Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1054.1 – Review of Interim Funded Service: Hyperbaric Oxygen Therapy for the Treatment of Chronic Non-Diabetic Wounds and Non-Neurological Soft Tissue Radiation Injuries

Applicants: Australian and New Zealand Hyperbaric Medicine Group (ANZHMG)
South Pacific Underwater Medicine Society (SPUMS)
Australian Healthcare and Hospitals Association (AHHA)
Australian Society of Anaesthetists (ASA)

Date of MSAC consideration: 54th meeting, 29 November 2011

1. Purpose of application

In February 2010 an application was received from the Australian and New Zealand Hyperbaric Medicine Group (ANZHMG), South Pacific Underwater Medicine Society (SPUMS), Australian Healthcare and Hospitals Association (AHHA) and Australian Society of Anaesthetists (ASA) requesting Medicare Benefits Schedule (MBS) listing of hyperbaric oxygen therapy (HBOT) for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries..

This treatment involves the use of a compression vessel known as a 'hyperbaric chamber' or 'compression chamber'. The treatment, however, is not 'device specific' and these devices are manufactured by many different companies, or purpose built for an individual location, in accordance with Australian and International Standards. The devices are capable of treating one person at a time (monoplace chamber) or more than one person at a time (multiplace chamber).

Hyperbaric oxygen therapy consists of a patient breathing 100% oxygen while situated within a treatment chamber at a pressure higher than sea level pressure (i.e. >1 atmosphere absolute or ATA). According to expert opinion, HBOT is considered clinically efficacious when 100% oxygen is delivered at pressures greater than 1.5 ATA, and in clinical practice is almost universally delivered at between 2 and 3 ATA. Treatment duration can vary from 45 to 300 minutes, although most treatments last from 60 to 120 minutes, for a variable number of sessions. A treatment chamber may accommodate a single patient (a monoplace chamber) or multiple patients and attendants as required (a multiplace chamber); Australian clinical practice and expertise is primarily with multiplace chambers.

Hyperbaric oxygen therapy is an established therapeutic modality for a range of health conditions, approved for 13 indications by the Undersea and Hyperbaric Medicine Society (UHMS). Chronic non-diabetic wounds and non-neurological soft tissue radiation injuries are among these, with HBOT treatment for both indications currently offered at a number of public hospitals and private hyperbaric facilities across Australia and reimbursed under MBS item 13015. HBOT also currently receives ongoing funding for the treatment of a range of other approved indications under MBS items 13020, 13025 and 13030.

The most common chronic wounds encountered in the Australian health care context are a consequence of diabetes, arterial and/or venous disease, and sustained pressure. Although the use of HBOT for treatment of diabetic wounds is currently covered by MBS item 13020, the current assessment focuses on the use of HBOT for chronic wounds where the primary causative factor is non-diabetic, such as arterial ulcers, venous ulcers, or pressure ulcers. As proposed by the applicant and confirmed by expert opinion, chronic wounds were defined as those where appropriate attempts to heal by means other than HBOT had failed over a period of no less than 12 weeks. Through the enhanced delivery of oxygen that it offers, HBOT is proposed to be of benefit in promoting healing and increasing vascularity in hypoxic tissues where an otherwise insufficient supply of oxygen prevents normal healing processes, such as chronic wounds and radiation-damaged soft tissue.

Radiotherapy is a common and well-established treatment of suitable malignancies across a variety of anatomical areas. However, in the process of treating cancer with radiation, anatomical structures that surround the cancer are also irradiated, and it is impossible to cure a tumour by radiotherapy without risk of normal tissue injury. A small proportion of patients will suffer with serious and persistent radiation-related injuries to surrounding soft tissue (e.g. hollow viscera, organs, overlying soft tissue including skin, blood vessels, muscle, and connective tissue) that can develop months or even years after radiation treatment. It is proposed that HBOT is effective in promoting healing and increasing vascularity in this radiation-damaged or necrotic soft tissue across all regions of the body. However, it should be noted that neurological tissue appears resistant to improvement from use of HBOT, and is not considered to be appropriate for treatment with HBOT.

2. Background

On two previous occasions, MSAC has assessed the safety, effectiveness and cost-effectiveness of HBOT.

MSAC assessment 1018-1020

Prior to 2001, treatment with HBOT for non-diabetic wounds and soft tissue radionecrosis had received ongoing public funding through the MBS. Conducted in 2000, MSAC assessment 1018-1020 examined the safety, effectiveness and cost-effectiveness of HBOT treatment across a diverse range of indications (MSAC 2001). This assessment concluded that insufficient or conflicting evidence was found for the use of HBOT for treatment of non-diabetic wounds and soft tissue radionecrosis. On 9 February 2001, the Minister for Health and Ageing accepted MSAC's recommendation that 'public funding should not be supported for HBOT administered in either a multiplace or monoplace chamber' (MSAC 2001, p. 93) for the treatment of non-diabetic wounds and soft tissue radionecrosis. It was later decided that access to the use of HBOT for these indications would be maintained through the MBS on an interim basis.

MSAC assessment 1054

In 2002, MSAC re-assessed the safety, effectiveness, and cost-effectiveness of HBOT, specifically as a secondary therapy for non-healing wounds in non-diabetic patients and in refractory soft tissue radiation injuries. This review incorporated new evidence generated since the initial review, including a small number of randomised controlled trial (RCT) studies providing moderate level II evidence. The assessment reported some clinical benefit for HBOT; positive clinical results were found regarding healing of non-healing wounds in non-diabetic patients, healing of tooth socket wounds following extraction from irradiated tissue, and reduction of healing complications in soft tissue grafts into irradiated tissue. However, MSAC concluded that the clinical evidence was inadequate to substantiate claims that HBOT was cost-effective in the treatment of non-healing wounds in non-diabetic patients and in refractory soft tissue radiation injuries.

From this assessment MSAC recommended that, in the absence of effective alternative therapies and in view of the progress of local data collections and an international trial, funding for HBOT should continue for existing MBS listed indications at eligible sites for a further three years. This recommendation was accepted by the Minister for Health and Ageing on 31 August 2004.

Current assessment (MSAC assessment 1054.1)

At present, treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries continues to receive interim funding under MBS item 13015 pending Ministerial decision informed from the MSAC recommendations in the current assessment.

