderate-quality evidence supports the addition of HBOT to standard wound care to promote short term wound healing and limb salvage among patients with diabetic foot ulcers with continued improvement at one year follow-up. There is insufficient evidence to determine the effect of HBOT on QOL or other health outcomes. There is also moderate-quality evidence suggesting that HBOT improves outcomes of late radiation tissue injury affecting bone and soft tissues. Moderate-quality evidence also suggests that HBOT reduces the risk of dying following TBI and may improve functional outcomes.

There is limited low-quality evidence suggesting that HBOT may improve healing when employed as an adjunct treatment for venous ulcers, flaps and grafts, crush injuries, and surgical reconstruction (without grafts or flaps) but more study is needed to support the current evidence. Low-quality evidence (due to mixed results) is inconclusive as to whether or not there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase of the disease. HBOT may reduce the rates of relapse infection among patients with refractory osteomyelitis but further good-quality studies are necessary to confirm this finding (very low quality evidence). Low-quality evidence suggests that 40- to 45-minutes of HBOT is effective in significantly relieving an acute migraine attack, but there is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or reduce the need for rescue medication.

Low quality evidence suggests that HBOT may decrease the risk of death and other major adverse coronary events in patients with ACS, and may decrease the risk of death and amputation in patients with gas gangrene.

Moderate-quality evidence suggests little benefit of HBOT for the treatment of MS. Low-quality evidence suggests no benefit of HBOT for preventing, relieving, or terminating cluster headaches. There is also no evidence that HBOT is beneficial among patients presenting with chronic sensorineural hearing loss. There is insufficient evidence,

primarily due to mixed results or an overall paucity of studies, to determine if HBOT is effective for the treatment of thermal burns, cerebral palsy, brain injuries other than TBI, delayed or non-union of fractures, bell's palsy, carbon monoxide poisoning, vascular dementia or malignant otitis externa.

Overall, there is a low quality of evidence to suggest that HBOT may be a cost-effective treatment under certain conditions and for certain populations and indications, but current data are insufficient to determine the most cost-effective uses of the technology.

There is moderate-quality evidence from across studies that harms associated with HBOT are usually mild, self-limiting, and with most resolving after the termination of treatment. The most common harms include myopia, barotrauma, claustrophobia, and oxygen toxicity. Life-threatening adverse events are rare but do occur on occasion and can include seizures and death.

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GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	**Balance between desirable and undesirable effects**	**Quality of evidence***	**Resource allocation**	**Variability in values and preferences**	**Coverage recommendation**	**Rationale**
Diabetic nonhealing wounds	Improved wound healing and limb salvage	Moderate	Moderate to high cost, offset by reduced hospitalization and other treatment costs	Moderate, favoring treatment	Recommended for coverage (*strong recommendation*), when criteria are met	Consistent evidence of effectiveness for improved wound healing for up to one year, based on 16 studies. Coverage criteria based on expert input supporting Medicare coverage criteria.
Venous ulcers	Possible improved healing	Low	Moderate	High	Not recommended for coverage (*weak recommendation*)	Two small trials find reduction in wound area, but no evidence for complete wound healing and no evidence of superior results after 30 days. Expert opinion does not recommend HBOT for this condition.
Compromised flaps and	Possible improved graft survival	Low	Moderate	Moderate	Recommended for coverage (*weak*	Four studies (3 RCTs) had mixed

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
grafts					*recommendation*)	results, with most evidence suggesting improved healing.
Surgical reconstruction without flaps and grafts	Unknown	Very Low	Moderate	High	Not recommended for coverage (weak)	The evidence is insufficient (no RCTs) to suggest that benefit exceeds harm.
Crush injuries	More complete wound healing	Low	Moderate	Moderate	Recommended for coverage (weak)	Evidence limited to one fair quality RCT showing more complete wound healing
Thermal burns	Unknown due to conflicting evidence	Very Low	Moderate	Moderate to high variability	Not recommended for coverage (*weak*)	Conflicting evidence from 2 RCTs prevents conclusions regarding efficacy.
Refractory osteomyelitis	Possible reduced rate of relapse	Very Low	Moderate	Moderate to high variability	Not recommended for coverage (weak)	Conflicting evidence from 2 trials prevents conclusions regarding efficacy .
Late radiation tissue injury	Improved outcomes	Moderate	Moderate	Low to moderate variability (preference towards treatment)	Recommended for coverage (*strong*)	Consistent evidence from 35 studies shows clinical improvement with HBOT
Brain injury – Acute TBI	Possible reduced risk of dying, unclear improvement in functional outcomes	Moderate	Moderate	Moderate variability	Not recommended for coverage (*weak*)	Evidence (7 studies) limited by high risk of bias and unclear clinical significance. Expert opinion does not recommend HBOT for this condition.
Brain injury other than TBI	Unknown	Very Low	Moderate	High variability	Not recommended for coverage (*weak*)	The evidence is insufficient (very poor quality) to suggest

