Review of interim funded service: *Hyperbaric oxygen therapy for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries*

November 2011

MSAC application 1054.1

Assessment report

☑ Advice of dissenting report 3/9/12
see http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1054.1

ISBN (Online) 978-1-74241-605-2

ISSN (Online) 1443-7139

First published (month & year to be added)

Paper-based publications

Internet sites

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at
http://www.msac.gov.au/

Printed copies of the report can be obtained from:

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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This report should be referenced as follows:
Hoggan B, Cronin P, Cameron A, Goodall S. (2011). *Hyperbaric oxygen therapy for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries*. MSAC Application 1054.1, Assessment Report. Commonwealth of Australia, Canberra, ACT.

Publication approval number: D0601

Contents

Tables

Figures

Executive summary

Assessment of hyperbaric oxygen therapy for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries

Purpose of application

An application 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 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) by the Commonwealth Department of Health and Ageing ('the department') in January 2010.

HBOT consists of a patient breathing 100 per cent oxygen while situated within a treatment chamber at a pressure higher than sea level pressure (ie >1 atmosphere absolute or ATA). According to clinical expert opinion, HBOT is considered clinically efficacious when 100 per cent 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, and may be delivered 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.

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.

HBOT is an established therapeutic modality for a range of health conditions, and is 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.

Chronic wounds, those that for various reasons do not respond to usual appropriate measures, are a common and significant health problem. They can arise in a variety of situations and may be associated with a number of pathological processes; more than one such process may be present in an individual and contribute to a wound. The most common chronic wounds encountered in the Australian healthcare context are a consequence of diabetes, arterial and/or venous disease, and sustained pressure. The use of HBOT for treatment of diabetic wounds is currently covered by MBS Item 13020, and 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 clinical 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.

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 (eg 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 to be resistant to improvement from use of HBOT, and is not considered to be appropriate for treatment with HBOT.

HBOT is not advocated to be used as a primary treatment for the treatment of chronic non-diabetic wounds and soft tissue radiation injuries. The place of HBOT is as a secondary intervention to be introduced after the exhaustion of primary treatment options with little or no improvement in patient outcomes. In this role it is used to promote healing before more invasive and severe treatment modalities are required.

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 in Table 1. The applicant does not propose any change to the descriptor for this Item.

Table 1 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

MBS: Medicare Benefits Schedule.

The applicant does not propose any change to details related to specialty groups performing the service, or patient restriction due to specific clinical indications or prior interventions. Their stated request is the restoration of full and ongoing funding for this Item, removing the requirement for Ministerial Determinations under subsection 3C of the Health Insurance Act.

A team from the Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S) was engaged to conduct a systematic review of the literature and an economic evaluation of HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries.

Current arrangements for public reimbursement

HBOT for the treatment of soft tissue radiation injury and radionecrosis and hypoxic problem wounds in non-diabetic patients was funded under MBS Item 13020 until 2001; as a result of MSAC assessment 1018-1020, use of HBOT for these indications was given a separate MBS Item number (13015), with funding maintained through the MBS on an interim basis. At present, this Item continues to receive interim funding pending Ministerial decision informed from the MSAC recommendations arising from the current assessment (MSAC assessment 1054.1).

HBOT currently receives ongoing funding for the treatment of a range of other indications (MBS Items 13020, 13025 and 13030). MBS Item 13020 is used to reimburse HBOT for the treatment of decompression illness, gas gangrene, air or gas embolism; diabetic wounds including diabetic gangrene and diabetic foot ulcers; necrotising soft tissue infections including necrotising fasciitis or Fournier's gangrene; or for the prevention and treatment of osteoradionecrosis.

With the exception of The Wesley Centre for Hyperbaric Medicine in Brisbane, the Hyperbaric Health facilities at Vaucluse and Berwick in Victoria and the Hyperbaric Health Facility at Mascot in Sydney, all comprehensive hyperbaric facilities are located in State teaching hospitals.

Background

MSAC has assessed the safety, effectiveness and cost-effectiveness of HBOT on two previous occasions; a summary of these assessments is provided below.

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. 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' for the treatment of non-diabetic wounds and soft tissue radionecrosis (MSAC 2001, p. 93). 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

MSAC subsequently 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 (MSAC 2004). This review incorporated new evidence generated since MSAC assessment 1018-1020, 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 assessment 1054 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. Hence, 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 application included 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 to be outside the remit of the current assessment.

Prerequisites to implementation of any funding advice

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

HBOT will continue to be provided only in 'comprehensive hyperbaric medicine facilities' as defined in MBS Note T1.1 (Commonwealth Department of Health and Ageing 2011b). 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 (Standards Australia 2002).

The applicant does not propose any change to the current definition of an appropriate physician as currently defined in the 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 SPUMS as a minimum requirement.

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.

HBOT offers a viable, safe and non-invasive treatment to promote healing in patients where conventional treatment therapies have been found to be ineffective. Indeed there may be a good argument to introduce HBOT earlier in the treatment pathway to potentially significantly improve patients' clinical outcomes and quality of life, and avoid the more radical and invasive treatment strategies otherwise used for these conditions.

Clinical need

Statistics informing on the exact prevalence, disability, and impairment of chronic non-diabetic wounds and soft tissue radiation injuries are difficult to obtain, particularly within the Australian healthcare context. For chronic non-diabetic wounds this is due to the variety of underlying aetiologies, the multiple processes that may be present in an individual and contribute to the wound, and the fact 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 these wounds and injuries are not common, they are expensive to treat. For example, in 2004 it was estimated that the costs to the Australian healthcare system related to the management of venous ulcers alone were $550–650 million (Leach 2004). Both the morbidity and prevalence of these

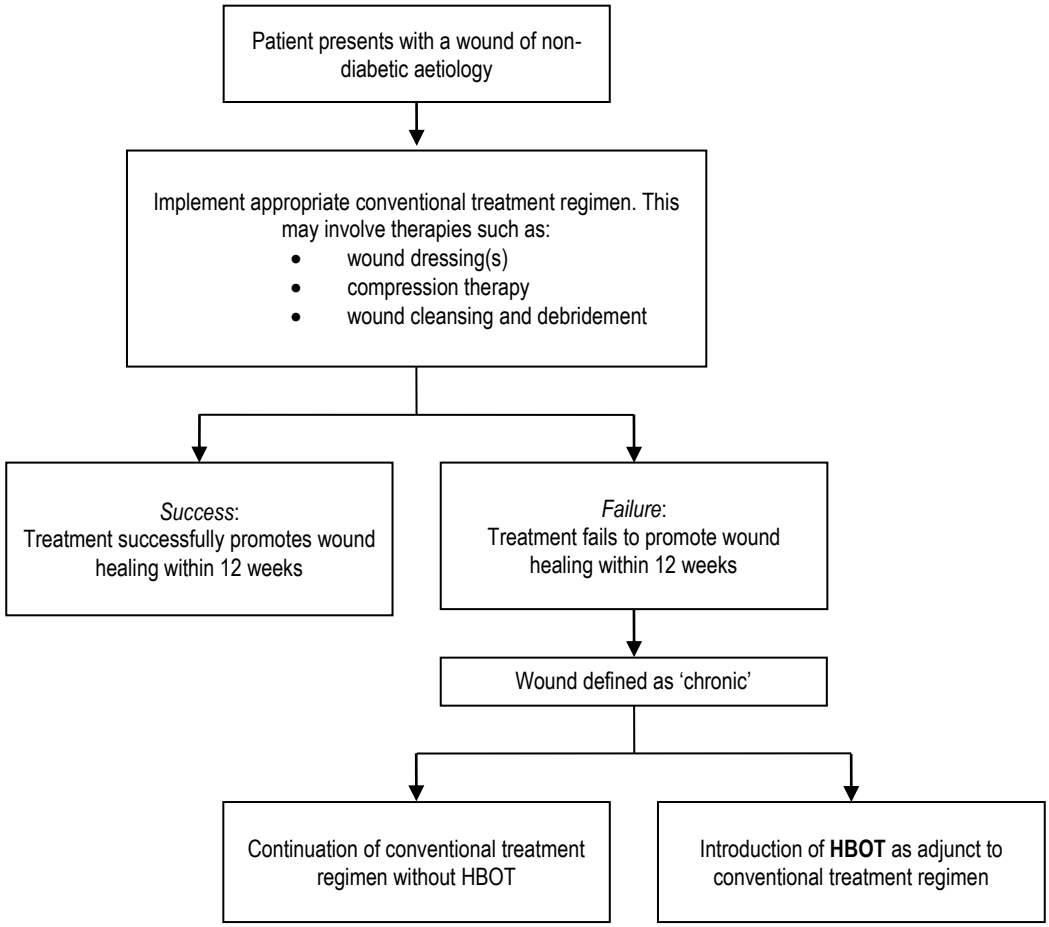
conditions are likely to increase with a patient's age. With an ageing population, the incidence of both chronic non-diabetic wounds and soft tissue radiation injuries in Australia has the potential to rise significantly, highlighting the importance of treatment options that are both clinically and cost effective.

MBS data show 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 (HTNA 2008). 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.

The clinical place of HBOT is somewhat unique within the clinical pathway of chronic wound and soft tissue radiation injury healing. It 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, to be 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.

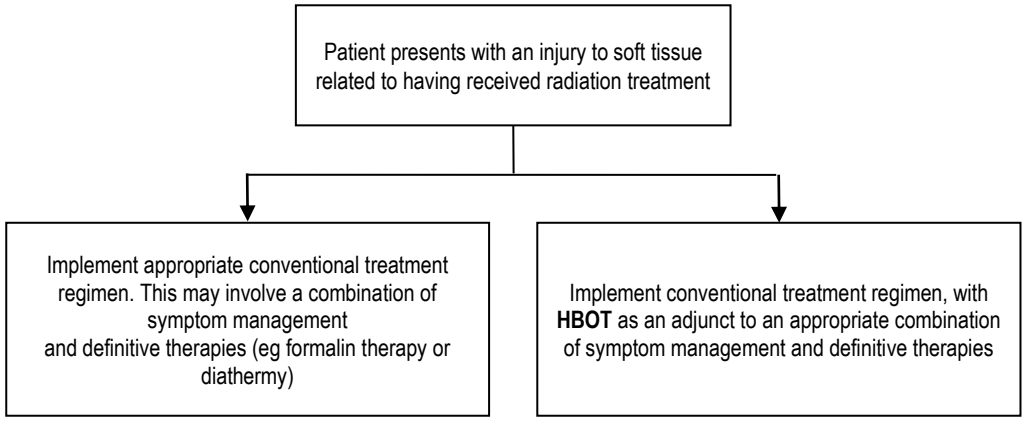
The current assessment commenced prior to the introduction of the Protocol Advisory Sub-Committee (PASC) process. As such, clinical management algorithms to address these specific points were not developed. The clinical flow charts provided in Figure 1 and Figure 2 are broad clinical pathways, developed in conjunction with the Advisory Panel, that illustrate the proposed place of HBOT in current patient treatment.

Figure 1 Clinical flow chart: HBOT for treatment of chronic non-diabetic wounds



HBOT: hyperbaric oxygen therapy.

Figure 2 Clinical flow chart: HBOT for treatment of non-neurological soft tissue radiation injuries



HBOT: hyperbaric oxygen therapy.

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.

Scientific basis of comparison

The overall evidence base regarding the use of HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries comprised high-level study designs, including RCTs and non-randomised comparative studies. Well-conducted secondary studies, such as systematic reviews and health technology assessments (HTA) that generally identified the same body of primary source evidence retrieved by the current assessment, were used to provide summary supporting data on the effectiveness of HBOT. The majority of retrieved studies were case series, which were used to supplement and substantiate the available comparative study evidence.

Comparative safety

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 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 were primarily barotraumas, visual changes, claustrophobia, and oxygen toxicity. The most common adverse events associated with HBOT were barotraumas and visual changes, particularly myopia, which were reported in five 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 one 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 one 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 as management with conventional conservative or symptomatic therapies (eg wound dressings and irrigation, debridement, stool softeners and bladder lavage.

Comparative effectiveness

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 assessment 1054.

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 that were 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 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 HTAs), which 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.

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 assessment 1054. Although uncontrolled, this study represents a sizeable body of collective clinical data from Australian hyperbaric

facilities, which measures the response of chronic problem wounds (those that have failed three months of standard treatment) to HBOT.

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 six months post-intervention. These data were supported by nine case series 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 six 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. One RCT with potential issues related to methodological quality showed that patients who received 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 arm lymphoedema or quality of life at 12 month 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 these improvements were not seen for fibrosis or telangiectasia.

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.

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 the available evidence.

Economic evaluation

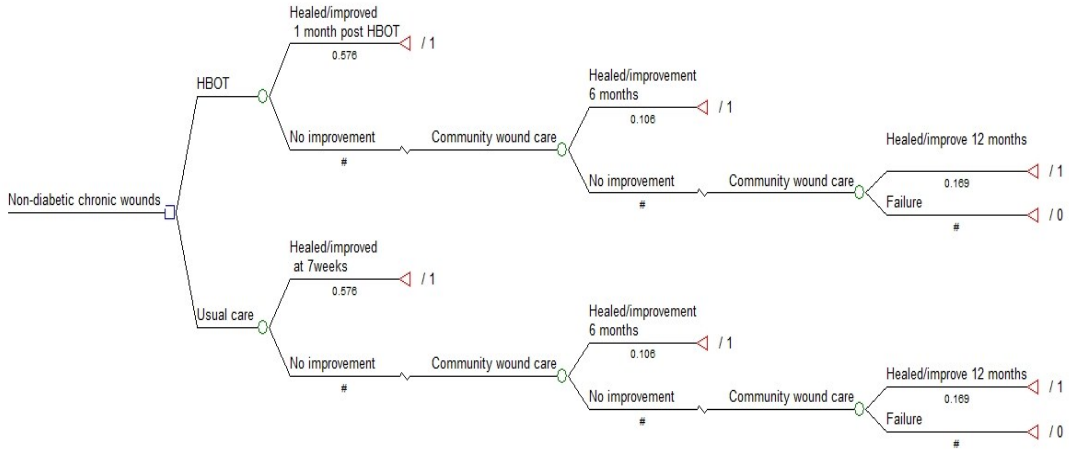
The economic evaluation adopted a cost-effectiveness analysis framework for soft tissue radiation injuries and a cost-minimisation analysis framework for chronic wounds. For both indications HBOT was compared to usual care. For chronic wounds the incremental costs were presented. For soft tissue radiation injuries, the incremental costs

per patient wound healed/improved were presented. This mixed approach was undertaken due to the lack of high-level evidence for effectiveness data for chronic wounds and quality of life data across both indications. A healthcare perspective was adopted.

Chronic non-diabetic wounds

A decision tree was developed to synthesise data from a variety of sources (Figure 3). Estimates of effectiveness were obtained from case series data (Hawkins and Bennett n.d.). 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, 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 the MBS. MBS average co-payment data were provided by the department.

Figure 3 Decision tree: chronic non-diabetic wounds



HBOT: hyperbaric oxygen therapy

There is considerable uncertainty around the estimates of usual care due to the complexity of the treatment pathway. Table 2 provides an estimate of the average costs used in the costing model. All costs represent the total average cost for a patient treated for one year.