The current assessment was initially proposed to be an update of MSAC assessment 1054; however, it was determined in consultation with the Advisory Panel that a number of modifications were required to the assessment methodology. These primarily consisted of amendments to the relevant evidence selection criteria to more closely reflect current clinical practice, based on the findings from the previous assessment and comprehensive documentation submitted by the applicant. It was subsequently agreed by the Advisory Panel that the present assessment should include and re-evaluate all relevant evidence regarding the safety, effectiveness and cost-effectiveness of HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injury. The current assessment takes into consideration the findings of the two previous publications, and recognises that some issues, such as descriptions of the procedure, general discussions of safety and primary studies previously identified as relating to the present indications, remain largely unchanged.

It should be noted that the applicant included in their submission a comprehensive evidence review that incorporated all treatment options for chronic non-diabetic wounds and non-neurological soft tissue radiation injury, and requested that HBOT be assessed within this broader context. However, given the inability for non-comparative studies to be used to determine an intervention's relative effectiveness within the MSAC process, this was deemed outside the remit of the current assessment.

3. Prerequisites to implementation of any funding advice

Four monoplace hyperbaric units are currently listed on the Therapeutic Goods Administration (TGA) Australian Register of Therapeutic Goods (ARTG). Multiplace chambers, as fixed installations, have been exempted from listing on the ARTG.

Hyperbaric oxygen therapy will continue to be provided only in 'comprehensive hyperbaric medicine facilities' as defined in MBS Note T1.1. The applicant has stated their explicit support for the current definition of a comprehensive hyperbaric medicine facility and the standards under which these facilities operate. Detailed requirements for a hyperbaric facility are outlined in Australian Standard AS-4774.2.

The applicant does not propose any change to the current definition of 'an appropriate physician' as currently defined in the Medicare Benefits Schedule (MBS). This service will continue to be provided by physicians with appropriate training and qualifications in the field of diving and hyperbaric medicine. To use the proposed item number, a practitioner must have the Diploma of Diving and Hyperbaric Medicine awarded by the South Pacific Underwater Medical Society as a minimum requirement.

4. Proposal for public funding

At present, the use of HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries is covered under MBS item 13015, listed below. The applicant does not support the current wording of the item descriptor for this item – preferring a change from "soft tissue radionecrosis" to "soft tissue radiation injury and necrosis". (MSAC's advice to the Minister suggests a revised item descriptor).

Item descriptor for MBS item 13015

Category 3 – THERAPEUTIC PROCEDURES
MBS 13015 HYPERBARIC OXYGEN THERAPY, for treatment of soft tissue radionecrosis or chronic or recurring wounds where hypoxia can be demonstrated, performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine, for a period in the hyperbaric chamber of between 1 hour 30 minutes and 3 hours, including any associated attendance.
Fee: $245.10 Benefit: 75% = $183.85 85% = $208.35

The applicant's proposed uses of HBOT are for treatment of:

- non-diabetic chronic or recurring problem wounds where hypoxia can be demonstrated, which have failed to heal after 12 weeks of standard care; and
- patients with late soft tissue radiation injury and necrosis excluding radiation injury to neurological tissue.

The most common chronic wounds encountered in Australia are a consequence of diabetes, arterial and/or venous disease, sustained pressure, and those as a result of therapeutic irradiation for the treatment of tumours. More than one such process may be present in an individual and contribute to the wound and they are more common in the elderly and those with multiple health problems.

The applicant cited the following contraindications to treatment in the following groups of patients:

- Untreated pneumothorax;
- Severe congestive cardiac failure;
- Previous or concurrent administration of bleomycin;
- Concurrent administration of Cisplatinum, Adriamycin or Disulphiram;
- Severe or untreated asthma;
- Severe COPD with history of carbon dioxide retention;
- History of inner ear barotraumas, sinus squeeze or difficulty ventilating the middle ear;
- Pregnancy;
- Known untreated active malignancy;
- Cardiac pacemaker (manufacturer dependent);
- High fever;
- Seizure disorder; and
- Congenital spherocytosis.

The applicant advised that this service can only be given in a facility that satisfies the Medicare definition of a 'comprehensive facility'. This includes the ability to treat intensively unwell individuals, including those intubated and ventilator dependent, and a 24 hour emergency service. This limits the provision of hyperbaric services to a secondary setting.

To date, the only hyperbaric facilities in operation are those based in hospitals with an intensive care capability within the metropolitan region of Australia. Patients are treated in a secondary or tertiary setting depending on the acuity of their case mix. For the proposed indications, HBOT is always a second-line treatment only to be considered following the failure to respond to more conservative measures such as dressing, debridement and antibiotics. No patients will be seen without referral from a primary care physician or specialist.

The physician may be trained in General Practice as a primary specialty, but for the purposes of the proposed item, will be acting as a secondary practitioner by referral from a specialist or primary care physician. The service will be provided by physicians with appropriate training and qualifications in the field of diving and hyperbaric medicine (awarded by the South Pacific Underwater Medical Society). The applicant does not propose any change to the current definition of an appropriate physician as currently defined in the MBS, nor to patient restriction due to specific clinical indications or prior interventions.

5. Consumer Impact Statement

Chronic non-diabetic wounds and soft tissue radiation injuries are distressing conditions that can significantly and adversely affect a person's life. Both can cause severe physical pain and hardship, with the potential for prolonged periods of disability, prevention of performing everyday activities, and the potential for serious adverse health outcomes if unsuccessfully treated.

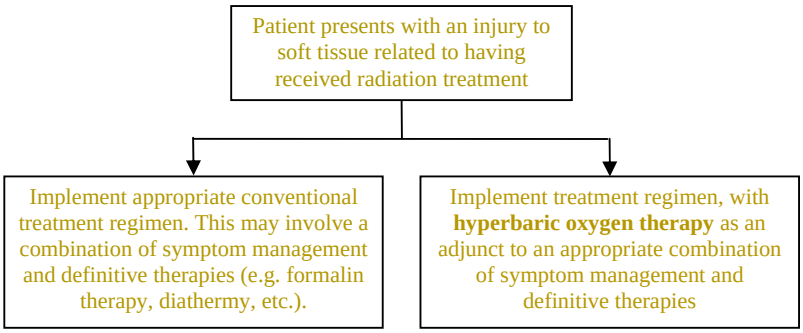
Both conditions require frequent, intense attention, symptomatic treatment and continual care. During treatment, people may have to cope with specialised devices or beds, lack of mobility, dressing changes, drainage, odour, clothing limitations, and sleep deprivation. As such, a non-healing wound or radiation injury can impede social interactions and may prevent a return to employment, forcing people to choose between a commitment to work and a commitment to the medical management of their condition, with both economic and psychological ramifications.