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
						that benefit exceeds harm.
Cerebral palsy	Unknown	Very Low	Moderate to high (chronic condition)	Moderate variability (some would prefer treatment in spite of insufficient evidence)	Not recommended for coverage (*strong*)	Conflicting evidence (2 RCTs) prevents conclusions regarding efficacy.
Migraine HA	Aborts HA after 40-45 minutes, but no effect on prevention or reduction in N/V or rescue meds	Low	Moderate to high (Chronic condition)	High variability	Not recommended for coverage (*weak*)	Lack of clinically important benefit based on 3 RCTs suggests that benefits do not exceed harms, particularly given logistic considerations
Cluster HA	No benefit	Very low	Moderate to high	High variability	Not recommended for coverage (*weak*)	The evidence is insufficient (2 studies) to suggest that benefit exceeds harm.
Multiple sclerosis	No benefit	Moderate	Moderate to high	Moderate variability	Not recommended for coverage (*strong*)	Nine studies had mixed results, with most (7) finding no benefit
Sensorineural hearing loss – acute	Unknown	Low	Moderate	Moderate variability	Not recommended for coverage (*weak*)	Conflicting evidence (8 RCTs) prevents conclusions regarding efficacy. Potential small benefit is likely not clinically significant.
Sensorineural hearing loss – chronic	No benefit	Low	Moderate	Low variability (preference against HBOT)	Not recommended for coverage (*strong*)	Evidence suggests no benefit from HBOT.
Delayed or non-healing fractures	Unknown	Very Low	Moderate	Low variability (preference against HBOT)	Not recommended for coverage (*weak*)	Lack of evidence (0 RCTs) prevents conclusions regarding

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
						efficacy.
Bell's palsy	Unknown	Very Low	Moderate	Moderate variability	Not recommended for coverage (*weak*)	Lack of evidence (0 RCTs) prevents conclusions regarding efficacy.
Malignant otitis externa	Unknown	Very Low	Moderate	Low variability (preference against HBOT)	Not recommended for coverage (*weak*)	Lack of evidence (0 RCTs) prevents conclusions regarding efficacy.
Vascular dementia	Unknown	Very Low	Moderate to high (chronic condition)	Moderate variability	Not recommended for coverage (*weak*)	Lack of evidence (1 small poor RCT) prevents conclusions regarding efficacy.
Acute coronary syndrome	Decreased risk of death and MACE	Low	Moderate	High variability	Not recommended for coverage (*weak*)	Evidence from 6 RCTs limited by high risk of bias; concerns regarding logistic considerations. Expert opinion does not recommend HBOT for this condition.
Gas gangrene	Decreased risk of death and amputation	Low	Moderate	Low to moderate variability (preference towards treatment)	Recommended for coverage (*strong*)	Consistent evidence (4 cohort studies) suggest decreased mortality; RCT may not be reasonable.

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

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POLICY LANDSCAPE

Quality Measures

No quality measures were identified when searching the National Quality Measures Clearinghouse.

Payer Coverage Policies

Coverage policies for selected payers are included here.

Medicare

A national coverage determination for hyperbaric oxygen therapy was identified in the Medicare Coverage Database. Indications and limitations of coverage are detailed in Appendix D.

Washington HTA Limitations of Coverage

Hyperbaric Oxygen Therapy is a covered benefit with conditions consistent with the criteria identified in the reimbursement determination.

Limitations of Coverage

1. Crush injuries and suturing of severed limbs; as an adjunct when loss of function, limb, or life is threatened.
2. Compromised skin grafts and flaps (not for primary management of wounds).
3. Chronic refractory osteomyelitis unresponsive to conventional medical and surgical management.
4. Osteoradionecrosis; as an adjunct to conventional treatment.
5. For prevention of osteoradionecrosis associated with tooth extraction in a radiated field.
6. Soft tissue radionecrosis; as an adjunct to conventional treatment.
7. Diabetic wounds 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.

Non-Covered Indicators

1. Brain injury including traumatic (TBI) and chronic brain injury
2. Cerebral Palsy
3. Multiple Sclerosis
4. Migraine or cluster headaches
5. Acute and chronic sensorineural hearing loss
6. Thermal burns
7. Non-healing venous, arterial and pressure ulcers

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

***High*:** The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

***Moderate*:** The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

***Low*:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

[1] Includes risk of bias, precision, directness, consistency and publication bias