Table 2 Costs of clinical pathways: chronic non-diabetic wounds

Description	Treatment	Cost
HBOT success (1 month)	1 year	$13,898
HBOT success (6 months)	1 year	$17,670
HBOT success (12 months)	1 year	$23,119
Usual care success (1 month)	1 year	$11,747
Usual care success (6 months)	1 year	$15,519
Usual care success (12 months)	1 year	$20,968
HBOT failure	1 year	$42,383
Usual care failure	1 year	$40,232

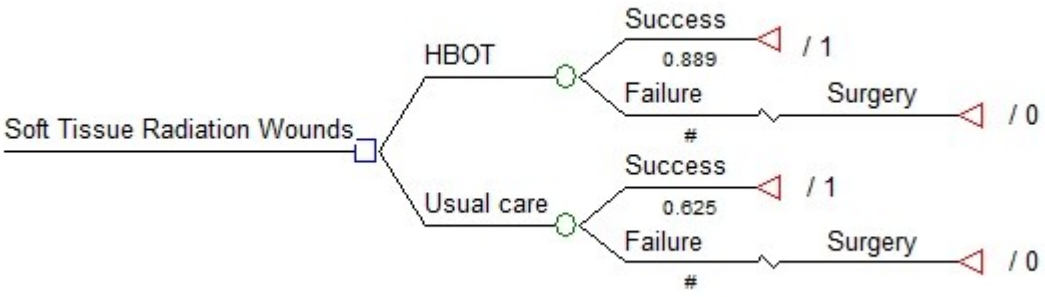
HBOT: hyperbaric oxygen therapy.

The total estimated one year cost of HBOT and usual care versus 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).

Non-neurological soft tissue radiation injuries

A decision tree was developed to synthesise data from a variety of sources (Figure 4).

Figure 4 Decision tree: non-neurological soft tissue radiation injuries



HBOT: hyperbaric oxygen therapy.

Estimates of effectiveness were obtained from a published RCT (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 and was further informed by the literature and the Advisory Panel. Unit costs were obtained from AR-DRG (Version 5.1 round 12 – Private) and the MBS. MBS average co-payment data were provided by the department.

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

For the base case analysis, significant/moderate improvement or complete wound healing was demonstrated in 88.9 per cent of patients who received HBOT for soft tissue radiation injuries, and the comparable figure for usual care was 62.5 per cent of patients. Therefore providing HBOT would result in an additional 26.4 per cent of patients being successfully treated. The average cost accrued in the HBOT-treated group was $11,753 per patient compared to $12,482 in the usual care group. Therefore this represents a cost savings of $728 per patient, meaning that HBOT dominates usual care (ie HBOT is less expensive and is more effective) (Table 3).

Table 3 Summary of cost-effectiveness analysis for HBOT: non-neurological soft tissue radiation injuries

Procedure	Total cost ($)	Total WH	Incremental cost	Incremental WH	ICER ($/WH)
Usual care	$12,482	0.625	$728		Dominated
HBOT	$11,753	0.889		0.264	

HBOT: hyperbaric oxygen therapy; ICER: incremental cost-effectiveness ratio; WH: wound significantly improved/healed.

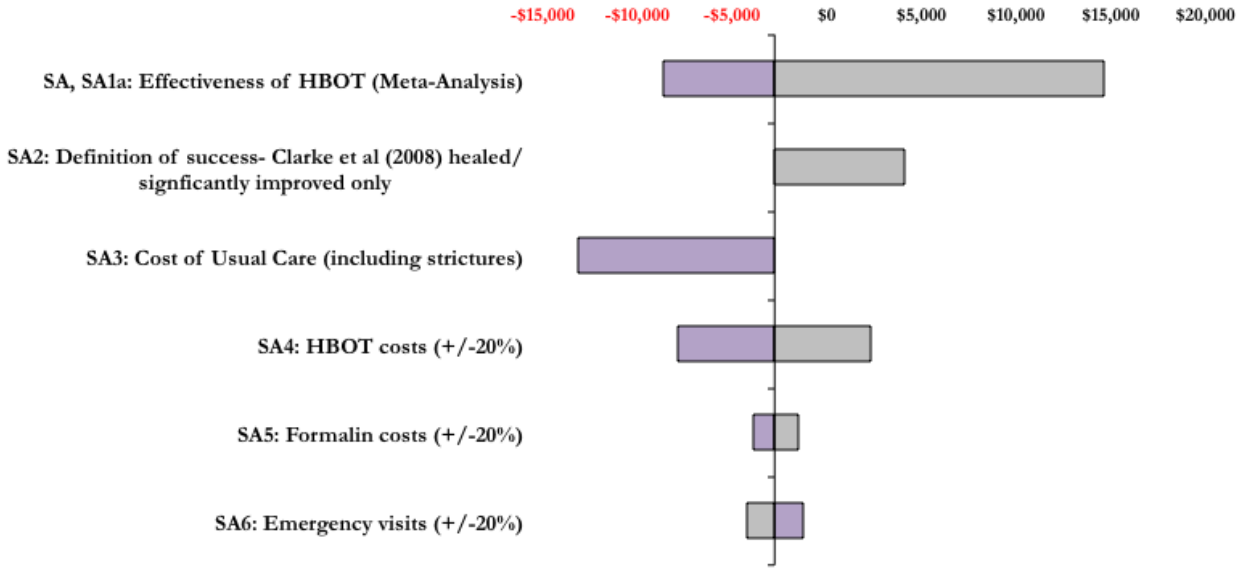
HBOT is less expensive than usual care because the additional cost of providing HBOT is more than offset by the reduction in costs of surgery for the additional patients who fail usual care.

The results of the sensitivity analysis are presented as a tornado diagram in Figure 5. The vertical axis on the graph represents the base case incremental cost-effectiveness ratio (ICER) of HBOT versus usual care which is -$2,759 (HBOT dominant). The bars to the left of the vertical axis represent a reduction in the ICER and the bars to the right

represent an increase in the ICER. The model is most sensitive to fluctuations in the effectiveness of HBOT.

Key uncertainties that drove the estimation of costs were the effectiveness of HBOT based on the 95% confidence interval (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 (2008) study (SA2) (base case was defined as healed, significantly and moderately improved).

Figure 5 Sensitivity analysis: non-neurological soft tissue radiation injuries



HBOT: hyperbaric oxygen therapy; SA: sensitivity analysis.

Overall conclusion with respect to comparative cost-effectiveness

Chronic non-diabetic wounds

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

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.

Financial/budgetary impacts

Chronic non-diabetic wounds

Table 4 Financial implications of chronic non-diabetic wounds per annum

	HBOT	Usual care
Total cost per patient	$24,366	$22,215
Number of patients	154	154
Breakdown of financial implications:		
Consumables	$2,509,378	$2,563,463
MBS Items	$692,317	$317,066
Patient out-of-pocket	$550,631	$540,542
Total financial implications	**$3,752,327**	**$3,421,071**
Incremental costs:		
Consumables	-$54,085	
MBS Items	$375,251	
Patient out-of-pocket	$10,090	
Total cost	**$331,256**	

HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefit Schedule.

As can be seen in Table 4, 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 Extended Medicare Safety Net (EMSN).

The analysis assumed 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 did 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 patients' quality of life may be substantial. Consequently the actual benefit to the patient of providing HBOT is likely to be underestimated.

Additionally, the model was 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.

Non-neurological soft tissue radiation injuries

If direct replacement of usual care occurred for soft tissue radiation injuries, the overall cost would be $2,221,321. If HBOT was used to treat 189 patients instead of usual care, there would be a cost savings of $137,679 per annum (Table 5). It is important to note that there has been 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.

Table 5 Financial implications of non-neurological soft tissue radiation injuries per annum

	HBOT	Usual care
Total cost per patient	$11,753	$12,482
Number of patients	189	189
Breakdown of financial implications:		
Consumables	$804,362	$1,708,461
MBS Items	$1,038,410	$374,197
Patient out-of-pocket	$378,549	$276,343
Total financial implications	**$2,221,321**	**$2,359,001**
Incremental costs:		
Consumables	-$904,099	
MBS Items	$664,214	
Patient out-of-pocket	$102,206	
Total cost	**-$137,679**	

HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

The analysis assumed that HBOT is superior to usual care in terms of clinical effectiveness. However, the analysis did 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 patients' quality of life may be substantial. Consequently the actual benefit to the patient of providing HBOT may be underestimated.

Additionally, the model was 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 had healed wounds in the HBOT group at 12 months compared to usual care. For this reason the model is likely to underestimate overall costs in the usual care group.

There were a number of limitations with the approach to the analysis including the lack of standard management of the treatment of soft tissue radiation wounds; that only the costs incurred in the first year of treatment were included in the model due to uncertainty in extrapolating beyond this time point; and the lack of data on the effectiveness of surgery for this patient group.

Overall conclusion with respect to comparative safety

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 were 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 was 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.

Overall conclusion with respect to comparative clinical effectiveness

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. However, 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 with conventional treatment without HBOT.

Good quality evidence was found that supports 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 with 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.

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.

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 of the arm with HBOT may not be appropriate.

Other relevant factors

HBOT is currently available for the treatment of patients who have ongoing problems with chronic wounds and ulcers, and patients who have suffered considerable morbidity from their diagnosis and treatment of cancer, and has been for some time. Many of these patients are disadvantaged physically and socially as a result of their illness. Withdrawal of this service would remove a possibly valid treatment option, potentially reducing these patients' quality of life.

Hyperbaric facilities function in a similar way to other specialist services such as cancer services and renal dialysis. When patients requiring the service are referred to the facility, networks of care and support, local accommodation, social work, etc are implemented to facilitate access to the treatment, ensuring equity of access. These established networks and systems ensure that patients requiring HBOT can access treatment from regional areas across Australia.

Data on the impact of HBOT on chronic non-diabetic wounds in the Australian healthcare context continues to be collected from the ongoing ANZHMG Wound Care study, a multi-centre prospective cohort study initiated following recommendations arising from MSAC assessment 1054. Three clinical trials examining the use of HBOT for treatment of various soft tissue radiation injuries, all part of a large study sponsored by the Baromedical Research Foundation, are due for completion in July 2012.

Input received from medical specialist members of the Advisory Panel highlighted a number of additional issues related to the current assessment, summarised below:

- Clinical expert opinion is that the evidence base for other treatment options for chronic non-diabetic wounds and non-neurological soft tissue radiation injuries, including for some treatments that currently receive MBS funding, is relatively poor. The evidence base in support of the use of HBOT is at least as good as that available for alternative treatments and therapies.
- The determination of the relative clinical and economic effectiveness of HBOT is confounded by a number of issues:
  - In this context, HBOT is an adjunctive treatment option added to a regime after the failure of conventional treatment to provide healing, and does not have a clear and direct comparator intervention.
  - For the indications of interest, there are no definitive 'gold standard' treatments available when conventional care is shown to be ineffectual.
  - There are ethical issues related to randomising patients to a placebo treatment due to risks associated with denial of treatment.
  - The established nature of HBOT as a therapeutic modality means there has been little impetus to conduct further large clinical trials.
- Clinical expert opinion indicates that the current MSAC assessment process may not be appropriate for an established therapeutic intervention such as HBOT. The current assessment should determine the relative merits of the treatment options available rather than simply examining a single, existing treatment option in isolation. Clinical expert opinion is that a patient-centred approach, where all options for the treatment of the nominated conditions are examined, would be optimal.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of hyperbaric oxygen therapy (HBOT), which is a therapeutic technology for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's Terms of Reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries.

Background

Hyperbaric oxygen therapy for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries

Previous MSAC assessments

On two previous occasions, MSAC has assessed the safety, effectiveness and cost-effectiveness of HBOT (MSAC 2001; 2004). A summary of these previous assessments is provided below.

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. MSAC assessment 1018-1020 examined the safety, effectiveness and cost-effectiveness of HBOT treatment across a large and diverse range of indications (MSAC 2001). However, this assessment concluded that insufficient or conflicting evidence was found for the use of HBOT for treatment of these two indications.

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' for the treatment of non-diabetic wounds and soft tissue radionecrosis (MSAC 2001, p.93). 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

MSAC subsequently 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 (MSAC 2004). This review incorporated new evidence generated since MSAC assessment 1018-1020, including a small number of randomised controlled trials (RCT).

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.

Despite this, in the absence of effective alternative therapies and in view of the progress of local data collections and an international trial, MSAC recommended that funding for HBOT should continue for 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)

While the current assessment was initially proposed to be an update of MSAC assessment 1054 (MSAC 2004), it was determined in consultation with the Advisory Panel that a number of modifications were required to the assessment methodology. These modifications primarily consisted of amendments to the relevant evidence selection criteria to more closely reflect current clinical practice, and were based on the findings from the previous assessment and the comprehensive application. These changes included the provision of more specific definitions of the HBOT procedure and chronic wounds, the exclusion of patients with radiation injury to neurological tissue, and clarification that studies would be considered if they included chronic wounds that were not a consequence of diabetes, regardless of whether the patient was diabetic. Given the potential impact of these changes on the scope of the assessment, it was 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. Hence, this assessment takes into consideration the findings of the two previous assessments 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 application included 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 to be outside the remit of the current assessment.

The procedure

HBOT is an established therapeutic modality for a range of health conditions, and is approved for 13 indications by the Undersea and Hyperbaric Medical Society (UHMS), the peak world body representing practitioners in the area of hyperbaric medicine (Feldmeier 2003). The UHMS defines HBOT as 'A treatment in which a patient breathes 100% oxygen while inside a treatment chamber at a pressure higher than sea level pressure (ie >1 atmosphere absolute or ATA)' (UHMS 2011). One ATA is defined as atmospheric pressure at sea level which is equivalent to 101.3 kilopascals (kPa) or 14.7 pounds per square inch (psi).

According to expert clinical opinion, HBOT is considered clinically efficacious when 100 per cent oxygen is delivered at pressures greater than 1.5 ATA, and in clinical practice is almost universally delivered at between 2 and 3 ATA. This distinction is important, as other forms of hyperbaric therapy are available that use air or air mixed with added oxygen instead of 100 per cent oxygen, delivered at a lower pressure than is possible through conventional HBOT.

Exposure to hyperbaric oxygen is measured jointly by the pressures used in single-treatment exposures and the duration and number of treatment sessions. Tolerance to therapy is dependent on these parameters. In general, HBOT is well tolerated if pressures do not exceed 3 ATA and the treatment session lasts less than two hours. Depending on the reason for HBOT, treatment duration can vary from 45 to 300 minutes, although

most treatments last from 60 to 120 minutes, and may be delivered for a variable number of sessions.