In many patients, these conditions do not respond to conventional and symptomatic treatment, and both can lead to serious complications that can significantly affect quality of life. In some cases, particularly with respect to soft-tissue radiation injuries, these complications can also be life threatening. If the patient does not respond to conventional therapies and chronic wounds or soft tissue radiation injuries continue to progress without healing, a more invasive surgical response such as surgical debridement or amputation (followed by extensive repair), thermal coagulation therapy, or formalin therapy are often required.

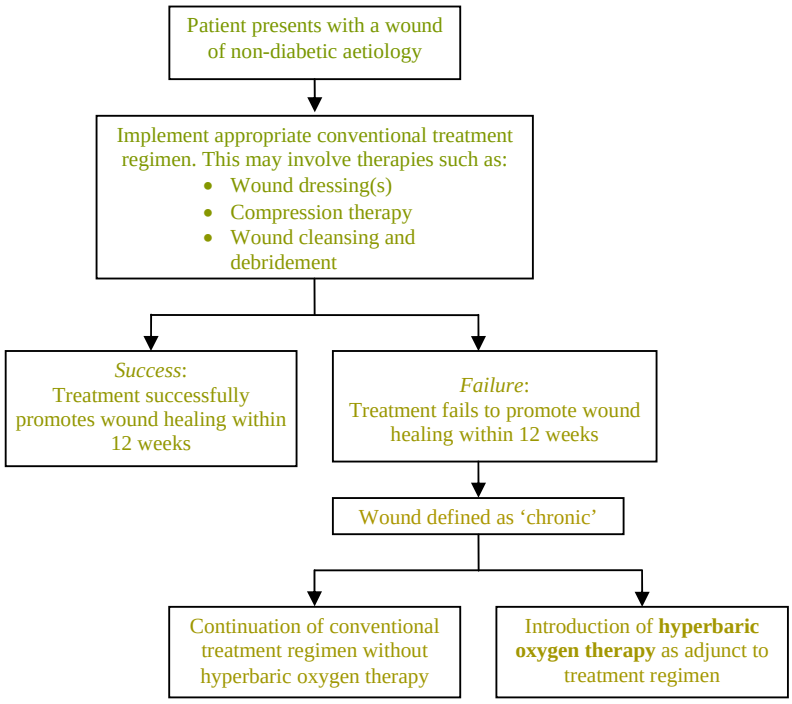
6. Proposed intervention's place in clinical management

HBOT is most commonly used as an adjunct to ongoing conventional therapies or symptomatic treatments, and aims to reverse the vascular compromise responsible for refractory wounds and soft tissue radiation injuries, promoting healing before more radical and invasive treatments are required. For these indications it is suggested for use as a secondary intervention, introduced after primary interventions and conventional therapies have failed to promote wound or radiation injury healing. As such, in this instance HBOT is used in addition to conventional therapies and symptomatic treatments, rather than in place of another current intervention.

Clinical flow chart: hyperbaric oxygen therapy for treatment of non-neurological soft tissue radiation injuries



Clinical flow chart: hyperbaric oxygen therapy for treatment of chronic non-diabetic wounds



7. Comparator to the proposed intervention

The range of available interventions available for the treatment of chronic non-diabetic wounds and soft tissue radiation injuries is sizeable and heterogeneous, depending on the nature of the chronic wound or radiation injury. In the majority of cases, a conventional treatment regimen consists of a complex combination of therapies. HBOT is most commonly used as an adjunct to ongoing conventional therapies, and not as a direct alternative. It is overly simplistic to suggest that for either treatment indication there is a single other therapy against which HBOT should be compared. In light of this and the limited comparative evidence found in MSAC assessment 1054, it was resolved in consultation with the Advisory Panel that restricting evidence selection to specific comparator treatments would be impractical and inappropriate. Given the clinical use of HBOT as an adjunct treatment to conventional therapy, the use of placebo or 'no treatment' were also deemed to be appropriate comparators.

The current assessment considered and included evidence that compared the use of HBOT to any procedures or treatments that did not use HBOT, including standard or conventional therapies (variously defined), normobaric oxygen, or placebo procedures. This incorporated all studies that employed a direct, head-to-head comparison methodology where the use of HBOT was a primary variable of consideration.

8. Comparative safety

The literature search identified 14 studies that reported safety for non-neurological soft tissue radiation injury, however, no studies examined safety with regards to chronic non-diabetic wounds.

Three systematic reviews investigated the safety of HBOT for non-neurological soft tissue radiation injuries and two systematic reviews investigated the safety of HBOT for chronic non-diabetic wounds.

All primary studies included in this assessment were reviewed for data related to adverse events occurring after treatment with HBOT. Fourteen studies encompassing 416 patients reported on mortalities occurring within their patient cohort during study follow-up. Twenty-five studies encompassing 634 patients made some quantification of safety outcomes or adverse events from HBOT treatment in their reporting of patient outcomes. Patient populations of interest within these studies ranged from four to 120. Although four studies reporting adverse events were comparative, none of these reported safety outcomes or adverse events for patients in comparator groups, preventing a direct safety comparison of adjunctive HBOT compared to conventional treatment without HBOT. Therefore, safety was reported and discussed in absolute terms.

No deaths were attributed to HBOT treatment. Reported patient mortalities generally occurred months or years after HBOT treatment, and were due to recurrence or progression of malignancies, progression of condition after failure to heal, or other unrelated causes.

As was found in the previous MSAC assessments of HBOT, adverse events related to treatment with HBOT for both indications were primarily barotraumas, visual changes, claustrophobia, and oxygen toxicity. The most common adverse events associated with HBOT were barotraumas and visual changes, particularly myopia (not permanent), which were reported in 5 to 10 per cent of all patients in those studies included for evaluation of safety. Claustrophobia and anxiety in the treatment chamber was reported in just over 1 per cent of patients in all studies included for evaluation of safety, while seizure or convulsion due to oxygen toxicity of the central nervous system was found to occur in less than 1 per cent of patients in all studies included for evaluation of safety. These adverse events are all considered to be minor and self-limiting, rarely lead to discontinuation of treatment, and where present usually resolve shortly after cessation of treatment.