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Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
870-897	Open wound, various locations
250.8	Diabetes with other specified manifestations
990	Effects of radiation, unspecified
854	Intracranial injury of other and unspecified nature
389.1	Sensorineural hearing loss
730.0-2	Osteomyelitis
346.9	Migraine headache
399.0	Cluster headache
340	Multiple sclerosis
343	Cerebral palsy
940-949	Burns
800-829	Fractures
351.0	Bell's palsy
380.14	Malignant otitis externa
986	Toxic effects of carbon monoxide
E868	Accidental poisoning by CO
E952	Suicide by gases
E962.2	Assault by gases
E982.1	Poisoning by CO, undetermined
290.40	Vascular dementia
410	Acute myocardial infarction
411.81	Acute coronary occlusion without infarction
040.0	Gas gangrene
ICD-9 Volume 3 (Procedure Codes)	
93.95	Hyperbaric oxygenation
CPT Codes	
99183	Physician attendance/supervision of hyperbaric oxygen therapy, per session
HCPCS Level II Codes	
C1300	Hyperbaric oxygen, full body chamber, per 30 minutes

Note: Inclusion on this list does not guarantee coverage

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Appendix C. HERC Guidance Development Framework

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

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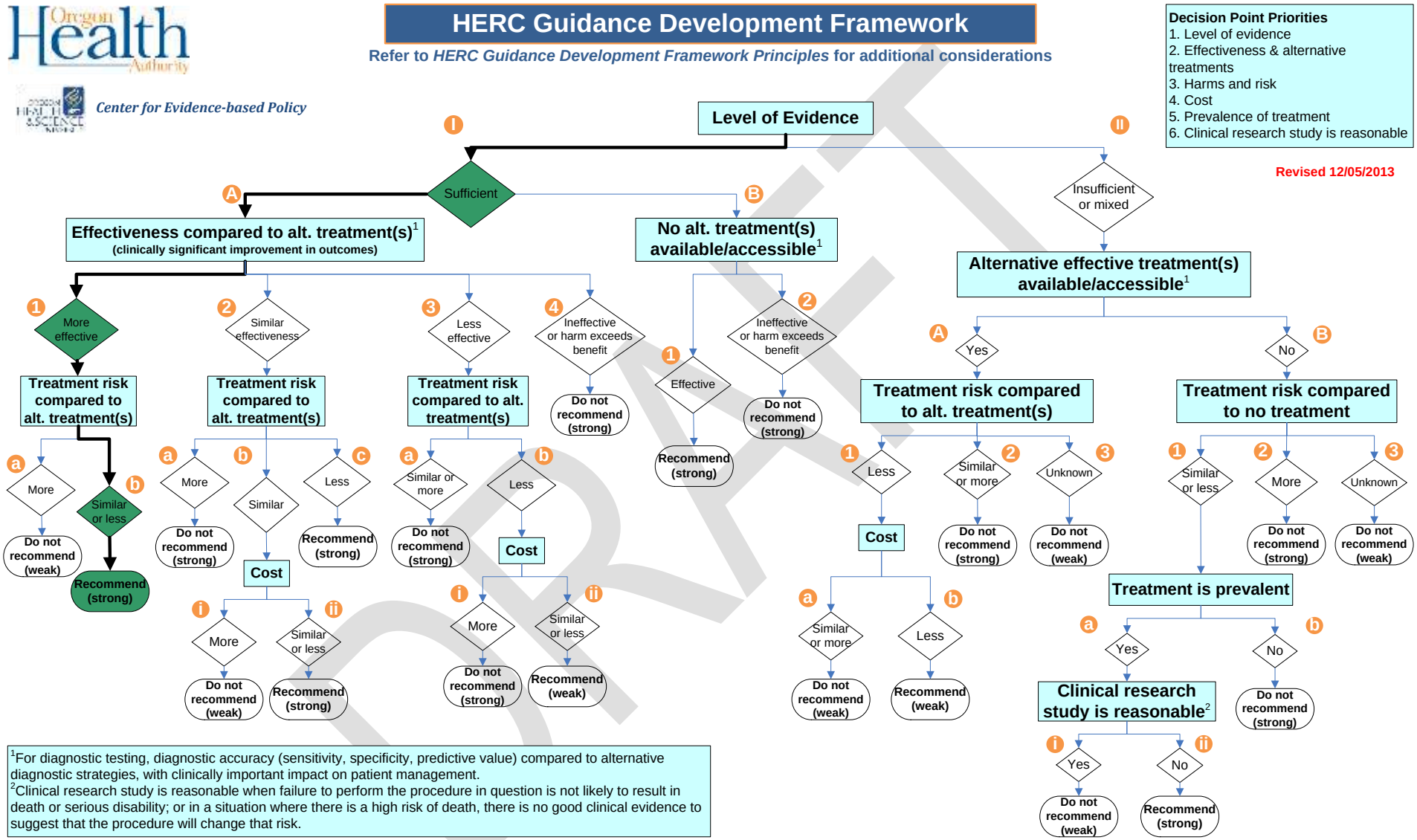
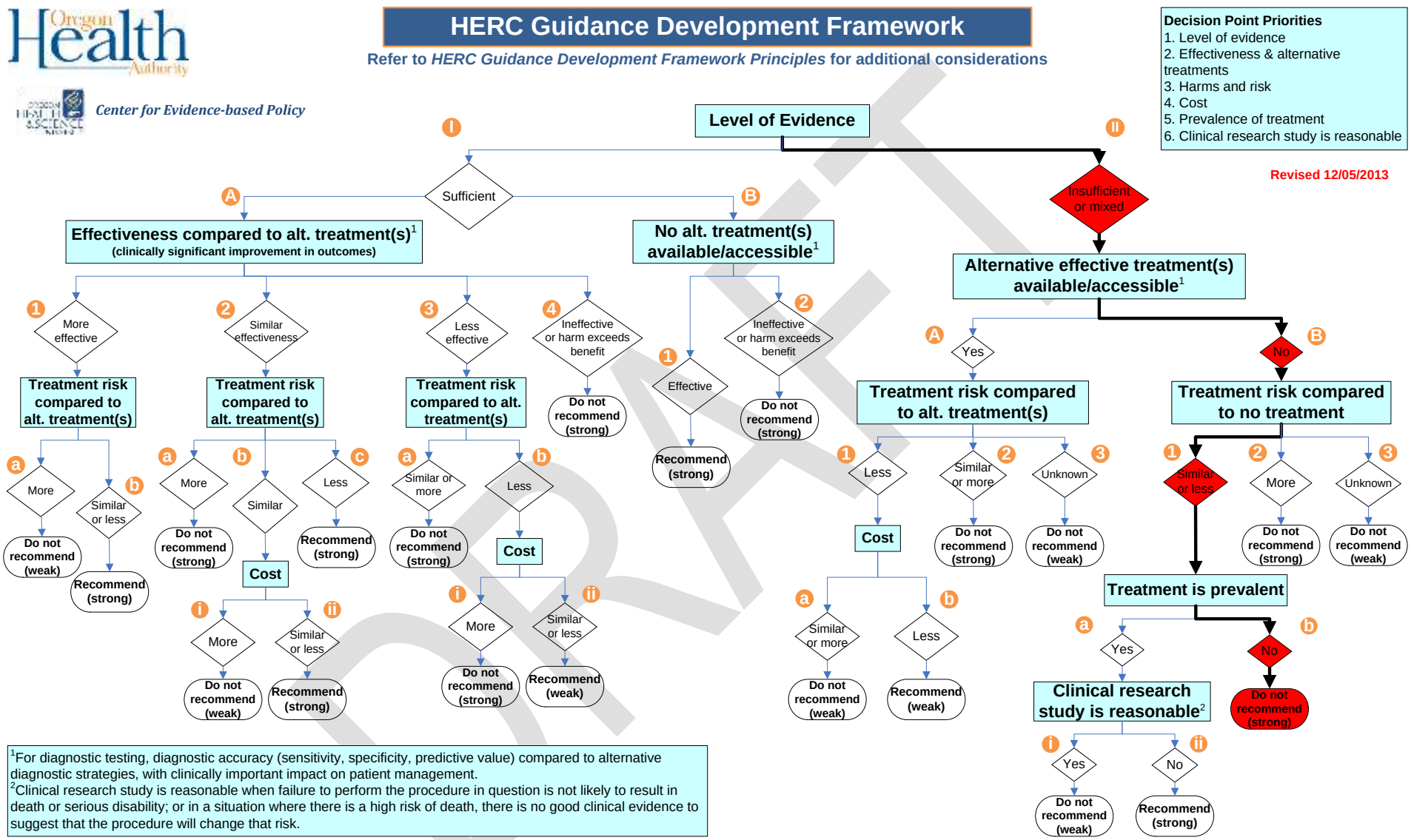
Diabetic nonhealing wounds; Venous ulcers; Compromised flaps and grafts; Crush injuries; Late radiation tissue injury; Gas gangrene