HBOT chambers are variously called hyperbaric chambers, recompression chambers or decompression chambers depending on clinical and historical context. A chamber may accommodate a single patient (a monoplace chamber) or multiple patients and attendants as required (a multiplace chamber). Monoplace chambers can be pressurised with either pure oxygen or air. In the case of the latter, oxygen is delivered to the patient via a mask, hood or endotracheal tube. The risk of fire may be increased in the event that pure oxygen is used to pressurise the chamber; however, this risk is minimised with appropriate safety measures. The smaller size of the chamber provides relative portability and lower cost, but imposes limits on ready access to the patient. Multiplace chambers can accommodate several occupants, including observers and medical and support personnel. Multiplace chambers are pressurised with air instead of oxygen, and patients undergoing therapy breathe pure oxygen through masks, hoods, or endotracheal tubes. The chamber's larger size allows personnel to enter and move about with relative ease in order to deal with acute problems. The risk of fire is also reduced by pressurisation with air and administration of pure oxygen through patient-specific devices.

It has been noted that there are marked regional variations in delivery systems used. While monoplace chambers are the most commonly-used type worldwide, Australian clinical practice and expertise is primarily with multiplace chambers, which are generally used by the majority of established hyperbaric facilities (MSAC 2001). According to expert clinical opinion, the therapeutic effect is the same regardless of the delivery system. As was the case for the two previous assessments, no attempt will be made in the current assessment to perform a comparative evaluation of the two types of delivery systems. The higher pressures that multiplace chambers can deliver were considered irrelevant to the assessment as the majority of treatments are administered at less than 3 ATA (MSAC 2001).

Intended purpose

Chronic non-diabetic wounds

In the majority of cases, wounds heal given simple measures such as surgical closure, cleansing and dressing, and removal of necrotic material. Chronic problem wounds are the subset of wounds that are indolent and do not respond to the usual appropriate measures. A chronic wound is any interruption in the continuity of the body's surface that requires a prolonged time to heal, does not heal, or recurs (Wysocki 1996). Chronic wounds arise in a variety of situations and may be associated with a number of pathological processes. The most common chronic wounds encountered in Australia are a consequence of diabetes, arterial and/or venous disease, and sustained pressure. More than one such process may be present in an individual and contribute to the wound (Dealey 1994). A recent longitudinal cohort study of chronic wounds in the Australian healthcare setting has demonstrated that such wounds may persist for many months and are highly resistant to therapy (Hawkins et al 2006). The latest report of this study suggests that at the time of referral to a hyperbaric service in Australia or New Zealand, the mean time of wounding is in excess of 16 months, while the mean wound area across all aetiologies is greater than 16 cm^2 (Hawkins and Bennett n.d.). For the purpose of the current assessment, chronic wounds were defined as those where appropriate attempts to heal by means other than HBOT have failed over a period of no less than 12 weeks.

Despite the wide range of causative pathologies, the common denominator in many wounds is tissue hypoxia. Wound healing is a complex and incompletely understood process. While it appears that in acute wounds healing is enabled by the initial hypoxia, low pH, and high lactate concentrations found in freshly injured tissue (Jensen et al 1986; Knighton et al 1983), some elements of tissue repair are extremely oxygen-dependent, for example collagen elaboration and deposition by fibroblasts and bacterial killing by macrophages (Hohn et al 1976; Niinikoski et al 1972). In a complicated balance between wound hypoxia and peri-wound oxygenation, it would seem that successful healing relies on adequate tissue oxygenation in the area surrounding the fresh wound. Certainly, wounds that lie in hypoxic tissue beds are those that most often display poor or absent healing (Niinikoski and Hunt 1972; Sheffield 1985).

As the insufficient supply of oxygen may prevent normal healing processes, intermittent presentation of oxygen to those hypoxic tissues through the use of HBOT, therefore, may allow a resumption of normal healing. The mechanisms of action for HBOT have recently been well summarised (Hopf and Holm 2008; Thom 2009). Experimental evidence suggests that repeated 'on-off' exposures produce an environment favourable to angiogenesis and healing when compared to air or oxygen at normobaric pressure (Marx et al 1990). The administration of HBOT in humans has been demonstrated to cause hyper-oxygenation of tissue, vasoconstriction, fibroblast activation, down-regulation of inflammatory cytokines, up-regulation of growth factors, antibacterial effects, potentiation of antibiotics, and a reduction in leukocyte chemotaxis (Cianci and Hunt 1993; Dimitrijevich et al 1999; Rabkin and Hunt 1988; Sheffield 1985; Stevens et al 1993; Zhao et al 1994). Elevation of wound oxygen tension may persist for some hours following HBOT, exerting therapeutic effects over an extended time period (Siddiqui et al 1997).

Using both clinical assessment and investigations designed to confirm significant peri-wound hypoxia, hyperbaric practitioners attempt to select wounds where a response to HBOT is considered likely. Often this decision is based on transcutaneous oxygen measurements of the peri-wound area, taken both while breathing air at normal pressure and on administration of hyperbaric oxygen. This procedure has been recently summarised by Australian authors (Smart et al 2006). It is proposed that this may increase the proportion of wounds that achieve healing and thereby enhance the quality of life in such selected patients.

Non-neurological soft tissue radiation injuries

Radiotherapy has become a well-established modality for the treatment of suitable malignancies in a wide variety of anatomical areas. While radiotherapy dosages are often modified for individual tumour factors, doses and fractionation schedules are reasonably grounded in emerging clinical evidence. There are an increasing number of people in the community with a history of successful radiotherapy intervention; however, a proportion of these will suffer with serious and persistent side effects of therapy.

In the process of treating cancer with radiation, anatomical structures that surround the cancer are also irradiated. These include hollow viscera and solid organs, the overlying soft tissue (including skin), the surrounding muscle, connective tissue, blood vessels and nerves. These tissues are collectively referred to as soft tissue, and the radiation injury and necrosis they can incur is known as soft tissue radiation injury. Soft tissue radiation injury is a particularly difficult condition to treat and for patients to live with (Allen-Mersh et al 1987; Andreyev 2005; Dent et al 1998; Gami et al 2003). Injuries can be

acute, occurring at the time of radiotherapy; these injuries are usually self-limiting, but can sometimes be severe. The irradiated tissues may also undergo a progressive deterioration in microvascularity with fibrosis and scarring, until there is insufficient oxygenation to maintain tissue integrity. This situation is frequently exacerbated by secondary infection in the ischaemic and hypoxic area. The delayed radiation damage becomes radionecrosis when a critical point is reached, and the tissue dies, becoming frankly necrotic. These late radiation injuries can occur months to years after radiotherapy, are progressive and do not spontaneously reverse (Marx and Johnson 1987). Other authors have found a similar progressive pattern for radiation injury to the neck (August et al 1996) and rectum (Yeoh et al 2004).

Histologically, radiation tissue damage manifests as a hypoxic, hypovascular and hypocellular lesion with progressive cell loss and fibrosis secondary to slow loss of the irradiated capillaries in the field. This type of slowly progressive lesion is essentially independent of the tissue irradiated, although some tissues are more sensitive to radiation effects than others (Rubin 1984; Rubin and Casarrett 1968; Trott 1984). The pathological process occurring in radiation injuries is similar throughout the body; for example, similar pathology to that observed in head and neck soft tissue radiation injury occurs after radiotherapy to the colon and rectum. There is general acceptance among radiation biologists that the underlying pathogenesis of radiation injury is common to all tissues, although the latency of onset and mode of expression of radiation injury can vary widely (Denham et al 2001; Travis 2001).

The intermittent application of oxygen through use of HBOT has been demonstrated by Marx and colleagues in experimental evidence using a rabbit ear model to improve vascularity and induce fibroplasia and angiogenesis in irradiated tissue. This was subsequently confirmed by serial transcutaneous oxygen measurements and biopsies in humans undergoing therapy for soft tissue radiation injury and osteoradionecrosis (Marx et al 1990; Marx and Johnson 1987; Marx et al 1985). HBOT likely achieves such improvements through a complex series of changes in affected tissues. Tissue oedema is probably improved through an osmotic effect of oxygen, while the establishment of a steep oxygen gradient across an irradiated tissue margin is a powerful angiogenic stimulus (Davis et al 1988; Hills 1999). In addition, improving oxygenation will improve white cell and fibroblast function, further enhancing wound healing (Mandell 1974).

Given the evidence that HBOT improves tissue vascularity and reverses the histopathological changes of soft tissue radiation injury, HBOT is generally regarded to be of benefit in reversing its clinical effects in many parts of the body. It should be noted, however, that evidence suggests that neurological tissue appears resistant to improvement from the use of HBOT, and little benefit of its use in such tissue has been reported (Feldmeier and Hampson 2002; MSAC 2004).

Clinical need and burden of disease

Chronic non-diabetic wounds

Chronic wounds are a common and significant health problem. Statistics informing on the full picture of their prevalence, disability, and impairment of chronic wounds are difficult to obtain (Macdonald and Ryan 2010). This is due to a number of factors such as the variety of underlying aetiologies, the multiple processes that may be present in an individual and contribute to the wound (Dealey 1994), and the fact that a great deal of wound care is delivered at home. It has been estimated that approximately one per cent

of the population of industrialised countries will experience a chronic leg ulcer at some time, and the prevalence in hospital patients has been estimated at 24 per cent (Baker et al 1991; Graham et al 2003; Stausberg et al 2005). One systematic review of ulcer prevalence including data from 22 reports suggested prevalence rates of open ulcers ranging from 0.12 to 1.1 per cent of the population, while the prevalence rate of open or healed ulcers was reported to be 1.8 per cent (Graham et al 2003).

While there is a paucity of data covering the overall epidemiology of chronic ulcers within the Australian healthcare context, the data that are available suggest that such wounds are expensive to treat, and are likely to cause significant morbidity which increases with age. With an ageing population, the incidence of chronic wounds in Australia has the potential to rise significantly, highlighting the importance of treatment options that are both clinically and cost effective.

Venous ulcers

Venous ulcers (also known as varicose or stasis ulcers) are caused by venous reflux or obstruction resulting in high venous pressure. They are the major cause of chronic wounds, and are generally regarded as making up 70 to 90 per cent of all cases of chronic wounds (Peters 1998).

Estimates for the prevalence of leg ulcers generally range from between 1.5 and 3 per 1000 population. Nelzen et al (1994) screened a Swedish population of 270,800 for all patients with current chronic leg ulcers, identifying 827. A random sample of 382 was studied in detail. Open ulcers of primarily venous cause comprised 54 per cent of the total, giving an overall prevalence of 0.16 per cent. The rate increased noticeably with age, particularly in patients aged 70 and older, and was higher in women than in men. The prevalence of chronic venous insufficiency with the presence of an active ulcer or history of a healed ulcer was studied among 1755 adults in a Brazilian country town (Maffei et al 1986). Chronic venous insufficiency with an active or healed ulcer was found in 3.6 per cent of the subjects. In men there was a great increase in the frequency of ulcers after 70 years; in women there was a progressive increase after 30 years of age. Fowkes et al (2001) provided one of the lowest estimates of venous ulcer prevalence, stating their approximate estimate of the prevalence of open venous ulceration in the adult population in Western countries to be about 0.3 per cent.

A Western Australian population of 238,000 was screened by Baker et al (1991), with the authors reporting a prevalence of chronic leg ulceration with venous abnormalities in 0.62 per 1000 population. The prevalence rate was found to increase to 3.3 per 1000 in patients 60 years or older, while chronic venous ulcers were found to be more common in women than men. At specialist ulcer clinics in Australian teaching hospitals, venous ulcers make up 60 to 80 per cent of all ulcers treated (Kruger et al 2003; Liew and Sinha 1998), with the majority managed by compression bandaging. In a longitudinal analysis of a consecutive group of patients treated at one Australian centre over a two year period, leg ulcers accounted for 5259 inpatient bed days, a mean of 44.2 days per patient; the estimated cost exceeded $2,750,000, averaging over $12,000 per admission (Gruen et al 1996). Annual costs of venous ulcer management in Australia have been estimated at $550–650 million (Leach 2004).

Arterial ulcers

Arterial ulcers are those in which there is evidence of arterial insufficiency and no evidence of other associated conditions such as venous insufficiency, diabetes mellitus or

connective tissue disorders. Peripheral arterial disease is commonly found in diabetic patients, making the incidence and impact of non-diabetic arterial ulcers in the community difficult to determine, and to date little data have been published. Furthermore, many studies reporting on prevalence of leg ulcers do not report prevalence by ulcer aetiology.

While the majority of chronic non-diabetic wounds are due to venous insufficiency, some authors have estimated that approximately 25 per cent are due to arterial insufficiency (Andersson et al 1993; Cullum et al 2002). Callam et al (1987) interviewed and examined 600 of 1447 patients with leg ulcers (including the foot) identified by a postal survey from a Scottish population of approximately a million. In this study, 22 per cent of ulcerated legs had clinical evidence of arterial insufficiency, compared to 76 per cent with evidence of venous disease. Cornwall et al (1986) screened a Health District of approximately 200,000 in North London for leg ulcers (excluding foot ulceration). One hundred patients (31 per cent of those referred to the study) were investigated in more detail. Arterial disease was present in 31 per cent of ulcerated legs, compared to 81 per cent that had venous disease; 22 per cent had concurrent venous and arterial disease. In both of these studies, only five per cent of patients had diabetes, minimising the possibility that diabetes were the primary cause of arterial ulcers. Of 827 patients with chronic leg ulcers identified by Nelzen et al (1991) in their cross sectional population study, ischaemic arterial ulcers were present in six per cent of patients, with arterial insufficiency the probable dominating causative factor in a further 12 per cent; this was compared to 54 per cent due primarily to venous insufficiency. Mixed ulcers with combined arterial and venous insufficiency were found to be common (22 per cent), as were patients with both diabetes and arterial impairment.

There appear to be few published figures that specifically relate to the prevalence of arterial ulcers within the Australian healthcare context. Baker et al (1992) identified 259 patients with chronic ulceration of the leg on screening a Western Australian population of 238,000. Of these, 242 patients (93 per cent of those referred to the study) with 286 chronically ulcerated limbs were fully assessed to determine the factors contributing to ulceration. Arterial disease was found in 27 per cent of limbs, compared to 67 per cent of limbs found to have venous disease. However, at least one other ulcer aetiology was present in over two-thirds of limbs with arterial disease; diabetes was present in almost one-fifth of limbs with arterial disease. The prevalence of chronic ulcers with an arterial component to their aetiology was found to increase with age.

Pressure ulcers

A pressure ulcer, also known as a pressure sore, decubitus ulcer or bed sore, is defined as a localised injury to the skin and/or underlying tissue, usually over a bony prominence, as a result of unrelieved pressure, or pressure in combination with shear (EPUAP and NPUAP 2010). Increased age, reduced mobility, and malnutrition constitute relevant risk factors; however, their respective impact on the genesis of ulcers remains unknown (Allman 1997).

Pressure sores are a typical complication in all healthcare settings, and are recognised worldwide as one of the five most common causes of harm to patients (Robinson 2005). Large multi-centre hospital studies show prevalence rates ranging from 9.2 to 15 per cent in the United States of America (USA) (Amlung et al 2001; Barczak et al 1997; Meehan 1990; 1994; Whittington et al 2000) and from 6.6 to 18.6 per cent in the United Kingdom (UK) (David et al 1983; O'Dea 1995; O'Dea 1999). A large multi-centre study across five

European countries found the prevalence of pressure ulcers to be 18.1 per cent (Vanderwee et al 2007). Prevalence in a non-hospital setting is harder to quantify due to the diversity of care settings, and prevalence rates vary considerably; in the USA and UK, prevalence rates reported in the community and by home healthcare agencies range from 2.5 to 29 per cent (Berquist and Frantz 1999; Ferrell et al 2000; Hallett 1996; Meehan et al 1999; Oot-Giromini 1993). Within nursing homes, prevalence rates range between 11.2 and 23 per cent in the USA (Brandeis et al 1995; Brandeis et al 1990; Burd et al 1992), and between 4.6 and 7.5 per cent in the UK (Potter 1994; Roberts 1994).