No evidence directly comparing HBOT to treatments or therapies without use of HBOT was available. However, the minor and self-limiting nature of adverse events related to this treatment suggests that clinical management with HBOT is of similar safety to management with conventional conservative or symptomatic therapies (e.g. wound dressings and irrigation, debridement, stool softeners, bladder lavage, etc.).

MSAC members agreed that any adverse events related to treatment with HBOT (for example, barotraumas, visual changes, claustrophobia and oxygen toxicity) were minor and self-limiting, and HBOT is of similar safety to conventional and conservative therapy.

9. Comparative effectiveness

A total of 39 publications were identified for the assessment of HBOT for the treatment of non-neurological soft tissue radiation injuries. There were six RCTs, two non-randomised comparative studies and 31 descriptive case series. One RCT and five case series were also included in this assessment of HBOT for the treatment of chronic non-diabetic wounds.

Evaluation of the relative effectiveness of HBOT for the treatment of chronic non-diabetic wounds was based primarily on one small RCT. Five case series publications provided supplementary data; however, it should be noted that three of these case series reported results from the ongoing ANZHMG Wound Care Study, a multi-centre Australian prospective cohort study initiated following recommendations arising from MSAC assessment1054.

Evaluation of the relative effectiveness of HBOT for the treatment of non-neurological soft tissue radiation injuries was based primarily on seven comparative studies, including five RCTs (reported across six publications). A range of soft tissue radiation injuries were examined in these comparative studies, including radiation proctitis, wounds within irradiated soft tissue of the head and neck, and radiation-induced soft tissue oedema. A total of 31 case series studies examining various soft tissue radiation injuries supplemented the available comparative study evidence.

As well as the included primary evidence, six well-conducted secondary studies (systematic reviews and health technology assessments), that generally identified the same body of primary source evidence retrieved by the current assessment, provided summary supporting data on the effectiveness of HBOT for both indications.

Non-neurological soft tissue radiation injuries

Two RCTs, one a placebo-controlled trial, showed a significantly higher probability of proctitis healing outcomes, improvement in radiation-induced morbidity and quality of life in patients receiving HBOT as an adjunct to conventional treatment compared to conventional treatment without HBOT, up to 6 months post-intervention. This data was supported by nine case series studies which, despite some heterogeneity in outcome reporting, generally showed marked healing and symptom response in over half of patients treated with HBOT.

With regards to soft tissue radiation injuries to the head and neck region, one RCT reported significantly better healing of dental extraction socket wounds within irradiated soft tissue for HBOT patients 6 months post-treatment, compared to a group receiving antibiotic therapy; similarly high rates of socket wound healing in HBOT patients were shown in four case series studies. One RCT with potential issues related to methodological quality showed patients receiving HBOT had significantly reduced rates of wound infection, wound dehiscence and delayed wound healing in myocutaneous grafts surgically introduced into irradiated tissue of the head and neck, when compared to patients treated without HBOT. The authors of a non-randomised comparative study examining post-surgery wound complications in irradiated soft tissues of the head and neck stated that treatment with HBOT appeared to have a beneficial effect on the healing process compared with treatment without HBOT; however, no direct statistical between-groups comparison was reported by the authors to verify this.

Two comparative studies, one an RCT, investigated the effect of HBOT on soft tissue oedema following irradiation for breast cancer. The RCT reported no statistically significant improvement in lymphoedema of the arm or quality of life at 12 months follow-up in patients who received HBOT as an adjunct to conventional treatment, compared to those who received conventional treatment without HBOT. The non-randomised comparative study showed significantly greater improvements in levels of pain, oedema and erythema of the chest wall as well as overall radiation-induced morbidity in patients treated with HBOT, but not in fibrosis and telangiectasia.

MSAC members discussed that:

- two RCTs and nine case studies showed improvement with radiation induced morbidity and quality of life for patients with proctitis;
- one RCT showed better healing for dental extraction socket wounds; reduced rates of wound dehiscence and delayed would healing in irradiated tissue for head and neck cancer; and
- one RCT showed no improvement with HBOT for radiation induced soft tissue lymphoedema after breast cancer.

MSAC agreed that for non-neurological soft tissue radiation injuries, the evidence base for improvement for proctitis was solid and to a lesser extent for head and neck.

Chronic non-diabetic wounds

The one included comparative study compared HBOT to placebo treatment for the healing of chronic non-diabetic leg ulcers. This RCT showed a significant initial decrease in wound area with HBOT compared to placebo, but this benefit was not found at 18 weeks after initiation of treatment. All included case series reports demonstrated beneficial outcomes from use of HBOT in wound healing or pain relief. Three of these reports were derived from the ANZHMG Wound Care Study, a multi-centre Australian prospective cohort study initiated following recommendations arising from MSAC assessment1054. Although uncontrolled, this study

represents a sizeable body of collective clinical data from Australian hyperbaric facilities measuring the response to HBOT, in Australian practice, of chronic problem wounds that have failed 3 months of standard treatment.

MSAC agreed with ESC that although there was improvement in the evidence in the size of the wound area and pain relief, there was overall insufficient evidence for the chronic non-diabetic patient group.

With regards to non-neurological soft tissue radiation injuries, the available evidence asserts that, in general, clinical management with HBOT is more effective than clinical management without HBOT. However, it should also be noted that the use of HBOT for radiation-induced soft tissue lymphoedema of the arm after treatment for breast cancer is not supported by available evidence.

With regards to chronic non-diabetic wounds, while the available evidence tentatively indicates a benefit for the use of HBOT, the overall body of evidence is currently insufficient to determine whether clinical management with HBOT is more effective than clinical management without HBOT.