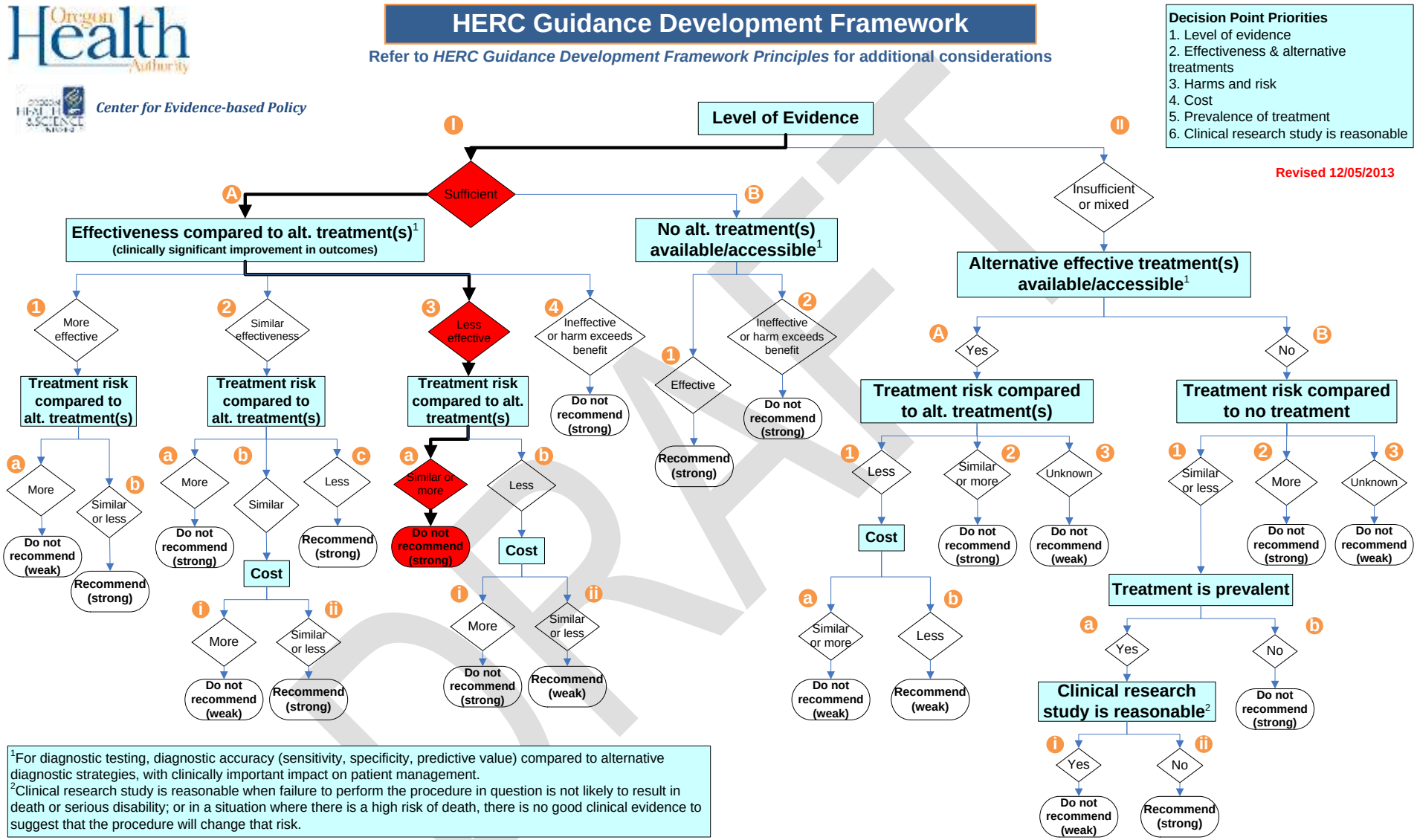


[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Cerebral Palsy



Chronic sensorineural hearing loss, Acute traumatic brain injury