Investigations of pressure ulcer point prevalence in Australian tertiary teaching hospitals have been undertaken since 1983 (Childs and Rimmington 1983), and good Australian prevalence data are currently available. Pressure ulcer prevalence survey studies have recently been conducted by a number of Australian states. The third Victorian pressure ulcer point prevalence survey (PUPPS 3) reported the presence of pressure ulcers in 17.6 per cent of patients across 86 public health services (Victorian Quality Council 2006). Two-thirds of pressure ulcers were acquired in hospital, while patients 60 years of age and older represented 80.8 per cent of those identified with an ulcer. The 2008 WoundsWest wound prevalence survey involved inspecting the skin of 3024 patients across 86 Western Australian health services for evidence of a wound (Mulligan et al 2008). Pressure wounds were identified in 12 per cent of patients, with many patients suffering multiple wounds. Sixty-five per cent of pressure ulcers were acquired in hospital. The 2008 Queensland Health pressure ulcer audit, conducted across 137 Queensland Health hospitals and residential care facilities, reported a pressure ulcer prevalence rate of 15.2 per cent (Queensland Health 2008). The prevalence of pressure ulcers in Australian nursing homes has been reported to be between three and 5.4 per cent (Klei et al 1996; Madsen and Leonard 1997; Rice 1996). Amongst patients receiving wound care in the home, pressure ulcer prevalence has been reported to range from six to 8.9 per cent in Australian populations (Asimus and Li 2011; Carville 2000; Carville and Lewin 1998).

In Australia, a recent study predicted an annual 95,695 cases of pressure ulcers with a median of 398,432 bed days lost, incurring median costs of $285 million (Graves et al 2005). This was considered by the authors to be a serious clinical and economic problem for a resource-constrained public hospital system. In the second Victorian pressure ulcer point prevalence survey (PUPPS 2), it was estimated that patients with pressure ulcers accounted for 44,406 additional bed days in Victorian public hospitals with a risk-adjusted cost of approximately $19 million (Victorian Quality Council 2005). Young (1997) estimated the cost of a severe (stage IV) pressure ulcer to be $61,230.

Non-neurological soft tissue radiation injuries

Radiotherapy is a well-established treatment of suitable malignancies in a variety of anatomical areas. Of the approximately 1.2 million new cases of invasive cancer diagnosed annually in the USA, for example, about half will receive radiation therapy (Jemal et al 2002), and of these, about half will be long-term survivors. However, radiation treatment is associated with a broad spectrum of normal-tissue reactions, and it is impossible to cure a tumour by radiotherapy without risk of normal tissue injury (Pasquier et al 2004). Serious, radiation-related complications developing months or years after radiation treatment will significantly affect between five and 15 per cent of long-term survivors who receive radiation therapy, although the incidence varies widely with dose, age and treatment site (Rubin and Casarrett 1968; Stone et al 2003; Thompson et al 1999; Waddell et al 1999).

As the overall number of patients who experience a soft tissue radiation injury is dependent on the number of patients receiving radiation treatment, the exact prevalence of such injuries is difficult to determine, and is further complicated by the diversity in radiation injury location and type. Soft tissue radiation injury is most commonly reported in the head and neck, chest wall, breast and pelvis; these anatomical areas are those most commonly irradiated and hold the greatest likelihood of survival for patients treated for cancer with radiotherapy. The incidence of various soft tissue injuries after radiation treatment in these regions is discussed below.

Head and neck soft tissue radiation injuries

Pernot et al (1997) reported on 1134 patients treated with external irradiation and/or brachytherapy for cancers of the oral cavity and oropharynx. They reported that four per cent of patients experienced soft tissue necrosis persisting longer than three months, and one per cent of patients experienced deep ulceration requiring surgery or repeated hospitalisations. The median duration of significant clinical illness was 11 months. Beumer et al (1972) examined 278 patients who had undergone radiation therapy for oral cancer, reporting a 6.5 per cent incidence of soft tissue necrosis of the oral cavity, of which 83 per cent healed spontaneously. Both of these studies reported that approximately one per cent of all radiotherapy patients experienced severe delayed soft tissue radiation injury to the oral cavity. Delayed laryngeal soft tissue radiation injury has been reported in less than one per cent of patients where dose fractionation of < 2 Gy to a total dose of < 70 Gy has been used (Fitzgerald and Koch 1999; Mendenhall et al 1988).

Breast and chest wall soft tissue radiation injuries

Up to 10 per cent of patients suffer some symptoms in their breasts after radiotherapy for breast cancer (Carl et al 2001). Oedema is a common adverse event from radiotherapy; in a population-based retrospective study in the south of England, 28 per cent of 1077 women remaining disease-free after treatment of breast cancer reported some degree of arm swelling (Mortimer et al 1996). Symptoms can be severe enough to impair ability to perform usual daily activities and have a major impact on social activities. The incidence of severe soft tissue necrosis is low, much less than one per cent, and has been reported to occur with radiation doses in the range of 50 to 60 Gy (Yu et al 2002).

Radiation injury to the bladder, rectum and pelvis

Delayed soft tissue radiation injury has been reported to affect between four and 22 per cent of individuals receiving radiation therapy to the pelvis (Chun et al 2004; Dent et al 1998; Eifel et al 1995; Mameghan et al 1994; Stone et al 2003; Thompson et al 1999). The overall incidence of chronic radiation injury to the bowel after radiotherapy to the pelvis is approximately one to five per cent (DuBrow 1994). The overall incidence of haemorrhagic cystitis after irradiation in the pelvis was reported to be 12.5 per cent in one series of 88 patients (Shiels et al 1986). For radiation to the prostate, the incidence of moderate to severe late complications in the bladder or bowel has been reported to be 8.3 per cent (Mameghan et al 1994). These figures are consistent with those reported by Potter et al (2000), who found significant bladder and rectal complications in 2.9 and 6.1 per cent of 189 patients, respectively, after radiation treatment for cervical carcinoma. They are also consistent with Anacak et al (2001), who reported delayed bladder and rectal radiation injuries in 8.5 and 2.0 per cent of 116 patients, respectively, after radiation treatment for gynaecologic malignancies. There is evidence that the reported number of cases with chronic radiation injury to rectum is a fraction of the true prevalence. Many

series have suggested an incidence of five per cent or less, but a review of published controlled trials of adjuvant therapies suggests that 30 per cent may be a more realistic figure (Ooi et al 1999). Because of a frequent lack of recognition and insufficient long-term follow-up, its true prevalence is unknown (Denton et al 2002a; Eifel et al 1995). The most important risk factor for injury to the gastrointestinal tract is the dose of radiation given. A study of patients with prostate cancer showed that doses of more than 70 Gy raised the likelihood of rectal bleeding after therapy (Donner 1998).

Australian hyperbaric treatment data

MBS data show that 15,579 services for Items specific to HBOT therapy were claimed in the 2010–11 financial year; data for HBOT services claimed since 1996 are shown in Table 8. Data presented at the 16th Annual Scientific Meeting of the Hyperbaric Technicians and Nurses Association (Gold Coast, 2008 August 14–17) showed that from July 2007 to June 2008, 1,435 patients underwent a total of 24,731 episodes of HBOT within Australian hyperbaric facilities (HTNA 2008). Of these, 189 patients (13%) were treated for soft tissue radiation injuries and 154 patients (10%) were treated for hypoxic, non-diabetic problem wounds. These figures help to provide some indication of the level of usage and clinical need for HBOT in the Australian context.

Existing procedures

Hyperbaric oxygen therapy is commonly suggested as a secondary intervention, introduced after primary interventions and conventional therapies have failed to promote wound or injury healing. It aims to reverse the vascular compromise responsible for chronic wounds and soft tissue radiation injuries, promoting healing before more radical and invasive treatments are employed. It may be used as a stand-alone treatment, but is most commonly used as an adjunct to ongoing conventional therapies or symptomatic treatments. It is important to note that HBOT is not proposed as an alternative therapy capable of inducing healing in the absence of good wound care (UHMS 2001).

A plethora of wound care products and treatment options are available, many at considerable cost. In some areas, dedicated wound care teams have been developed in an attempt to maximise successful healing and contain costs through improved efficiency. In the majority of cases, a complex combination of therapies is used as part of a conventional wound treatment regimen. Wound care strategies include diagnosing the cause, maintaining proper nutrition, controlling infection, treatment of the underlying pathology (eg optimal diabetes care with blood glucose control, vein surgery or arterial reconstruction), systemic treatment aimed at improving the local wound environment (eg nutrition supplements, pentoxifylline, aspirin, flavonoids, thromboxane alpha-2 agonists or suledoxide) and local treatment aimed at improving the wound environment (eg dressings, topical negative pressure, pressure-relieving mattresses, ultrasound, application of growth factors or skin grafting). There are many others, with choice of treatment highly dependent on the underlying aetiology of the wound. In practice, wound management is often a sequential and fruitless search for a successful combined approach.

Examples of treatments for soft tissue radiation injuries include formaldehyde, formalin therapy, diathermy, thermal coagulation therapy, antibiotics, penicillin, and various symptomatic treatments; again, in many cases a conventional treatment regimen will consist of a complex combination of treatment options. As with chronic wounds, the

final decision on treatment modalities will depend highly on factors such as patient presentation and clinical expertise.

It should be noted that it was not within the remit of the current assessment to evaluate the relative quality of evidence for existing therapies and procedures; evidence on these therapies and procedures was only included where a direct comparison of effectiveness with HBOT was reported.

Marketing status of technology

Four monoplace hyperbaric units are currently listed on the Australian Register of Therapeutic Goods (ARTG), and are shown in Table 6. Multiplace chambers, if fixed installations, are currently exempt from listing on the ARTG.

Table 6 ARTG listings for HBOT

ARTG number	Sponsor name	ARTG label name	Approval date	Intended purpose
147088	Hyperbaric Health Pty Ltd	Perry Baromedical Corporation monoplace hyperbaric chamber	7/11/2007	The monoplace hyperbaric chamber system provides non-invasive hyperbaric 100% oxygen therapy to an operating pressure of 303.9kPa to treat acute and chronic medical conditions.
147142	Uvec Pty Ltd	Divex Ltd hyperbaric chamber	8/11/2007	To provide hyperbaric oxygen to patients via a sealed mask for therapeutic purposes.
148448	Fink Engineering Pty Ltd	Sechrist Model 3300E/ER hyperbaric chamber	13/12/2007	The Sechrist Model 3300E/ER Hyperbaric Chamber is to administer 100% oxygen at pressure greater than ambient, up to 3 atmospheres absolute (30 psi) of pressure.
182494	Fink Engineering Pty Ltd	Fink FESL, FEDL, FETL and FEQL hyperbaric chambers	27/4/2011	The purpose of the Fink range of hyperbaric chambers is to administer 100% oxygen to patients at hypo and hyperbaric pressures.

ARTG: Australian Register of Therapeutic Goods; HBOT: hyperbaric oxygen therapy.

Current reimbursement arrangements

HBOT for chronic non-diabetic wounds and non-neurological soft tissue radiation injuries was first included for reimbursement on the MBS in 2001 and continues to receive interim funding under the following Item number (Commonwealth Department of Health and Ageing 2011b):

> **MBS Item 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 between 1 hour 30 minutes and 3 hours, including any associated attendance.

In addition, HBOT is currently funded for treatment of a range of other indications (MBS Items 13020, 13025 and 13030). All current MBS entries for the use of HBOT are provided in Table 7.

Table 7 MBS Item numbers and descriptions for HBOT services

Item number	Description
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: $240.75 Benefit: 75% = $180.60 85% = $204.65
13020	HYPERBARIC OXYGEN THERAPY, for treatment of decompression illness, gas gangrene, air or gas embolism; diabetic wounds including diabetic gangrene and diabetic foot ulcers; necrotising soft tissue infections including necrotising fasciitis or Fournier's gangrene; or for the prevention and treatment of osteoradionecrosis, 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: $244.60 Benefit: 75% = $183.45 85% = $207.95
13025	HYPERBARIC OXYGEN THERAPY for treatment of decompression illness, air or gas embolism, 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 greater than 3 hours, including any associated attendance - per hour (or part of an hour) Fee: $109.35 Benefit: 75% = $82.05 85% = $92.95
13030	HYPERBARIC OXYGEN THERAPY performed in a comprehensive hyperbaric medicine facility where the medical practitioner is pressurised in the hyperbaric chamber for the purpose of providing continuous life-saving emergency treatment, including any associated attendance - per hour (or part of an hour) Fee: $154.45 Benefit: 75% = $115.85 85% = $131.30

HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.
Source: Commonwealth Department of Health and Ageing 2011c.

The respective number of services claimed each year for all MBS Items related to HBOT services since 1996 is shown in Table 8. The data indicate that the vast majority of HBOT services claimed relate to Items 13015 and 13020, and show a relatively stable base of utilisation for HBOT since the introduction of MBS Item 13015 in 2001–02.

Table 8 Number of services claimed for MBS Items for HBOT services, by financial year

	Number of services claimed				
Year	**Item 13015[a]**	**Item 13020**	**Item 13025**	**Item 13030**	**Total**
1996–97	-	1,607	12	1	1,620
1997–98	-	2,657	11	0	2,668
1998–99	-	5,133	20	1	5,154
1999–2000	-	7,663	17	0	7,680
2000–01	-	10,330	18	1	10,349
2001–02	2,820	7,236	37	0	10,093
2002–03	3,626	5,615	21	1	9,263
2003–04	4,059	4,790	13	1	8,863
2004–05	4,348	4,674	20	2	9,044
2005–06	4,392	5,475	22	0	9,889
2006–07	4,682	5,841	14	0	10,537
2007–08	5,035	5,490	9	0	10,534
2008–09	4,803	5,324	6	4	10,137
2009–10	6,124	6,120	15	2	12,261
2010–11	8,910	6,657	12	0	15,579

a Prior to 2001, soft tissue radionecrosis and chronic or recurring wounds were funded under MBS Item 13020. After 2001, the two conditions were separately identified under MBS Item 13015.
-: not applicable; HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Approach to assessment

Objective

To determine, through a structured assessment, whether there is sufficient evidence in relation to safety, effectiveness and cost-effectiveness to recommend ongoing public funding for HBOT as a treatment for chronic non-diabetic wounds and non-neurological soft tissue radiation injuries. The approach to this assessment, including methodology and criteria, was comprehensively described prospectively in a Protocol document.

Clinical expert advice

An Advisory Panel with expertise in hyperbaric medicine, radiation oncology, and plastic and reconstructive surgery was established to provide guidance to the evaluators to ensure that the assessment was clinically relevant and accounted for consumer interests. Membership of the Advisory Panel is provided in Appendix B.