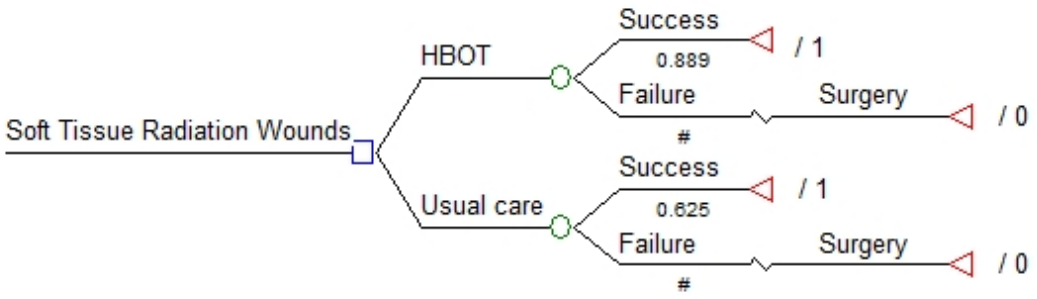
10. Economic evaluation

The economic evaluation adopted a cost-effectiveness analysis framework for soft tissue radiation injuries (STRIs) and a cost-minimisation analysis framework for chronic non-diabetic wounds. For both indications HBOT was compared to usual care. For STRI, the incremental costs per patient wound healed/improved were presented. For chronic wounds the incremental costs were presented. This mixed approach was undertaken due to lack of high level evidence for effectiveness data for chronic wounds and quality of life data across both indications. A health care perspective was adopted.

Non-neurological soft tissue radiation injuries

A decision tree was developed to synthesise data from a variety of sources:

Decision tree: Soft tissue radiation injuries



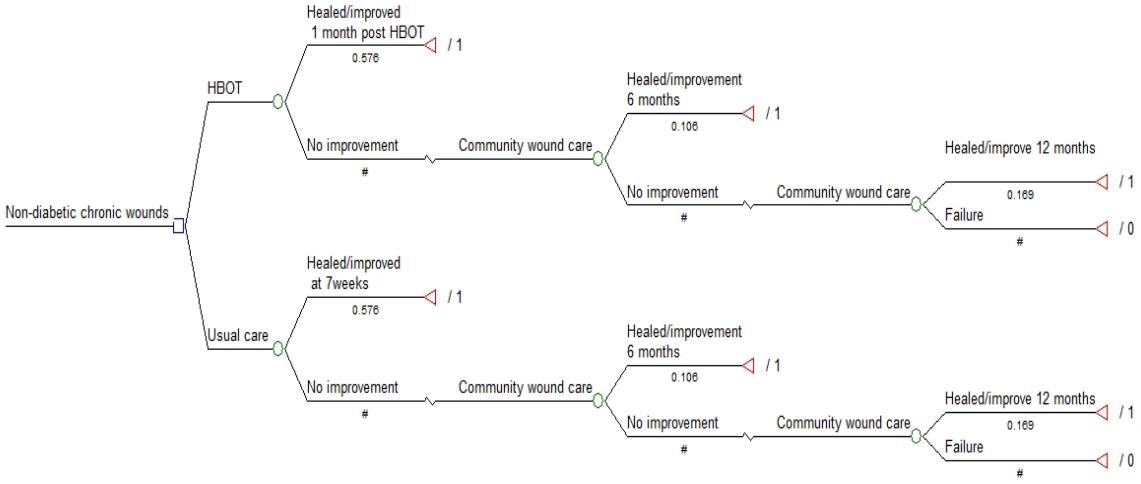
Estimates of effectiveness were obtained from a published randomised controlled trial (Clarke et al 2008). MBS item numbers were determined by the Advisory Panel and resource use was obtained by analysis of MBS claims data provided by the Department of Health and Ageing, the literature and the Advisory panel. Unit costs were obtained from Australian Refined Diagnostic Related Group (AR-DRG) Version 5.1 round 12 – Private) and MBS data. MBS average co-payment data were provided by the Department of Health and Ageing.

The results indicate that HBOT is a cost-effective alternative to usual care for the treatment of soft tissue radiation injuries. There is considerable uncertainty around the estimates of usual care due to the complexity of the treatment pathway.

Chronic non-diabetic wounds

A decision tree was developed to synthesise data from a variety of sources:

Decision tree: Chronic wounds



Estimates of effectiveness were obtained from case series data (Hawkins and Bennett, 2011). The MBS item numbers were determined by the Advisory Panel and resource use was obtained by analysis of MBS claims data provided by the Department of Health and Ageing, the literature and the Advisory panel. Unit costs were obtained from AR-DRG Version 5.1 round 12 – Private) and MBS data. MBS average co-payment data were provided by the Department of Health and Ageing.

There is considerable uncertainty around the estimates of usual care due to the complexity of the treatment pathway.

The results indicate that usual care is a less expensive option for the treatment of chronic wounds, ceteris paribus. There is uncertainty around the comparative effectiveness of HBOT and usual care. While the available evidence tentatively indicates a benefit for the use of HBOT, the overall body of evidence is currently insufficient to determine whether clinical management with HBOT is more effective than clinical management without HBOT.

Non-neurological soft tissue radiation injuries

For the base case analysis, significant/moderate improvement or complete wound healing was demonstrated in 88.9 per cent of patients that received HBOT for soft tissue radiation injuries, the comparable figure for usual care is 62.5 per cent of patients. Therefore providing HBOT would yield an additional benefit of 26.4 per cent successfully treated patients. The average cost accrued in the HBOT treated group is $11,753 per patient compared to $12,482 in the usual care group. Therefore this represents a costs savings of $728 per patient. This means that HBOT dominates usual care (i.e. HBOT is less expensive and is more effective).

The reason that HBOT is less expensive than usual care is because the additional cost of providing HBOT is more than offset by the reduction in costs of surgery for the additional patients that fail usual care.

Key uncertainties that drive the estimation of costs were the effectiveness of HBOT based on the 95% CI of a meta-analysis completed as part of the evaluation (SA, SA1a) and the definition of success, which considered only those patients who were healed or significantly improved in the Clarke et al (Clarke et al 2008) study (SA2) (base case is defined as healed, significantly and moderately improved).

The analysis assumes that HBOT is superior to usual care in terms of clinical effectiveness. However, this analysis does not take into account improvements in quality of life following successful treatment or any reduction in quality of life following surgery or due to unsuccessful treatment. Evidence suggests that the impact on patient's quality of life may be substantial. Consequently the actual benefit to the patient of providing HBOT may be underestimated.

Additionally, the model is restricted to patient costs that are incurred in the first year of treatment only. Depending on the success of surgery, a proportion of patients will incur additional usual care costs beyond this timeframe. These costs are likely to be greater in the usual care group, since more patients have healed wounds in the HBOT group at 12 months compared to usual care. For this reason the model is likely the underestimate overall costs in the usual care group.