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

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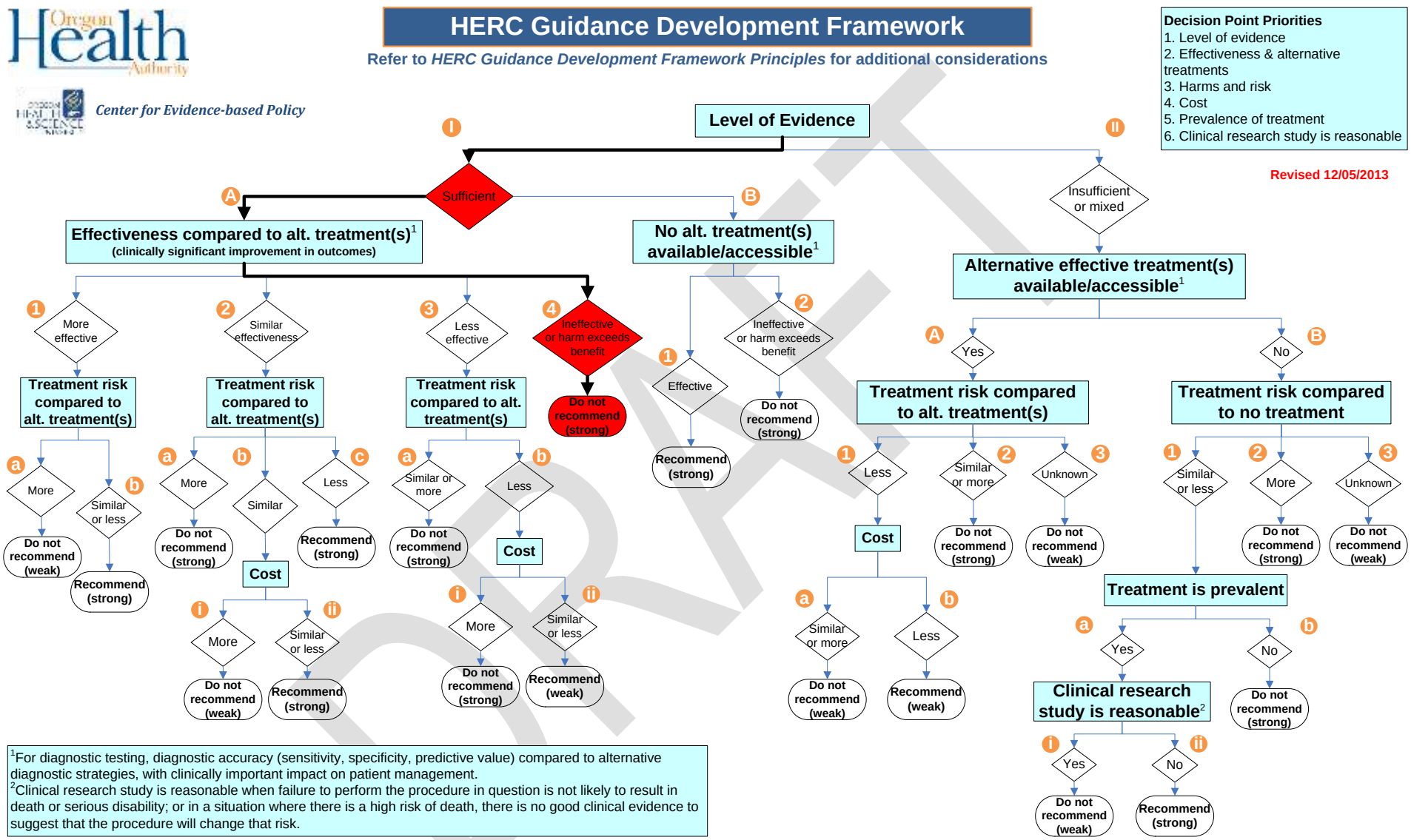
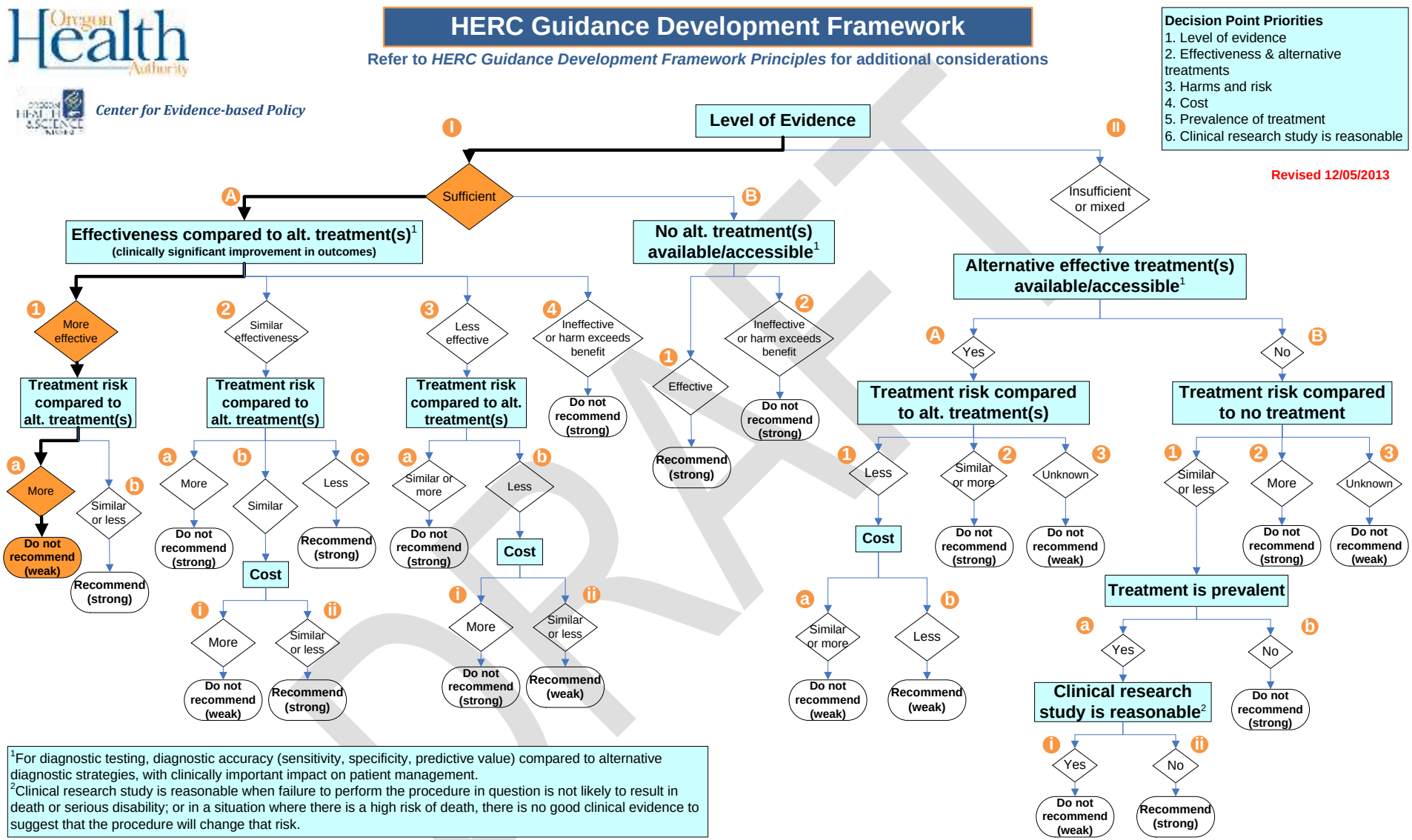
Multiple sclerosis