Clinical decision pathway

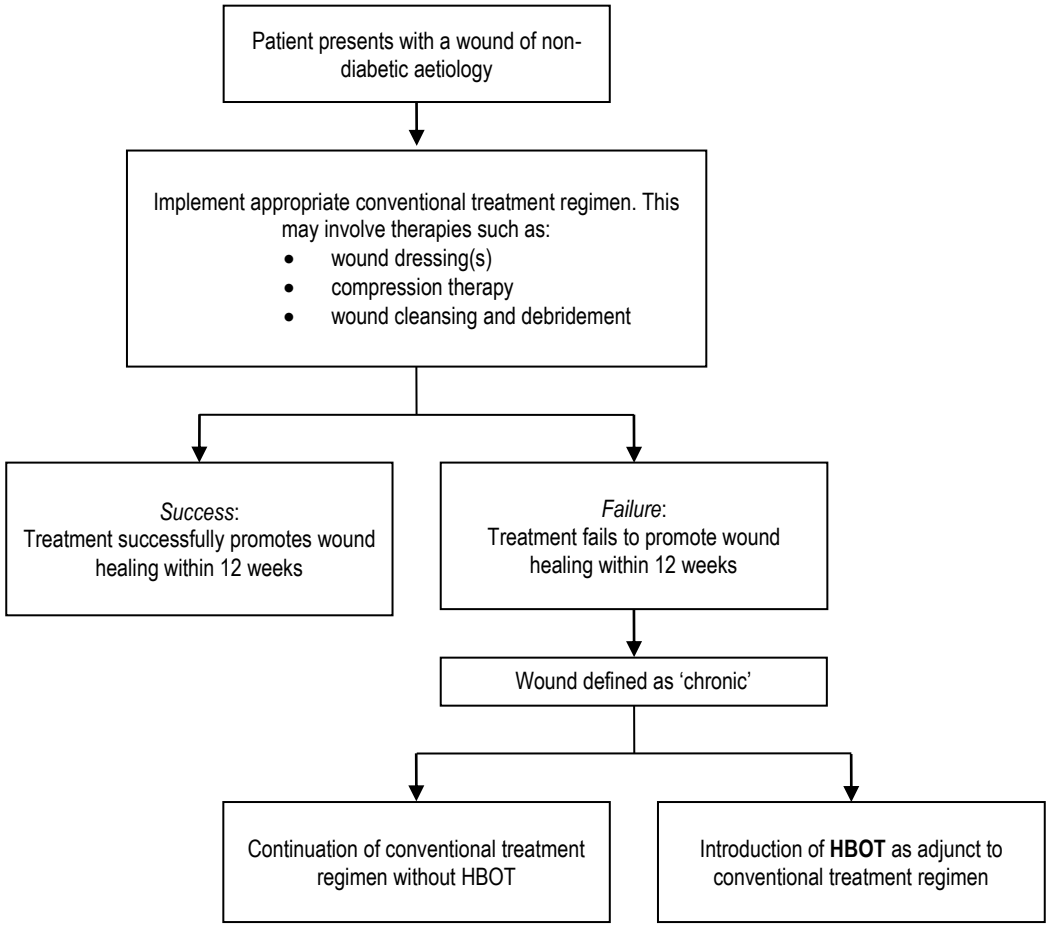
PICO (population, intervention, comparator, outcomes) criteria are used to develop well-defined clinical questions for each assessment. This involves focusing the question on the following four elements (Richardson et al 1995):

- the target population for the intervention;
- the intervention being considered;
- the comparator or current intervention, ie that mostly likely to be replaced or supplemented by the new intervention;
- the clinical outcomes most relevant to assessing safety and effectiveness.

Clinical questions can be defined in part through the development of flow charts. Flowcharts help define the place of the intervention within the clinical management of a condition, including whether the intervention will be used incrementally, or will replace a current intervention. This assists with identifying the correct comparator for the intervention against which safety, effectiveness and cost-effectiveness can be measured.

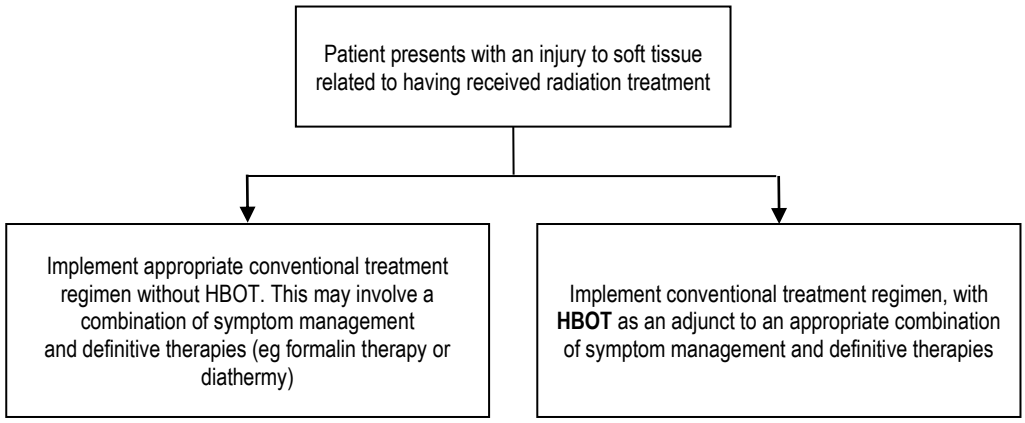
The suggested flow charts provided below in Figure 6 and Figure 7 are clinical pathways developed in conjunction with, and agreed upon by, the Advisory Panel for this assessment of HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries. These flowcharts were developed specifically to inform this review; previous evaluations of HBOT for these indications did not report clinical pathway flowcharts (MSAC 2001; 2004).

Figure 6 Clinical flow chart: HBOT for treatment of chronic non-diabetic wounds



HBOT: hyperbaric oxygen therapy.

Figure 7 Clinical flow chart: HBOT for treatment of non-neurological soft tissue radiation injuries



HBOT: hyperbaric oxygen therapy.

Comparator

As previously described, the range of available interventions available for the treatment of chronic non-diabetic wounds and soft tissue radiation injuries is sizeable and relatively heterogeneous, depending on the nature of the wound or injury. 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. Therefore, the current assessment included evidence that compared 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.

Research questions

Safety

1. What is the safety of HBOT as an adjunct to conventional treatment in the management of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries, when compared to conventional treatment without HBOT?

Effectiveness

1. What is the effectiveness of HBOT as an adjunct to conventional treatment in the management of chronic non-diabetic wounds, when compared to conventional treatment without HBOT?

2. What is the effectiveness of HBOT as an adjunct to conventional treatment in the management of non-neurological soft tissue radiation injuries, when compared to conventional treatment without HBOT?

Cost-effectiveness

1. What is the cost-effectiveness of HBOT as an adjunct to conventional treatment in the management of chronic non-diabetic wounds, when compared to conventional treatment without HBOT?

2. What is the cost-effectiveness of HBOT as an adjunct to conventional treatment in the management of non-neurological soft tissue radiation injuries, when compared to conventional treatment without HBOT?

Review of literature

As previously discussed, while the review methodology for this assessment was based primarily on that employed in MSAC assessment 1054 (MSAC 2004), a number of modifications were made to the evidence search and selection methodology based on the findings from the previous assessment and the evolution of the available body of evidence since the previous assessment was conducted. Based on the clinical pathway and research questions, this updated approach is described in detail below.

Literature sources and search strategies

Searches of literature were conducted via bibliographic databases, while updated listings of reports were located and searched through electronic internet databases and websites of HTA agencies; a full listing is provided in Appendix C. As the present assessment aimed to 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 medical literature was searched to identify relevant studies and reviews from database inception to December 2010.

A sensitive search strategy identified a wide range of studies and indications, which required some clinical expert input for determination of their eligibility for inclusion under the entity 'soft tissue radiation injuries'. The use of such a sensitive strategy reduced the possibility that relevant studies may be missed. The search terms from MSAC assessment 1054 (MSAC 2004) were mostly retained, with those used for searching Medline in the present assessment listed in Table 9. The full search strategy, based on a Medline platform, is reported in Appendix C. Similar text words, indexing terms and use of Boolean operators were employed when searching other databases.

Table 9 Search terms applied

Area of enquiry	Search terms
Chronic non-diabetic wounds	**MeSH headings** Wounds and Injuries, Ulcer, Skin Ulcer **Text words** wound*, ulcer*, leg, foot, skin, varicose, venous, chronic, stasis, arterial, decubitus, pressure, bedsore
Non-neurological soft tissue radiation injuries	**MeSH headings** Radiotherapy **Text words** radiation*, radiotherap*, damage*, injur*, wound*, destruction, necrosis, oedema, edema, proctitis, enteritis, cystitis, radionecrosis
Hyperbaric oxygen therapy	**MeSH headings** Hyperbaric Oxygenation **Text words** hyperbar*, high pressure, oxygen*, HBO*, multiplace chamber, monoplace chamber

HBO: hyperbaric oxygen; MeSH: Medical Subject Headings.

Selection criteria

The criteria used to select evidence for inclusion in the current assessment, incorporating appropriate PICO criteria, are outlined in Table 10. These criteria were formulated according to the methodology of the MSAC assessment 1054 and updated in consultation with the Advisory Panel based on preliminary scoping searches and information provided by the applicant.

Table 10 Selection criteria for inclusion of studies

Selection criteria	Conditions
Study design and publication type	Systematic reviews and clinical studies (including randomised controlled trials, non-randomised comparative studies, and case series) were included. Case series were included if enrolment was consecutive or the study included all patients treated within a specified time period. Non-systematic reviews, case reports, articles identified as preliminary reports where results are published in later versions, articles in abstract form, letters, editorials, and animal, in-vitro and laboratory studies were excluded.
Population	Patients with chronic non-diabetic wounds that have failed to heal within 12 weeks through use of conventional therapies. Patients with non-neurological soft tissue radiation injuries.
Intervention	HBOT, defined as exposure to 100% oxygen at ≥ 1.5 atmospheres absolute for at least one hour in a monoplace or multiplace hyperbaric chamber.
Comparator	Procedures not using HBOT, including, but not limited to: • standard or conventional therapies (variously defined) • normobaric oxygen • placebo procedures.
Outcomes	Safety All clinical and patient-relevant outcomes characterising short-term and long-term safety (eg mortality rates, decompression illness, oxygen toxicity, barotrauma, myopia, claustrophobia). Effectiveness All clinical and patient-relevant outcomes characterising short-term and long-term effectiveness (eg wound/soft tissue radiation injury healing, time to healing, symptom reduction, quality of life, LENT-SOMA score, Common Toxicity Criteria).
Language	Non-English language articles were not included unless they appeared to provide a higher level of evidence than English language articles.

HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic.

For the purposes of this assessment, systematic reviews were included only if they met all five of the following criteria for systematic reviews, as proposed by Cook et al (1997):

1. focused clinical question;
2. comprehensive sources and explicit search strategy;
3. use of explicit, reproducible and uniformly applied criteria for article selection;
4. rigorous critical appraisal of included studies;
5. qualitative or quantitative data synthesis.

Although the results of case series studies are inherently prone to bias and confounding, an effort was made to mitigate this issue by only including case series if there was sufficiently strong implication that patients were not actively selected for study participation (ie if enrolment was consecutive or if all patients presenting within a specified time frame were included).

Search results

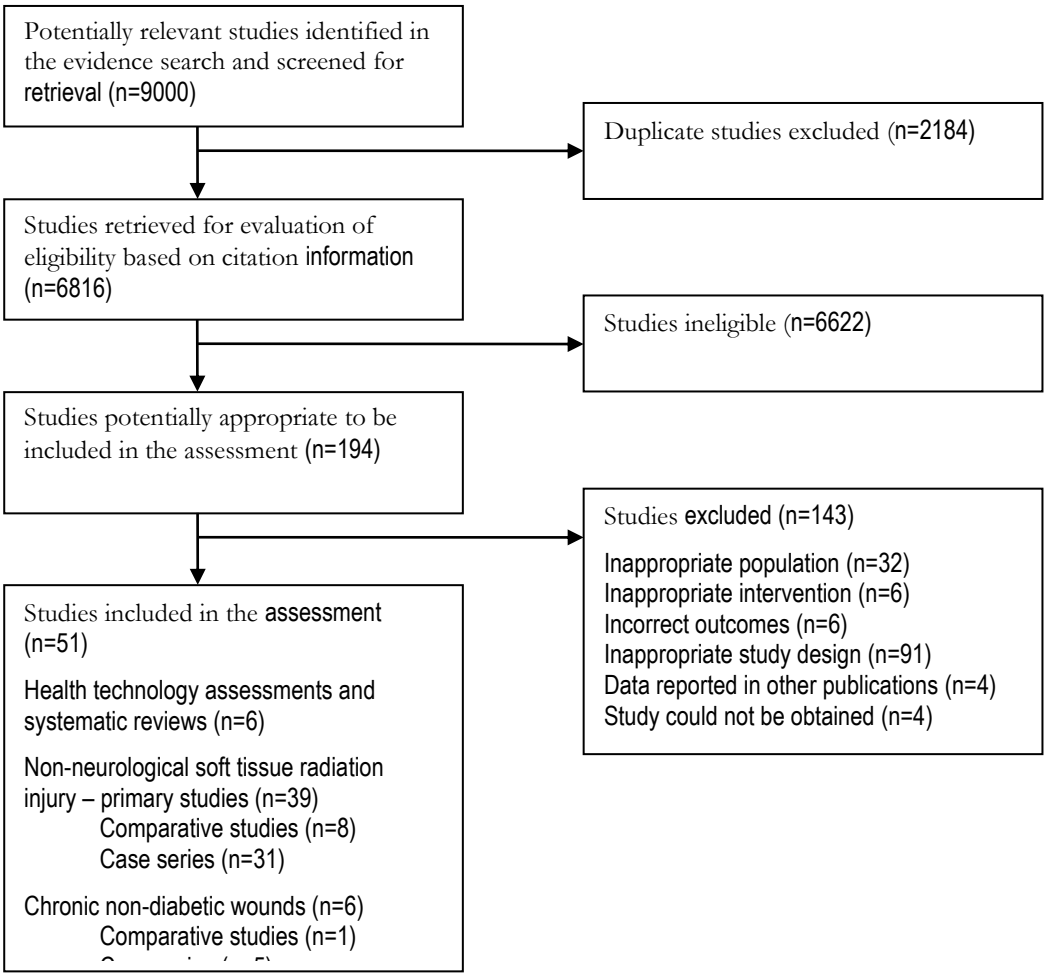
The process of study selection for this report went through four phases:

1. All reference citations retrieved from all literature sources were collated into a Reference Manager database.
2. Duplicate references were removed.
3. Studies were excluded, on the basis of the citation information, if it was obvious that they did not meet the pre-specified inclusion criteria. All other studies were retrieved for full-text assessment.

4. Studies were included to address the research questions if they met the pre-specified criteria applied by the evaluator on the full-text articles. Those articles meeting the inclusion criteria formed the evidence base.