There were a number of limitations with the approach to the analysis including: there is no standard management to the treatment of soft tissue radiation wounds; only the costs incurred in the first year of treatment were included in the model due to uncertainty in extrapolating beyond his time point; there is a lack of a data on the effectiveness of surgery for this patient group.

The results indicate that HBOT is a cost effective alternative to usual care for the treatment of soft tissue radiation injuries. There is considerable uncertainty around the estimates of usual care due to the complexity of the treatment pathway.

MSAC members noted the cost effectiveness model does not take into account improvements in quality of life and underestimates cost of care beyond 12 months. MSAC noted the ESC comment that the model is not particularly robust.

MSAC agreed HBOT for soft tissue radiation injuries is less expensive due to the reduction in costs of surgery. However, there is considerable uncertainly due to complexity of usual care, and the assumptions in the model (a) that all patients who are not successfully treated with HBOT or usual care undergo surgery, and (b) that the effectiveness of surgery is zero, bias the model in favour of HBOT.

Chronic non-diabetic wounds

The assessment report provides an estimate of the average costs used in the costing model. All costs are the total average cost for a patient treated for one year. The total estimated one-year-cost of HBOT and usual care vs. usual care only is: $24,365.60 and $22,214.74 respectively. This represents an incremental cost of $2,150 ($2,437 MBS plus $65 out of pocket items minus incremental gain of $351 consumables).

MSAC noted the cost minimisation model does not take into account improvements in quality of life and underestimates cost of care beyond 12 months, with the assessment report only providing an estimate of the average costs used in the costing model.

The results indicate that usual care is a less expensive option for the treatment of chronic wounds, ceteris paribus. There is uncertainty around the comparative effectiveness of HBOT and usual care. While the available evidence tentatively indicates a benefit for the use of HBOT, the overall body of evidence is currently insufficient to determine whether clinical management with HBOT is more effective than clinical management without HBOT.

MSAC noted that the applicant did not seek any change to the fees as currently defined in the MBS under Item number 13015: Fee: $245.10 Benefit: 75% = $183.85 85% = $208.35, for both indications.

The out of pocket expenses for chronic non diabetic wounds would be $3,576 per patient per year and out-of-pocket expenses for some patients would contribute to the Extended Medicare Safety Net (EMSN).

The out of pocket expenses for radiation proctitis would be $2,002 per patient per year and would contribute to EMSN.

11. Financial/budgetary impacts

Statistics giving the exact prevalence, disability, and impairment of chronic non-diabetic wounds and soft tissue radiation injuries are difficult to obtain, particularly within the Australian health care context. For chronic non-diabetic wounds this is due to the variety of underlying aetiologies, that multiple processes may be present in an individual and contribute to the wound, and that a great deal of wound care is delivered at home. For soft tissue radiation injuries, the number of patients experiencing a soft tissue radiation injury is dependent on the number of patients receiving radiation treatment, and there is also considerable diversity in radiation injury location and type.

The data that are available suggest that, although not common, such wounds and injuries are expensive to treat; for example, in 2004 it was estimated that the costs to the Australian health care system related to the management of venous ulcers alone were $AU550–650 million. Both the morbidity and prevalence of these conditions are likely to increase with a patient's age. With an ageing population, the incidence of both chronic non-diabetic wounds and soft tissue radiation injuries in Australia has the potential to rise significantly, highlighting the importance of treatment options that are both clinically and cost effective.

MBS data shows that 15,579 services for items specific to HBOT therapy were claimed in the 2010-11 financial year; of these, 8,910 were related to HBOT treatment of chronic non-diabetic wounds and soft tissue radiation injuries. Data presented at the 16th annual scientific meeting of the Hyperbaric Technicians and Nurses Association reported that between July 2007 and June 2008, 189 patients were treated for soft tissue radiation injuries while 154 patients were treated for hypoxic, non-diabetic problem wounds. In that period 5,035 services were claimed on the MBS for HBOT treatment of chronic non-diabetic wounds and soft tissue radiation injuries. If all patient treatments were claimed under the MBS, this constitutes an average of approximately 15 treatment sessions per patient. While not definitive, these figures help to provide some indication of the level of usage and clinical need for HBOT in the Australian context.

If direct replacement of usual care occurred for soft tissue radiation injuries, the overall cost would be $2,221,321. If HBOT were used to treat 189 patients instead of usual care, there would be a cost savings of $137,679 per annum. It is important to note that there is an increasing trend of utilisation since 2007 and as a result this may underestimate future financial implications. All of the cost savings are related to consumable costs. Out of pocket costs are considerable and likely to impact upon the EMSN.

As can be seen in the assessment report, if direct replacement of usual care occurred for chronic non-diabetic wounds, the overall cost would be $3,752,327. If HBOT was used to treat 154 patients instead of usual care, there would be an incremental cost of $331,256 per annum. All of the cost savings are related to consumables. Out of pocket costs are likely to impact upon the EMSN.

For non-neurological soft tissue radiation injuries, 189 patients per annum would use HBOT with a cost of $804,362 for consumables, $1,038,410 borne by the MBS and $378,549 for patient out-of-pocket costs.

For chronic non-diabetic wounds, 154 patients per annum would use HBOT with a cost of $2,509,378 for consumables, $692,317 borne by the MBS and $550,631 for patient out-of-pocket costs, totalling $3,752,327.

Other cost considerations

The analysis assumes that HBOT is not significantly different from usual care in terms of clinical effectiveness. This is likely to underestimate the cost of usual care. In addition this analysis does not take into account improvements in quality of life following successful treatment or any reduction in quality of life following surgery or due to unsuccessful treatment. Evidence suggests that the impact on patient's quality of life may be substantial. Consequently the actual benefit to the patient of providing HBOT is likely to be underestimated.

Additionally, the model is restricted to patient costs that are incurred in the first year of treatment only. A proportion of patients will incur additional usual care costs beyond this timeframe and these are likely to escalate for those patients who fail treatment.

12. MSAC Key Issues

As was reported in previous MSAC assessments of HBOT, adverse events related to treatment with HBOT are generally minor and self-limiting, rarely lead to discontinuation of treatment, and where present usually resolve shortly after cessation of treatment. Comparative data for the safety of HBOT as an adjunct to conventional treatment with reference to conventional treatment without HBOT was not available. However, based on absolute data, HBOT can be considered to be a safe and well-tolerated intervention, for which serious, life-threatening adverse events and fatalities are very rare.