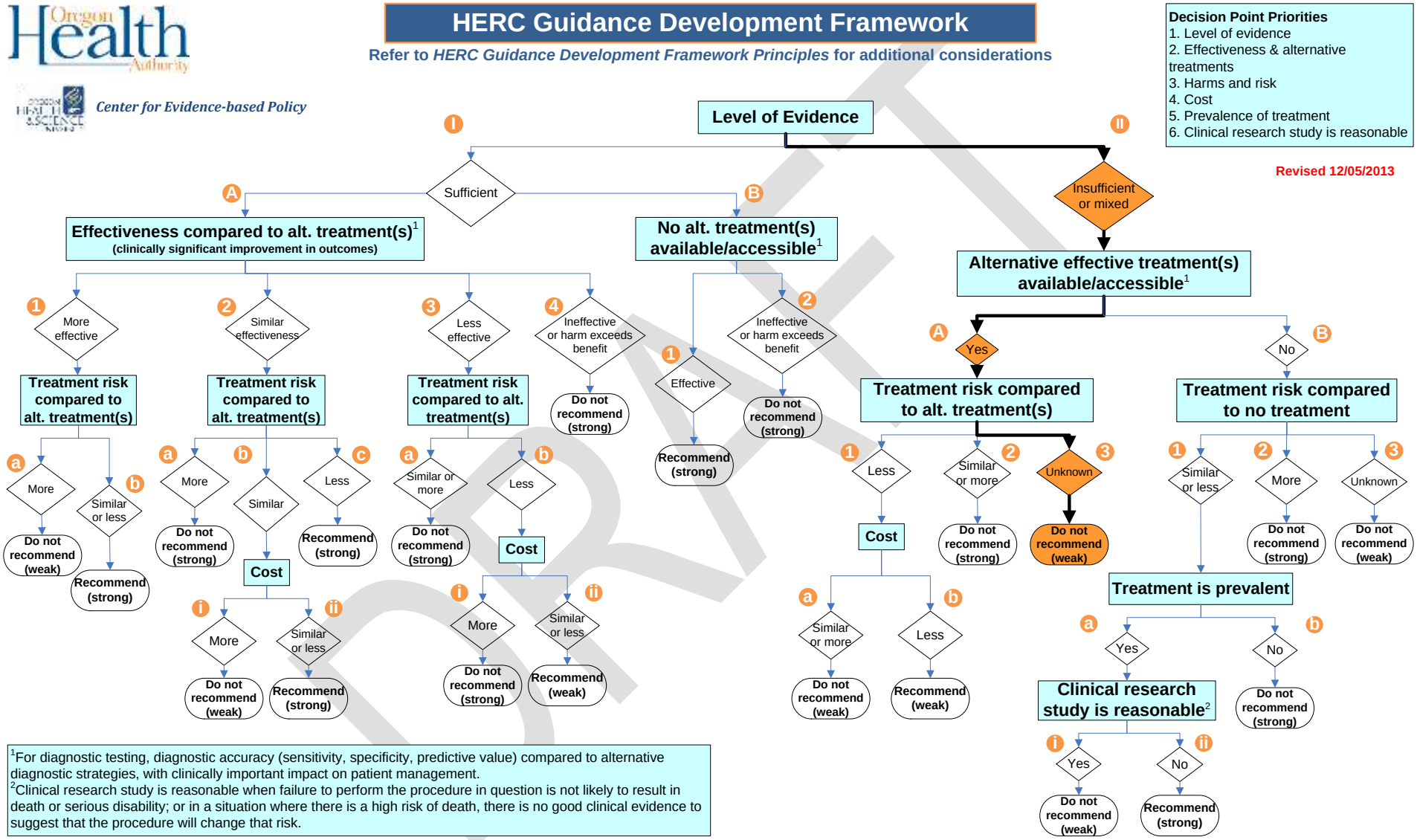
[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Acute coronary syndrome