Any doubt concerning inclusion at phase four was resolved by consensus between two evaluators. The results of the process of study selection are provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart in Figure 8.

Figure 8 Summary of the process used to identify and select studies for the review



Adapted from Liberati et al (2009).

Data extraction and analysis

Data were extracted by one evaluator and checked by a second using standardised data extraction tables developed a priori. Data were only reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. If no data were reported for a particular outcome then no value was tabulated. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies, including numerator and denominator information.

Included studies

All primary studies that were retrieved for full-text review and found to meet the eligibility criteria for inclusion are listed in Appendix D, stratified by indication and level of evidence.

Studies that were retrieved for full-text review but were found to be ineligible according to the inclusion criteria are provided in Appendix E with reasons for exclusion.

Appraisal of the evidence

Appraisal of the evidence was conducted at three stages:

1. appraisal of the applicability and quality of individual studies included in the review;
2. appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the intervention;
3. integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2009).

These dimensions (Table 11) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 11 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 12.

Strength of the evidence

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs (levels of evidence) by the type of research question being addressed (see Table 12).

Table 12 Designations of levels of evidence according to type of research question

Level	Intervention[a]
I[b]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo randomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ non-randomised, experimental trial[c] ▪ cohort study ▪ case-control study ▪ interrupted time series with a control group
III-3	A comparative study without concurrent controls: ▪ historical control study ▪ two or more single arm study[d] ▪ interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

[a] Definitions of these study designs are provided in NHMRC 2000, p. 7–8.

[b] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i. utilise A versus B and B versus C, to determine A versus C with statistical adjustment for B).

[d] Comparing single arm studies ie case series from two studies. This would also include unadjusted indirect comparisons (ie utilise A versus B and B versus C, to determine A versus C but where there is no statistical adjustment for B).

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: NHMRC (2009).

Quality

Included studies were critically appraised for study quality according to the guidelines in Chapter 8 of the Cochrane Reviewers' Handbook (Higgins and Green 2011). Included RCTs were examined with respect to the adequacy of allocation concealment and blinding (if possible), handling of losses to follow-up, and any other aspect of the study design or execution that may have introduced bias, with reference to the Consolidated Standards of Reporting Trials (CONSORT) statement (Altman et al 2001). Two evaluators critically appraised each of the included studies, and any differences in interpretation were resolved through discussion. A quality score was not assigned, instead the quality of the included studies was described in a narrative fashion, and any important quality issues were highlighted in the discussion of outcomes.

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and *p*-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000). Studies need to be appropriately to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

For intervention studies of HBOT it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95% confidence interval (CI) included only clinically important effects.

Relevance of evidence

The outcomes being measured in this report were assessed as to whether they were appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome were avoided (NHMRC 2000).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2009). Five components are considered essential by the NHMRC when judging the body of evidence:

1. the evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients;
2. the consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction, ie homogenous or heterogeneous findings;
3. the potential clinical impact - appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;
4. the generalisability of the evidence to the target population;
5. the applicability of the evidence - integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (see Table 13).

Table 13 Body of evidence assessment matrix

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base[a]	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with low risk of bias or a systematic review/several level III studies with low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies/systematic reviews with high risk of bias
Consistency[b]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population[c]	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

[a] Level of evidence determined from the NHMRC evidence hierarchy (Table 12).
[b] If there is only one study, rank this component as 'not applicable'.
[c] For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.
Source: NHMRC (2009).

Results of assessment

Primary evidence for the use of HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries included higher level study designs such as RCTs and non-randomised comparative studies. Well-conducted secondary studies (systematic reviews and HTAs) that generally identified the same body of primary source studies that was retrieved by the current assessment were used to provide summary supporting data on the effectiveness of HBOT. The majority of studies retrieved were case series which were used to supplement and support available comparative study evidence. The evidence base retrieved for the current assessment is outlined below.

Ongoing clinical trials

Websites of clinical trials agencies were searched to identify relevant ongoing or unpublished clinical trials related to the use of HBOT for chronic non-diabetic wounds and non-neurological soft tissue radiation injuries. These websites included the Australian Clinical Trials Registry (www.anzctr.org.au), ClinicalTrials.gov (www.clinicaltrials.gov), Current Controlled Trials (www.controlled-trials.com), and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp).

As of 16 August 2011, a total of eight trials investigating the use of HBOT for treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries were identified (Appendix F). Seven related to soft tissue radiation injuries. Five of these were ongoing trials, of which three were part of a large study sponsored by the Baromedical Research Foundation due for completion in July 2012. The one trial that related to chronic non-diabetic wounds was an Australian randomised, double blind, placebo-controlled trial examining the effectiveness of HBOT for healing chronic venous leg ulcers. At the time of retrieval, this trial had not yet begun recruiting participants.

It should also be noted that two trials identified in the search have subsequently been published and included in the current assessment (Clarke et al 2008; Gothard et al 2010).

Health technology assessments and systematic reviews

The list of electronic databases and websites of international HTA agencies searched for HTAs and systematic reviews can be found in Appendix C. One HTA was identified which met inclusion criteria and was of relevance to this report (Ritchie et al 2008). In addition, four Cochrane reviews (Bennett et al 2005; Denton et al 2002a; Denton et al 2002b; Kranke et al 2004) and one other systematic review (Goldman 2009) of relevance meeting the inclusion criteria were identified through the systematic literature search.

Study descriptions

Health technology assessments

The HTA by Ritchie et al (2008) investigated the clinical and/or cost effectiveness of HBOT. The review was based on a horizon scanning report produced by the Agency for Healthcare Research and Quality (AHRQ), USA and attempted to identify all indications for which HBOT has been suggested as an appropriate intervention. Many of the included indications were outside the scope of this current MSAC assessment. Multiple

databases were searched and the search dates were restricted to between 2005 (when the AHRQ report was published) and July 2007. In the absence of systematic reviews and RCTs, other controlled studies (eg cohort and case control studies) were considered. Case series were only considered if no high level evidence was available and were assessed in the context of a high likelihood of bias. A further literature search was conducted in October 2007 to identify papers on decompression sickness or gas/air embolism as these conditions were excluded from the AHRQ report. Paediatric studies and reports published in languages other than English were excluded from the literature searches. Reports considering the safety of HBOT were included. A list of the sources searched and the search strategies were provided in an Appendix whilst inclusion and exclusion criteria were provided in a table in the body of the report. Two researchers independently screened all titles and abstracts to ensure the relevance and consistency of the selected literature, and were involved with data abstraction. Discrepancies were resolved by consensus. The Scottish Intercollegiate Guidelines Network (SIGN) methodology checklists were used to assess the quality of the selected studies, though formal quality scores were not assigned.

Systematic reviews

Chronic non-diabetic wounds

The Cochrane review by Kranke et al (2004) investigated the use of HBOT for chronic wounds including diabetic foot ulcers, venous leg ulcers and arterial ulcers of the lower limb. The systematic review by Goldman (2009) examined the use of HBOT for limb salvage and healing of chronic wounds (including diabetic foot ulcers, arterial ulcers, venous stasis ulcers, calciphylaxis and vasculitic ulcers), as well as an adjunct for surgical reconstruction and for treatment of osteomyelitis.

With regards to evidence searches, Kranke et al (2004) searched Medline from 1966–2003, EMBASE from 1974–2003 and CENTRAL – Issue 1, 2003, while the Cochrane Wounds Group Specialised Trial Register was searched on 6 February 2003. A detailed and targeted search strategy was employed and provided. Other resources, including contacting experts in the field and leading hyperbaric therapy centres and asking for additional relevant data in terms of published and unpublished RCTs, hand-searching relevant hyperbaric textbooks and conference proceedings, and contacting authors of relevant studies to request details of unpublished or ongoing investigations, were also utilised. One review author was responsible for hand-searching and identification of appropriate studies for consideration, while three reviewers independently evaluated the quality of the relevant trials for each review and extracted the data. Goldman (2009) searched the Medline database from 1978 to 2008 inclusive. Retrieved citations were informally compared with the bibliography of the Cochrane review by Kranke et al (2004), and any additional studies identified were included. Bibliographies of included studies were also reviewed for additional relevant citations. It should be noted that the review by Goldman was a single author review, which may result in the introduction of bias into the results.

Kranke et al (2004) provided detailed inclusion criteria, including any participant with a chronic wound associated with venous or arterial disease, diabetes mellitus or external pressure. As the review aimed to compare wound care regimens that included HBOT with similar regimens that excluded HBOT, only RCTs were included. HBOT was prospectively defined as having been administered in a compression chamber between pressures of 1.5 and 3.0 ATA, with treatment times between 30 minutes and 120 minutes daily or twice daily. Goldman (2009) stated that for inclusion in the review, citations must

have described original human research with wound healing, tissue salvage or limb salvage as the primary outcome variable. As well as RCTs, Goldman also included non-randomised comparative studies (including cohort studies and retrospective analyses) and case series. The HBOT intervention was not explicitly stated for the purposes of evidence selection, but it was noted that HBOT is generally defined as compression of the whole body with at least 1.4 ATA of pure oxygen.

Quality of included studies was critically appraised by Kranke et al (2004) using the Oxford quality scoring system (Jadad et al 1996). Relative risk (RR) analysis was used for dichotomous outcomes. A fixed effects model was used where there was no evidence of significant heterogeneity between studies, and a random effects model when heterogeneity was likely. In the case of missing data, authors planned to employ sensitivity analyses. Goldman (2009) critically appraised included studies narratively within the review, and assigned quality of evidence to studies according to criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (Atkins et al 2004). While some meta-analyses and quantitative data synthesis were conducted, these were not applicable to the indications of interest to the present assessment. For these indications, results from articles were tabulated and discussed narratively.

Non-neurological soft tissue radiation injuries

The Cochrane review by Bennett et al (2005) examined the use of HBOT for late radiation tissue injury of the head and neck tissues, bladder, chest wall, bowel, neurological tissue and bone. One Cochrane review by Denton et al (2002a) investigated the use of HBOT amongst a number of other non-surgical interventions for the treatment of late radiation proctitis, while a second Cochrane review by Denton et al (2002b) evaluated HBOT amongst a range of non-surgical interventions for the treatment of late radiation cystitis.

The three Cochrane reviews examining HBOT for non-neurological soft tissue radiation injuries (Bennett et al 2005; Denton et al 2002a; Denton et al 2002b) each employed searches of Medline, EMBASE, CINAHL and the Cochrane Register of Controlled Trials. Bennett et al (2005) also searched the Database of Randomized Trials in Hyperbaric Medicine (DORCTIHM), while both reviews by Denton et al (2002a; 2002b) also searched the Science Citation Index and CancerCD databases. Appropriate search dates and detailed search strategies were provided in each of these reviews, with the strategies used in both reviews by Denton et al centring primarily on the condition under review (radiation proctitis and cystitis) rather than particular interventions. In addition, each Cochrane review searched other resources including grey literature, contacting experts in the field and leading hyperbaric therapy centres and asking for additional relevant data in terms of published and unpublished RCTs, hand-searching relevant hyperbaric textbooks and conference proceedings, and contacting authors of relevant studies to request details of unpublished or ongoing investigations. In each of the Cochrane reviews, multiple authors took part in identifying and deciding on appropriate studies for inclusion, evaluating the quality of the relevant studies and extracting the data.

In terms of inclusion and exclusion criteria, Bennett et al (2005) included any participants with late radiation tissue injury (including necrosis) of any tissue type. Patients treated with large dose radiation therapy, likely to induce relatively early necrosis, were also accepted. The reviews by Denton et al were more specific in their participant inclusion criteria, including patients treated with radiotherapy for a pelvic malignancy and

subsequently developing late radiation proctitis (Denton et al 2002a) or cystitis (Denton et al 2002b) continuing from completion of radiotherapy for more than three months, or occurring more than three months after completion of radiotherapy. Regarding study type, Bennett et al (2005) included RCTs and pseudo-RCTs that compared the effect of a regimen including HBOT with any treatment regimen not including HBOT. Both reviews by Denton et al (2002a; 2002b) included these study types as well as well-designed cohort and case control studies, and longitudinal surveys or case histories. Bennett et al (2005) prospectively defined HBOT as being administered in a compression chamber between pressures of 1.5 and 4.0 ATA, with treatment times between 30 minutes and 120 minutes daily or twice daily. Neither review by Denton et al explicitly defined the parameters of the HBOT procedure.

In all three Cochrane reviews (Bennett et al 2005; Denton et al 2002a; Denton et al 2002b), quality of the included studies was critically appraised by multiple authors using the guidelines of the Cochrane Handbook, with discrepancies resolved by consensus. Bennett et al (2005) utilised an RR analysis for dichotomous outcomes. Fixed effects models were used where there was no evidence of significant heterogeneity between studies and a random effects model when heterogeneity was likely. Both reviews by Denton et al (2002a; 2002b) expressed dichotomous data as an odds ratio, while continuous data were converted to weighted mean differences with standard errors. Uncertainty in each treatment was expressed using CIs. Both fixed and random effects models were used to calculate a weighted average of the treatment effects across the studies under review. Sensitivity analyses were employed if appropriate.

Safety

Systematic reviews

Chronic non-diabetic wounds

In the Cochrane review by Kranke et al (2004) only two trials reported adverse events; however, both trials studied patients with diabetic foot ulcers, and so were not of relevance to this report. In the systematic review by Goldman (2009), typical adverse events related to HBOT were discussed narratively, with no specific safety data related to the included studies reported.

Non-neurological soft tissue radiation injuries

In the Cochrane review by Bennett et al (2005), one study was identified that reported five deaths at one year follow-up (Clarke et al 2008); however, this crossover study did not identify the original treatment allocation. No comparative data was provided on adverse outcomes in this study, only overall figures for adverse events in all patients completing HBOT treatment. Neither of the Cochrane reviews by Denton et al (2002a; 2002b) quantified adverse events, describing adverse events only as transient, minor and related to brief aural and visual barotrauma.

Effectiveness

Health technology assessments

Whilst the HTA by Ritchie et al (2008) investigated the clinical effectiveness of HBOT for many indications, only the findings from those which pertain to this MSAC assessment are discussed. For chronic non-diabetic wounds the results for different aetiologies were presented separately, with venous and pressure ulcers the two indications of relevance to this assessment. For soft tissue radiation injury, Ritchie et al

(2008) included studies that examined injury to neurological tissue; however, only studies reporting on non-neurological soft tissue injuries were of relevance to this assessment.

With respect to venous ulcers, Ritchie et al (2008) identified eight secondary studies (five systematic reviews and three HTAs) that reported on an RCT undertaken by Hammarlund and Sundberg (1994). The secondary studies reported that patients managed with HBOT experienced significantly greater reductions in mean wound area than the control group at four (22% ± 13% versus 3.7% ± 11%; p=0.0088) and six weeks (35.7% ± 17% versus 2.7% ± 11%; p=0.0004) after initiation of treatment, although there was no statistically significant increase in the proportion of ulcers healed in the HBOT group. The secondary studies noted that this was a very small RCT in which the randomisation process was inadequately described, concurrent treatments were not reported and only limited patient characteristics were provided. As such, it was suggested that the results be viewed with caution. One of the systematic reviews (ECRI 2001) included two case series, but in the absence of a control group and given the poor reporting of the studies, they were not considered to add to the evidence base. Ritchie et al (2008) noted that approximately half of the secondary studies that investigated venous ulcers concluded that there was insufficient evidence to determine whether HBOT plus standard care was more effective than standard care alone, while other studies interpreted the results as sufficient to indicate benefit for HBOT in the healing of chronic venous ulcers.