Adverse events associated with most conservative and symptomatic therapies for chronic non-diabetic wounds and soft tissue radiation injuries are expected to be relatively minor or negligible. Although HBOT is widely regarded to be a safe and well-tolerated intervention, the determination of the relative safety of HBOT is hampered by a lack of comparative evidence in this area, and the potential for significant heterogeneity in what study authors defined as constituting an adverse event.

Good quality evidence was found supporting the use of HBOT as an adjunct to conventional treatments for non-neurological soft tissue radiation injuries, demonstrating similar rates of wound and mucosal healing as well as other beneficial patient outcomes across a range of soft tissue types. This evidence asserts that HBOT as an adjunct to conventional treatment provides significantly greater clinical benefit to patients for the treatment of non-neurological soft tissue radiation injuries when compared to conventional treatment without HBOT. However, it should be noted that available studies currently do not support the use of HBOT for radiation-induced soft tissue lymphoedema of the arm after treatment for breast cancer.

While low level evidence was found within the Australian healthcare context that indicates a potential benefit in healing and pain relief for the use of HBOT, the overall body of published evidence is currently insufficient to determine the relative clinical effectiveness of HBOT as an adjunct to conventional treatment for chronic non-diabetic wounds, compared to conventional treatment without HBOT.

With respect to non-neurological soft tissue radiation injuries, the conclusions regarding the effectiveness of HBOT are moderated to some degree by the methodological quality of the included studies. The majority of comparative studies retrieved for this indication were of mediocre or poor methodological quality, an issue also acknowledged in the previous MSAC assessment (MSAC assessment 1054) and a number of included secondary studies. As it is known that effect sizes in RCTs are overestimated if particular methodological parameters are not addressed sufficiently, results from particular comparative studies should be interpreted with caution. In the case of HBOT, blinding of participants to treatment allocation is challenging; however, other important aspects of high quality comparative studies, such as appropriate randomisation methodology and concealment of allocation from investigators, were generally not consistently conducted or reported.

Available evidence generally does not support the use of HBOT for radiation-induced soft tissue lymphoedema of the arm after treatment for breast cancer. This may be due to the different physiological nature of lymphoedema to other soft tissue radiation injuries examined by the current assessment. As such, the treatment of radiation-induced soft tissue lymphoedema with HBOT may not be appropriate.

In the case of chronic non-diabetic wounds, the conclusions that can be drawn from the evidence regarding the relative effectiveness of HBOT are severely limited by a paucity of high quality studies, with only one low-powered comparative study retrieved. The remaining studies included to assess effectiveness outcomes for HBOT were all case series, which are of limited value in determining the effectiveness of an intervention due to their proneness to bias.

MSAC agreed that the evidence is weak for chronic non-diabetic wounds, however, there is good quality evidence for non-neurological soft tissues radiation injuries (proctitis, and head and neck), and mixed evidence for proctitis vs breast cancer lymphoedema.

MSAC members noted that there was uncertainty around cost-effectiveness in terms of the sensitivity analysis as the applicant had modified the definition of success which resulted in cost savings.

MSAC agreed:

- there are two evidence bases for the two indications; soft tissue radiation injuries and refractory wounds in non-diabetic patients;
- HBOT has no clear comparator and it is therefore difficult to gather evidence when HBOT is already established as a treatment modality; and
- there is a reduction in costs for soft tissue radiation injuries due to cost savings in the reduction of surgery and the healing rate is higher.

13. Other significant factors

MSAC noted:

- the two dissenting views from the hyperbaric oxygen clinicians on the advisory panel;
- the overall body of published evidence is currently insufficient to determine the relative clinical effectiveness of HBOT as an adjunct to conventional treatment for chronic non-diabetic wounds, compared to conventional treatment without HBOT.
- serious concerns were raised about the cost-effectiveness results as the technology is more expensive;
- the change in proctitis care (Clarke study – pelvic radio therapy) and that treatment of prostate cancer is changing, therefore HBOT may become redundant as the best evidence available for HBOT at present is for a treatment that may not be required.
- that there may be other indications or patient groups that have not been included in this evaluation;
- that the pre-anaesthetic consultation item (sub-speciality anaesthetics) was not included in the evaluation;
- that there is uncertainty of usual care because of the lack of available evidence and the homogenous nature of it;
- that standard procedures / guidelines for those who perform HBOT could be developed to standardise the approach.

MSAC noted ESC advice that there is no mention of ‘non-diabetic’ in the current item descriptor, yet it appears in MBS item number 13020.

MSAC members agreed that the item descriptor 13015 be changed to remove reference to ‘radionecrosis’ and exclude patients with lymphoedema of the arm following breast cancer.

14. Summary of consideration and rationale for MSAC’s advice

MSAC reviewed two indications for hyperbaric oxygen therapy (HBOT): treatment of chronic or recurring non-diabetic wounds where hypoxia can be demonstrated and treatment of non-neurological soft tissue radiation injuries.

For both indications, MSAC recognised that HBOT is used to manage a small number of patients with clear clinical need at small overall financial cost to the MBS; affirmed that HBOT is added to other treatments rather than replacing other treatments; and re-affirmed that HBOT is clinically safe, with adverse events being minor and self-limiting, such as barotraumas and

visual changes in 5% to 10% of patients, claustrophobia and anxiety in about 1% of patients, and seizures in less than 1% of patients. These events did not interrupt the delivery of HBOT.

MSAC reviewed comparative effectiveness and cost-effectiveness separately for the two indications.

Soft tissue radiation injuries

MSAC agreed that the terminology of "soft tissue radionecrosis" is no longer clinically appropriate for use in the item descriptor. Accordingly, MSAC preferred the terminology of "treatment of localised non-neurological soft tissue radiation injuries" to identify this eligible patient population. Furthermore, MSAC noted that patients with radiation necrosis would not be referred for HBOT.

MSAC reviewed a randomised sham-controlled trial of HBOT in 150 patients with radiation proctitis not responding to other treatment for at least three months (Clarke et al, 2008) as strong evidence of comparative clinical effectiveness. This trial confirmed that the blinding in the trial by use of a sham was effective (demonstrating that participants could not guess whether or not they had received HBOT), and also reported that participant characteristics were reasonably equivalent at baseline. Follow-up was reasonable, with 80% analysed after completion of HBOT (generally consisting of 30 sessions) and before cross-over. Given the cross-over design, benefits and harms could not be compared beyond this time point.