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Brain injury other than TBI; Migraines; Cluster headache; Acute sensorineural hearing loss; Delayed or non-healing fractures; Bell's palsy; Malignant otitis externa; Vascular dementia; Thermal burns



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

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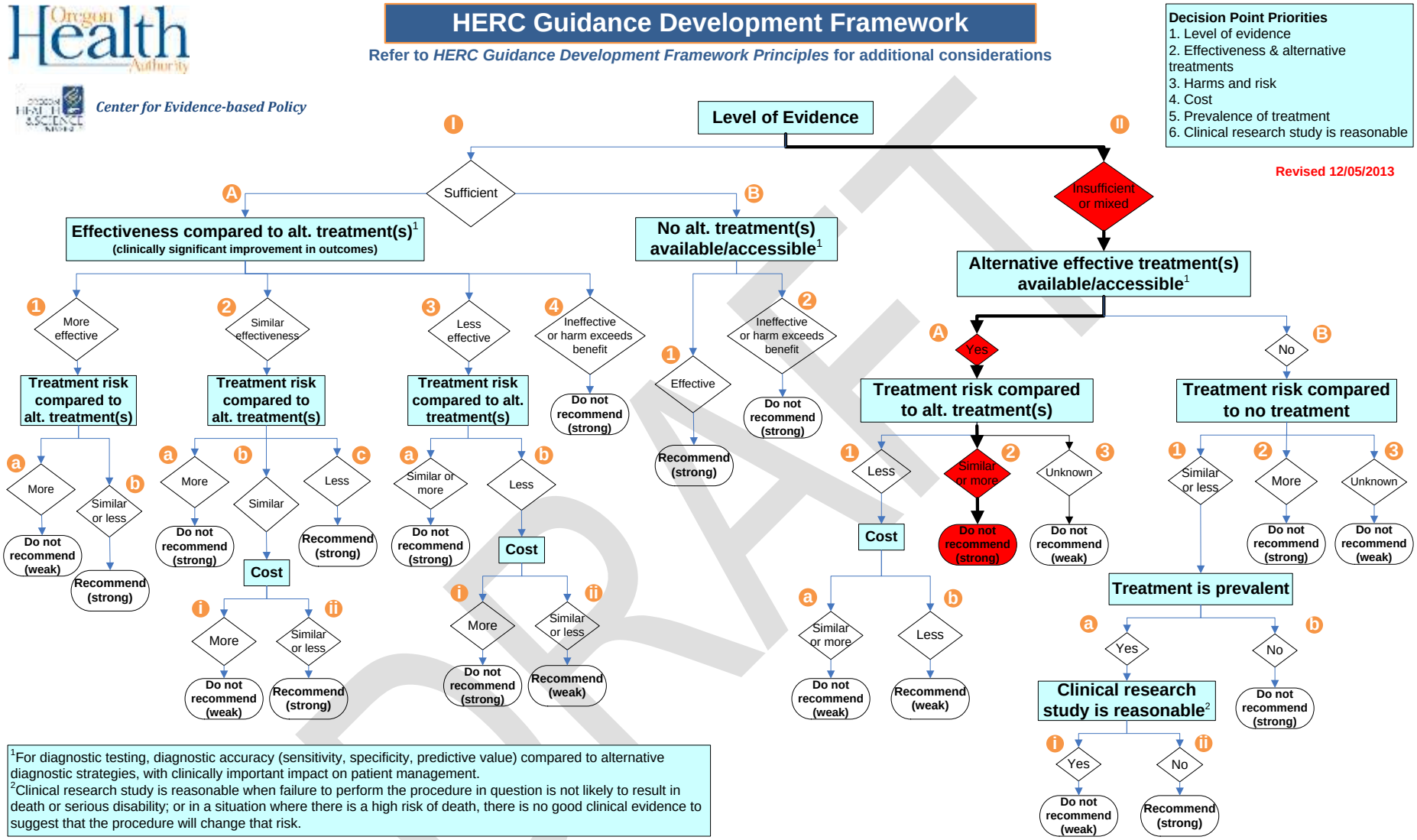
Surgical reconstruction without flaps and grafts; Refractory osteomyelitis



Appendix D. CMS National Coverage Determination

National Coverage Determination: Hyperbaric Oxygen Therapy

Publication Number: 100-3
Manual Section Number: 20.29
Effective Date: 6/19/2006

Indications and Limitations of Coverage

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.

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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 insufficiency.
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.

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