With respect to pressure ulcers, Ritchie et al (2008) identified three secondary studies (one HTA and two systematic reviews) that each included a study by Rosenthal and Schurman (1971). This study reported that 22 of 38 pressure ulcers healed completely in the group receiving HBOT and five of 38 reduced in size by greater than 50 per cent, compared to zero of six ulcers healed or reduced in size by greater than 50 per cent in the control group; however, the study by Rosenthal and Schurman (1971) did not meet the inclusion criteria of the present assessment as it was unclear whether the ulcers treated were chronic in nature. All three secondary studies concluded that it was unclear from the evidence whether HBOT plus standard care is more effective than standard care alone for treatment of pressure ulcers.

A total of eleven secondary studies (three HTAs and eight systematic reviews) examining the use of HBOT for soft tissue radiation injuries met the inclusion criteria of Ritchie et al (2008). This included Cochrane reviews by Bennett et al (2005) and Denton et al (2002a; 2002b) that are discussed in detail below, as well as reviews that were systematic in their methodology but did not meet the inclusion criteria for the present assessment (Denton and Maher 2003; Feldmeier and Hampson 2002; Pasquier et al 2004; Wang et al 2003). One RCT of relevance to the present assessment, described in detail later in this report, was also included (Clarke et al 2008). Numerous case series studies were retrieved by Ritchie et al (2008), but did not add to the evidence base. Despite variability in the rigour with which secondary studies were conducted, all appeared to identify the same small number of primary source studies which were concluded to be generally poor in methodological quality.

Given that it identified four RCTs studying the effects of HBOT on late radiation tissue injury, Ritchie et al (2008) stated that the Cochrane review by Bennett et al (2005) provided the strongest evidence base for this indication. The RCT by Clarke et al (2008) that examined patients with problematic radiation proctitis was reported by Bennett et al (2005) in abstract form (Clarke et al 2004), but was reported by Ritchie et al (2008) in full detail. A statistically significant benefit in healing (odds ratio=5.93, 95% CI 2.04–17.24;

p=0.02) and late radiation-induced morbidity (p=0.0019) was reported immediately after the initial treatment allocation in patients who received HBOT, compared to those receiving a placebo treatment. Ritchie et al (2008) deemed the results of this RCT to be fairly robust. A report by Marx (1999) examining patients who required major soft tissue surgery or flaps in previously irradiated head and neck tissue was also discussed. It was noted that few details of the trial were available, but that Bennett et al (2005) reported that there was a statistically significant higher likelihood of wound dehiscence in the control group compared with patients in the HBOT group (RR=8.67; 95% CI 2.73–27.49; p=0.0002). Ritchie et al (2008) also identified a number of secondary studies that all reported on an RCT by Marx et al (1985) that compared the effectiveness of HBOT to antibiotic therapy for preventing the development of osteonecrosis in patients who had previously received radiation therapy to the head or neck and required tooth extraction. It was noted that the study was carried out some time ago and was not blinded, but provided the primary evidence for this indication. Patients receiving HBOT were found to have a statistically greater likelihood of healing of all tooth sockets than those receiving antibiotic prophylaxis (RR=1.4; 95% CI 1.1–1.7; p=0.009).

Most studies included in the secondary literature comprised case series and case studies that generally reported improvements in outcome following HBOT therapy, with some review authors suggesting that this indicated a healing benefit for HBOT in patients with radiation injuries. However, the results of these studies were prone to bias and confounding and could not be used as a basis for treatment recommendations. Ritchie et al (2008) concluded that there was some evidence of a benefit of HBOT in treating radiation-induced proctitis, for patients requiring head or neck surgery to previously irradiated tissue and for preventing the development of osteoradionecrosis following dental treatment, with further high-quality studies required. There was insufficient evidence to determine the usefulness of HBOT in treating late soft tissue radiation tissue injury at other sites.

Systematic reviews

Chronic non-diabetic wounds

Whilst the Cochrane review by Kranke et al (2004) investigated the clinical effectiveness of HBOT for diabetic ulcers, only the results for venous, arterial and pressure ulcers are of relevance to this assessment. Only one study was found that reported primary and secondary outcomes related to venous ulcers, a RCT by Hammarlund and Sundberg (1994) that compared HBOT to placebo treatment. No eligible trials were found investing the use of HBOT for arterial and pressure ulcers. A significantly greater reduction in wound area was found in the HBOT group when compared to the placebo group (35.7% versus 2.7%) immediately after completion of treatment (six weeks after initial session). While the reduction in wound area was greater in HBOT patients at 18 weeks (55.8% compared to 29.6%), this was found to be a statistically non-significant difference. No statistically significant difference was found in the proportion of ulcers healed at 18 weeks in the HBOT group when compared to the placebo treatment, and a pre-planned sensitivity analysis examining the effect of allocation dropouts did not alter the results. It was concluded by Kranke et al (2004) that the routine management of venous, arterial and pressure ulcers with HBOT is not justified by the evidence in their review.

Goldman (2009) also reported on the clinical effectiveness of HBOT for diabetic ulcers; however, only the results related to arterial, venous stasis and vasculitic ulcers are of relevance to this assessment. One study was found to have healing of arterial ulcers as

the primary outcome variable (Grolman et al 2001). However, two-thirds of included patients suffered from diabetes mellitus, with the author noting the significant overlap between diabetes and peripheral arterial disease; it was also not stated how long wounds had been present. Consequently, this study was considered unsuitable for incorporation into the present assessment. One RCT was found to have healing of chronic venous ulcers as the primary outcome variable (Hammarlund and Sundberg 1994). Although Goldman (2009) also noted the significantly greater reduction in wound area for the HBOT group compared to the placebo treatment after four weeks (74% of baseline wound area compared to 96%) and six weeks (64% compared to 98%) of treatment, no comparison was made between treatment groups with respect to the healing results at 18 weeks. One case series of 35 patients was found that reported healing of chronic vasculitic leg ulcers as a primary outcome (Efrati et al 2007). Complete healing was found in 80.0 per cent of patients who had received HBOT, partial healing in 11.4 per cent, and no healing in 8.6 per cent. Goldman (2009) concluded that there was a moderate level of evidence that HBOT promotes healing of venous stasis ulcers and refractory vasculitic ulcers. It was also concluded that the cost-effectiveness of HBOT needs to be considered, especially for venous leg ulcers, for which less expensive alternate strategies are likely to be available.

Non-neurological soft tissue radiation injuries

Bennett et al (2005) accepted 10 studies into their Cochrane review of HBOT for the treatment of late radiation tissue injuries. Five of these studies (Clarke et al 2004; Clarke et al 2008; Marx 1999; Marx et al 1985; Sidik et al 2007a) were of relevance to the current MSAC assessment. The authors identified a study by Sidik et al (2007a) but were not able to obtain a copy, while Clarke et al (2004) was the preliminary abstract form of a study subsequently published in full by Clarke et al (2008). As such, the results from only three studies (Clarke et al 2008; Marx 1999; Marx et al 1985) are discussed. The study by Clarke et al (2008) is reported in detail later in this assessment. A non-significant probability of complete resolution of radiation proctitis after HBOT compared to placebo treatment was observed. However, a significantly better outcome with respect to complete resolution or significant improvement of radiation proctitis was observed for participants receiving HBOT (46 %) versus placebo treatment (27%). Analysis revealed that five patients would have to be treated with HBOT in order to achieve one extra favourable outcome. Significant improvements in Late Effects Normal Tissues – Subjective Objective Management Analysis (LENT-SOMA) score (5.0 versus 2.6) and physical functioning (Expanded Prostate cancer Index Composite (EPIC) Bowel Bother subscale) at completion of treatment (14.1% versus 5.8% improvement) were also observed in patients receiving HBOT. Bennett et al (2005) included the RCT by Marx et al (1985), also reporting that there was a significantly greater probability of healing of the tooth socket after extraction with the administration of HBOT; 35 of 37 (95%) patients randomised to HBOT achieved healing of all sockets, versus 26 of 37 (70%) in the control group. Analysis revealed that four patients would have to be treated with HBOT in order to achieve one extra favourable outcome. The RCT by Marx (1999) was reported by Bennett et al (2005) to show a statistically significant higher likelihood of wound dehiscence in the control group compared with patients in the HBOT group. Bennett et al (2005) concluded from these studies that there is some evidence that HBOT improves outcomes for radiation proctitis and prevents the development of osteoradionecrosis following tooth extraction in an irradiated field; thus, the application of HBOT to selected patients and tissues may be justified. Whilst methodological issues regarding some of the studies included in the review demand cautious interpretation of

results, the pathology of radiation injury suggests that other tissues, such as the bladder, are also likely to respond to HBOT.

Denton et al (2002a) examined a range of non-surgical interventions for late radiation proctitis. The authors identified nine studies with respect to treatment with HBOT, of which seven were retrospective case series, one was a prospective observational case series (Williams et al 1992) and one was an RCT of radiation proctitis published only in abstract form (Clarke et al 2004; subsequently published in full as Clarke et al (2008)). Denton et al (2002a) noted the heterogeneous characteristics of the case series, such as patient characteristics and baseline condition, HBOT treatment administered, and assessments of response; the degree of benefit and the cumulative effect or duration of response from HBOT could not be quantified from the included studies due to the methodology and quality of the data. It was noted by the authors that a similar pattern of evidence was also found for the majority of other treatment modalities examined. Denton et al (2002a) concluded that although certain interventions look promising and may be effective for the treatment of radiation proctitis, the single small studies available provided an insufficient body of evidence overall. It should be noted that while the authors recommended that placebo controlled studies are required to establish the effectiveness of particular treatments, their review was conducted before the publication of the full results of the placebo-controlled RCT on the use of HBOT by Clarke et al (2008).

Denton et al (2002b) examined a range of non-surgical interventions for late radiation cystitis. A total of 19 studies examining the use of HBOT for radiation cystitis fitted the stated inclusion criteria, of which all were case series, with only one being a prospective case series (Bevers et al 1995). Due to the selection, publication bias and methodology of these studies, these reports could not be amalgamated to produce an overall response rate, but Denton et al (2002b) stated that the minimum reported response for this intervention was 60 per cent, for a minimum duration of two months. A similar pattern of evidence was also found for the majority of alternative treatment options, with the authors concluding that it was difficult to draw any firm conclusions on the treatment of radiation cystitis based on the body of evidence available at that time.

Descriptive characteristics of included studies

Chronic non-diabetic wounds

Six primary study articles were identified for inclusion in the assessment of HBOT for the treatment of chronic non-diabetic wounds (Appendix D). This included one comparative study providing level II evidence, the Swedish RCT by Hammarlund and Sundberg (1994), which was reported previously in the original MSAC assessment of HBOT for non-healing, refractory wounds in non-diabetic patients (MSAC 2004).

As well as the comparative study, five descriptive case series articles providing level IV evidence met the inclusion criteria. Note that the publications by Hawkins et al (2006), Hawkins and Bennett (n.d.) and Sidhom et al (n.d.) report data from the same study.

Non-neurological soft tissue radiation injuries

A total of 39 publications were identified for the assessment of HBOT for the treatment of non-neurological soft tissue radiation injuries (Appendix D). Of these, six were articles on RCTs providing level II evidence (Clarke et al 2008; Gothard et al 2010; Marx 1999;

Marx et al 1985; Sidik et al 2007a; Sidik et al 2007b). Note that the two publications by Sidik et al report on data from the same study, hence a total of five randomised cohorts were available to inform on the effectiveness of HBOT for non-neurological soft tissue radiation injuries. Three of these studies were conducted in the USA, while one was conducted in each of the UK and Indonesia. With respect to the indications of interest, two studies investigated the treatment of radiation proctitis, one investigated wounds in irradiated soft tissues of the head and neck region, one examined treatment of soft tissue oedema following irradiation for breast cancer, and one examined the healing of soft tissue flaps introduced into irradiated tissue.

Two non-randomised comparative studies were also retrieved for inclusion. The German study by Carl et al (2001) was a prospective non-randomised comparative study with concurrent controls (level III-2 evidence) that investigated treatment of soft tissue oedema following irradiation for breast cancer. In Sweden, Neovius et al (1997) conducted a retrospective non-randomised comparative study with historical controls (level III-3 evidence) examining the treatment of wounds in irradiated soft tissues of the head and neck region.

Four of the included comparative studies (Carl et al 2001; Marx 1999; Marx et al 1985; Neovius et al 1997) were reported in the previous MSAC assessment of HBOT for refractory soft tissue radiation injuries (MSAC 2004).

Thirty-one descriptive case series assessing the effect of HBOT on a range of soft tissue radiation injuries were also deemed to meet the inclusion criteria. All case series provided level IV evidence.

Duplication of results

The articles from Hawkins and Bennett (n.d.) and Hawkins et al (2006) both reported clinical wound healing data from the ongoing ANZHMG Wound Care study. It was determined in consultation with the Advisory Panel that due to the particular relevance of this study, results from both articles would be reported in the current assessment. The report by Hawkins et al (2006) provides published peer-reviewed results from the first year of the study, while the unpublished case series by Hawkins and Bennett provided updated data from the sixth year of the study.

The article by Hampson and Corman (2007) provides clinical healing results on radiation cystitis that update the results of a cohort reported in three earlier publications (Chong et al 2005; Corman et al 2003; Norkool et al 1993). This article also discusses clinical results on healing of radiation proctitis; however, these results are reported in greater detail by Marshall et al (2007).

The articles by Sidik et al (2007a; 2007b) report on the same study population; however, the two articles report on distinctly different clinical outcomes, with no duplication of results identified.

Critical appraisal of comparative studies

Randomised controlled trials

Study quality was appraised according to the methods outlined in Chapter 8 of the Cochrane Reviewers' Handbook (Higgins and Green 2011), with reference to the

CONSORT statement (Altman et al 2001). Summaries of the methodological quality of the five RCTs included for the assessment of HBOT for chronic non-diabetic wounds and non-neurological soft tissue radiation injuries are provided in Appendix G and described below.

Chronic non-diabetic wounds

The RCT by Hammarlund and Sundberg (1994) compared HBOT to a placebo treatment of normobaric air for the healing of chronic non-diabetic leg ulcers. The methodological quality of this study is discussed below.

Study design

Sample size and participants

A total of 16 patients were recruited for the RCT. The authors reported that, based on previous studies, they felt eight patients in each treatment group would be sufficient to show significant changes in wound healing; however, no power calculations to determine appropriate sample size were reported.

Eligibility criteria for recruitment were clearly stated by the authors. Patients were considered for inclusion in the study if they had had leg ulcers for more than one year and blood pressure levels within normal ranges. Criteria for exclusion were wounds that showed any tendency to heal (by visual inspection) during the two months before the study, patients with a smoking habit, or any concomitant chronic disease such as diabetes mellitus or collagen disease.