Using a composite score ("SOMA-LENT") assessing subjective symptoms such as stool frequency, pain and mucosal loss, objective measures such as bleeding ulceration and stricture, and management strategies of these symptoms and measures, this trial reported a statistically significant difference of 2.75 ($p=0.019$) from an average baseline score of 12.7 (endpoint score of 10.23 for sham and 7.48 for HBOT). At cross-over, patients subsequently receiving HBOT improved further. Follow-up beyond cross-over up to five years confirmed further improvement, but not complete resolution of the radiation proctitis.

The results of this trial were supported by the results of a 6-month non-blinded randomised trial in 65 patients with radiation proctitis (Sidik et al, 2007a and 2007b) and consistent with two of three other randomised trials (healing of dental extraction socket wounds, Marx et al 1985 and patients with irradiated head an neck tissues, Marx 1999) and case series data. However no benefit was demonstrated in a fifth randomised trial (Godhardt et al, 2010) of women with radiation-induced lymphoedema following breast cancer.

MSAC considered that these results were sufficiently representative of all soft tissue radiation injuries, except that HBOT is not supported for radiation-induced soft tissue injury in the presence of lymphoedema. This exclusion is because of the lack of a demonstrated effect in the randomised trial in patients with lymphoedema of the arm after treatment for breast cancer. MSAC further noted that there were five ongoing randomised trials in radiation injuries, including radiation cystitis, laryngeal irradiation, radiation-induced xerostomia and irradiation of the mandible.

MSAC agreed with its Evaluation Sub-Committee (ESC) that the conclusion of cost-saving in the economic evaluation was unlikely to be realised due to bias favouring HBOT in the assumptions that all patients not receiving HBOT would receive corrective surgery that would not be effective. Thus the cost of HBOT might not be exceeded by subsequent reductions in surgery. In addition, the number of HBOT sessions assumed in the model (23) was less than the planned number in Clarke et al 2008 (30), but more than the number derived from a 2007-08 survey reported at a conference [16th ASM HTNA] of 5035 services rendered for 343 patients with either radiation injuries or chronic non-diabetic wounds (15). Despite these and other uncertainties identified by ESC, MSAC considered that use of HBOT in this setting would be acceptably cost-effective, even if not necessarily cost-saving, including by reference to the sensitivity analyses provided in the assessment report.

In relation to financial implications, MSAC noted that the risk of wider usage and costs to the MBS over time would most likely come from using HBOT earlier in the management of the condition rather than trying other treatment options first.

MSAC also noted great uncertainty around the average number of treatments patients have in Australia, and whether patients who achieve success with HBOT are referred sooner or later in their condition, considering most patients use HBOT after conservative treatments have failed. MSAC also noted that there would likely to be a decreasing need for HBOT due to the use of more targeted radiation therapies that reduce radiation injury to adjacent tissue, as well as the limited number of comprehensive hyperbaric facilities available in Australia.

Chronic or recurring non-diabetic wounds

MSAC primarily relied on the only available randomised placebo-controlled trial of HBOT in 16 patients (8 patients in each group) with chronic non-diabetic leg ulcers not responding to other treatment for at least two months (Hammarlund & Sundberg, 1994) as the strongest evidence of comparative clinical effectiveness. MSAC noted that the other case series data, including data collected in Australia during the period of interim funding on the MBS, did not represent stronger evidence because these case series data were non-comparative.

The results of the Hammarlund & Sundberg, 1994 trial indicated a statistically significant difference in the reduction in wound size of 33% (95% CI: 19%, 47%), corresponding to a 3% reduction for placebo and a 36% reduction for HBOT, at the end of treatment (six weeks after commencement of treatment). At 18 weeks after treatment, there was a similar improvement on average across the eleven patients available for follow-up (five receiving placebo and six receiving HBOT), resulting in a non-statistically significant difference of a similar magnitude in the reduction in wound size of 30% (95% CI: -23%, 82%), corresponding to a 26% reduction for placebo and a 56% reduction for HBOT. MSAC noted that a more convincing outcome would have been complete resolution of the wound and concluded that these results provided weak evidence in relation to any additional overall clinical effectiveness of HBOT over usual treatment.

MSAC noted that the economic evaluation for this indication assumed no additional effectiveness of HBOT and concluded that adding HBOT is more expensive than usual care in these patients. MSAC concluded that this extra expenditure was not justified by the weak evidence of additional clinical effectiveness.

MSAC noted that this indication had been publicly funded prior to 2001 when MSAC had advised the Minister that funding no longer be supported based on assessments 1018-1020. In 2002, in considering assessment 1054, MSAC supported MBS funding on an interim basis for a further three years and, in 2004, this advice was accepted.

MSAC noted the current assessment report, the dissenting report from some members of the advisory panel, and the response of the applicants.

MSAC considered that continuing interim funding would not serve a useful purpose because providing further opportunities to generate any more convincing comparative data was unlikely to be successful. MSAC also noted that a cessation of MBS funding for this indication would reduce access of some patients to this treatment.

15. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, effectiveness and cost-effectiveness of Hyperbaric Oxygen Therapy for the treatment of localised non-neurological soft tissue radiation injuries (that have not responded to usual treatments), excluding lymphoedema following breast cancer, MSAC supports continued public funding for HBOT for this indication.

Proposal to change current item descriptor:

THERAPEUTIC PROCEDURES MBS

MBS item number	Description	Fee	Benefit
	HYPERBARIC OXYGEN THERAPY, for treatment of localised non-neurological soft tissue radiation injuries (*excluding radiation-induced soft tissue lymphoedema of the arm after treatment for breast cancer*) or (*in the absence of lymphoedema*) performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine, for a period in the hyperbaric chamber of between 1 hour 30 minutes and 3 hours, including any associated attendance.	$245.10	75% = $183.85 85% = $208.35

After considering the strength of the available evidence in relation to the safety, effectiveness and cost-effectiveness of Hyperbaric Oxygen Therapy for the treatment of chronic non-diabetic wounds MSAC does not support public funding for this indication on the basis of insufficient evidence that it is more effective and acceptably cost-effective compared to usual care without HBOT.

16. Context for decision

This advice was made in accordance with MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

17. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The Assessment Report is available at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1054.1.