The authors noted that the decision was made to randomise patients stratified by two age groups (<50 years and 50–75 years) to ensure the two groups were generally similar in age distribution. Patients were also comparable for gender distribution. Other pre-intervention demographic or clinical characteristics were not reported.

Randomisation, concealment, implementation and blinding

Patients were randomised to treatment through the use of sealed envelopes, and allocation was concealed through treatment being described only as 'gold gas' or 'silver gas' treatment. As patients entered the study, an envelope was drawn and the patient was placed on the gas supply given by the instruction. The study was double-blind in design, with treatment gas blinded to all patients and evaluators; a technician connected the 'gold gas' and 'silver gas' pipes to an oxygen or air supply on the basis of a coin toss. Due to the nature of the chamber, patients in both groups were able to receive treatment at the same time.

Interventions and outcomes

The HBOT and comparator interventions were generally adequately described, with treatment pressure, number, length and frequency of sessions all described. However, the oxygen concentration received by each treatment group was not explicitly stated, described only as 'oxygen' or 'air'.

The primary outcome, wound healing quantified through the relative reduction in wound area over time, was appropriate and well described by the authors.

Results reporting and analysis

Numbers analysed and statistical methods

The authors did not conduct calculations to determine statistical power, and did not explicitly state whether an intention-to-treat or per-protocol analysis was conducted.

Techniques used for statistical analysis were appropriate and well reported, but an alpha level for statistical significance was not prospectively identified.

Outcomes and estimations

Reporting of the primary outcome of the study, relative reduction in wound area over time, was generally well reported, with all patients included in between-groups comparisons at the completion of the treatment protocol six weeks after the initial session. However, although individual patient results were reported, no statistical comparison of the treatment groups was reported at 18 weeks after the initial session (12 weeks after completion of the treatment protocol). No subgroup analyses were conducted.

The study utilised mean values as an indicator of central tendency, with standard deviation provided as a measure of estimation where appropriate.

Adverse events were not reported by the authors.

Follow-up and losses to follow-up

Patients were followed up for a period of 18 weeks after their first treatment session, with comparisons between treatment groups occurring up to six weeks after their first treatment session. It was not stated whether follow-up was of sufficient duration to observe healing end-points; the authors noted a continuing effect on wound healing was found at 18 weeks after treatment cessation (at six weeks), indicating that healing end-points may not have been fully reached by that stage.

No losses to follow-up were reported at the completion of the treatment protocol six weeks after the first session. At 18 weeks after the initial treatment session (12 weeks after completion of the treatment protocol), five patients had been lost to follow-up.

Non-neurological soft tissue radiation injuries

Summaries of the methodological quality of the five RCTs included for the assessment of HBOT for the treatment of non-neurological soft tissue radiation injuries (Clarke et al 2008; Gothard et al 2010; Marx 1999; Marx et al 1985; Sidik et al 2007a; Sidik et al 2007b) are provided in Appendix G and described below.

Study design

Sample size

Across the five RCTs, sample sizes ranged from 58 (38 in HBOT group and 20 in comparator group) to 160 (80 in each treatment group). Two studies reported having more than 50 patients in both treatment groups (Clarke et al 2008; Marx 1999).

Only Gothard et al (2010) reported undertaking power calculations to determine the sample size necessary to detect statistically meaningful outcome differences between

treatment groups, which were based on the results of a pilot study (Gothard et al 2004). The remaining four studies did not report undertaking power calculations or discuss appropriateness of sample sizes.

Participants

Four of the five RCTs clearly described their eligibility criteria for recruitment of patients, with one not reporting any criteria for patient recruitment (Marx 1999). As the indications treated in these studies were diverse in nature, the inclusion criteria applied by each differed considerably. Inclusion criteria were generally open to all patients suffering the particular radiation injury examined within the study, with relatively few limitations applied. Sidik et al (2007a; 2007b) only included patients aged 55 years or younger, meaning that patients included in this study were generally younger than those included in the other RCTs. Marx et al (1985) specified that patients were to have received at least 6,000 cGy of radiation to the mandible, while Gothard et al (2010) included only patients who had experienced an increase in arm volume of 15 per cent or greater after radiation treatment. The studies by Clarke et al (2008) and Sidik et al (2007a; 2007b) were the only RCTs to specify duration of symptoms in their inclusion criteria. Clarke et al (2008) included only patients whose diagnosis of radiation proctitis had been present for at least three months and had failed to respond to standard therapies. Sidik et al (2007a; 2007b) included patients with radiation proctitis proven by proctoscopy and biopsy, present for one to six months.

Exclusion criteria were more consistent across RCTs. Patients were generally excluded if they had comorbidities that precluded the use of HBOT or were likely to adversely affect healing outcomes. The most commonly reported comorbidity used for the exclusion of patients was the presence of a new or recurrent malignancy. Some studies excluded patients if they were unwilling or unable to complete a complete course of HBOT treatment, generally 20 to 30 sessions, plus adequate follow-up. As well as these criteria, Marx et al (1985) excluded patients who had received irradiation less than six months or more than 15 years before treatment, or received chemotherapy (including any steroid drugs) less than six months before treatment. Clarke et al (2008) excluded 29 patients from enrolment in the study for unspecified 'other reasons'.

Three of the five RCTs provided baseline characteristics for patients (Clarke et al 2008; Gothard et al 2010; Sidik et al 2007a; Sidik et al 2007b). Treatment groups were generally well matched for demographic variables and clinical characteristics. In the two studies where gender was reported (Clarke et al 2008; Gothard et al 2010), considerably more females than males were enrolled, due primarily to the nature of the cancer treated with radiation therapy; all patients in the study by Sidik et al (2007a; 2007b) were also assumed to be female as all received radiation treatment for cervical cancer. Marx (1999) and Marx et al (1985) did not provide detailed patient characteristics.

With regards to radiation therapy received, three RCTs reported detailed information (Clarke et al 2008; Gothard et al 2010; Sidik et al 2007a; Sidik et al 2007b), with treatment groups appearing relatively well matched. The studies by Marx (1999) and Marx et al (1985) reported only on the minimum levels of radiation dose received by included patients.

With regards to other outcome measures such as arm volume, radiation-induced morbidity and quality of life, patients were also generally well matched at baseline in each RCT. However, in the study by Clarke et al (2008), patients in the HBOT treatment

group appeared to have considerably poorer baseline scores on the 'Bowel Bother' subscale of the EPIC quality of life questionnaire; this was not statistically evaluated or discussed by the authors.

Randomisation, concealment and implementation

Of the five RCTs, three provided details on the random allocation of patients to treatment (Clarke et al 2008; Gothard et al 2010; Sidik et al 2007a; Sidik et al 2007b). Clarke et al (2008) used a block randomisation process developed by external biostatisticians and well described in the study. Sidik et al (2007a; 2007b) also reported using a block randomisation process, but provided no details on the block size or stratification. Gothard et al (2010) reported only that patients were randomised at a ratio of 2:1 (HBOT:control) through a telephone call to an external randomisation service, but gave no further details.

Only one RCT reported on concealment of treatment allocation. Clarke et al (2008) reported that although the local principal investigator was unblinded, the randomisation sequence became available only when irretrievable entry of each patient's demographic information, medical history, and clinical characteristics had been performed.

Marx (1999) and Marx et al (1985) did not describe methods of randomisation or processes of concealment.

Blinding

Four of the five RCTs utilised a comparator that was considerably different to HBOT, such as penicillin (Marx et al 1985) or best standard care (Gothard et al 2010; Sidik et al 2007a; Sidik et al 2007b). As such, blinding of patients to treatment allocation was not possible in these studies, and Sidik et al (2007a; 2007b) acknowledged this as a limitation of their study. None of these studies reported blinding of assessors to patient treatment allocation, which may have led to biases in their evaluation of patient outcomes.

The one RCT that compared HBOT to a placebo treatment (Clarke et al 2008) used a double-blind methodology. Patients receiving placebo treatment experienced a brief compression of the hyperbaric chamber to simulate HBOT, with the chamber then slowly decompressed. When surveyed after treatment, no correlation was found between patients' presumption of the treatment they had received and the treatment they had actually received. Patients' referring physicians, who acted as the assessors in the study, were blinded to patients' treatment allocation.

Interventions and outcomes

The HBOT intervention was poorly detailed by Marx (1999), who reported the number of HBOT sessions received by patients and stated that HBOT was used as an adjunct to major soft tissue surgery or the introduction of a soft tissue flap, but provided no further details on the procedure such as pressurisation of the chamber, or the length and frequency of sessions. The remaining studies generally described the HBOT procedure adequately.

The intervention used as a comparator to HBOT was poorly detailed in three RCTs. Sidik et al (2007b) described the comparator intervention only as symptomatic treatment with vitamins B and C as necessary. Gothard et al (2010) described the comparator

intervention only as continued best standard care for lymphoedema, without the use of HBOT. Marx (1999) described the comparator intervention only as major soft tissue surgery or the introduction of a soft tissue flap, without HBOT as an adjunct treatment.

Healing of radiation injuries or wounds was reported to be an outcome of interest in three RCTs (Clarke et al 2008; Marx et al 1985; Sidik et al 2007b). In the majority of studies, assessment of healing outcomes was a function of clinical impression alone, opening studies to differences in interpretation and potential bias. As reported in previous assessments of HBOT (MSAC 2001; 2004), the primary outcome reported by Marx et al (1985) was the clinical diagnosis of osteoradionecrosis after dental extractions in irradiated tissue. However, for the purposes of this assessment, soft tissue wound healing was defined as the absence of osteoradionecrosis (ie exposed bone in the extraction socket) at follow-up, and was considered an appropriate effectiveness outcome. In the studies by Clarke et al (2008) and Sidik et al (2007b), criteria for evaluation of proctitis healing were not explicitly defined, and it was unclear whether healing outcomes were assessed objectively. Clarke et al (2008) acknowledged that the assessment of proctitis healing was a function of clinical impression alone, open to differences in interpretation between assessors; it should be noted, however, that assessors in this study were blinded to patient allocation, and the validated and reproducible LENT-SOMA scale was used as a primary outcome measure to lessen subjectivity and bias. Sidik et al (2007b) established diagnosis and progress of proctitis through proctosigmoidoscopy and histopathology. The study by Marx (1999) examined clinical outcomes of wound infection, wound dehiscence and delayed wound healing, with wound infection and dehiscence differentiated into minor and major states. The authors defined, but did not objectively quantify, the clinical outcomes.

All RCTs that reported late radiation-induced morbidity and quality of life (Clarke et al 2008; Gothard et al 2010; Sidik et al 2007a) described outcome measures used, with most utilising commonly used and validated instruments for patient assessment. These included relatively objective measures such as the LENT-SOMA scale. One exception to this was Gothard et al (2010), who utilised an unpublished quality of life scale for upper limb lymphoedema that had been developed and validated by a lymphoedema practitioner. While the scale was reported to consist of 12 questions designed to assess pain, self-awareness and restrictions to everyday activities in a similar format to the UK Short Form 36 (SF-36) Health Survey, no further details were provided by the authors.

Results reporting and analysis

Numbers analysed

One RCT reported undertaking calculations to determine statistical power. The study by Gothard et al (2010) had a sufficient sample size to provide 90 per cent power to detect an eight per cent absolute difference between treatment groups in the primary outcome, reduction of volume in the affected arm relative to the normal arm at 12 month follow-up (1-sided 5% significance level); however, the authors also noted that the small sample size may have reduced the size of treatment effect that could be reliably detected.

Four of the five RCTs did not explicitly state whether analyses were conducted on an intention-to-treat or per-protocol basis. Clarke et al (2008) did report a between-groups comparison of healing results on an intention-to-treat basis, considering the results if: all patients for whom they had no results had shown improvement; all patients for whom they had no results had not shown improvement; and for both groups, half of those for whom they had no results had shown improvement and half had not.

Statistical methods

Techniques used for statistical analysis were well described in three of the five RCTs; the studies by Marx (1999) and Marx et al (1985) did not report on the exact type of statistical methods used for comparison. However, the statistical methods that were used were appropriate across all studies. Only one study (Gothard et al 2010) prospectively identified an alpha level (0.05) for statistical significance.

Outcomes and estimations

Outcomes that were of primary interest to each RCT were generally well reported, with statistical comparison of treatment groups conducted where appropriate. With regards to outcomes of secondary interest, reporting of results was poorer, with a potential publication bias towards reporting results only for significant and positive outcomes. Clarke et al (2008) reported statistical comparisons between treatment groups for healing outcomes and radiation-induced morbidity, but did not compare groups on the EPIC quality of life measure. The authors stated that data were collected using the Short Form 12 (SF-12) General Health Function Survey, but no results from this measure were reported. Gothard et al (2010) reported statistical comparisons between treatment groups for relative reduction in arm volume, but did not report between-groups comparisons on other measures (ie lymphatic clearance rate, arm fluid volume change and quality of life). The authors stated that data was collected using the SF-36, but no results from this measure were reported. Subgroup analyses were not conducted in any of the studies.

Mean values were the most commonly reported indicator of central tendency, with some measure of estimation (eg standard deviation, 95% CI, interquartile range) employed where appropriate by the majority of studies.

Adverse events were poorly reported overall, with only two RCTs (Clarke et al 2008; Gothard et al 2010) reporting safety outcomes. Clarke et al (2008) provided detailed descriptions of adverse outcomes, while Gothard et al (2010) only briefly discussed individual incidents.

Follow-up and losses to follow-up

The RCT by Marx (1999) did not report length of follow-up or timing of patient evaluation. Follow-up length in the other four RCTs varied from immediately after treatment (Clarke et al 2008) to six months (Marx et al 1985; Sidik et al 2007a; Sidik et al 2007b) and 12 months post-treatment (Gothard et al 2010). Clarke et al (2008) reported following patients for up to a maximum of five years, but for the purposes of this assessment comparisons of relative effectiveness could only be made on patient evaluations conducted immediately after completion of the initial treatment protocol. After this evaluation, patients in the placebo comparator group were crossed over to receive HBOT, precluding further between-groups comparisons.

Gothard et al (2010) based their length of follow-up on the results of a pilot study which showed improvements in arm volume outcomes for at least 12 months after treatment with HBOT (Gothard et al 2004). Otherwise, studies generally did not explicitly state whether follow-up was of sufficient duration to observe healing end-points. However, there is clinical evidence to suggest that hyperbaric oxygen-induced tissue angiogenesis and recovery becomes measurable after eight HBOT sessions and plateaus at 20 sessions, even with further HBOT treatment (Beehner and Marx 1983; Marx 1984); both Marx et

al (1985) and Sidik et al (2007a; 2007b) referenced this point. Clinical expert opinion was that, provided the patient receives no further radiation to exacerbate the injury, the healing end-point is considered to be relatively durable from shortly after treatment.

Losses to follow-up were reported in all five of the RCTs. Marx (1999) and Marx et al (1985) reported on all patients randomised to treatment at follow-up. Clarke et al (2008) reported that 30 of 150 randomised patients did not receive or complete the treatment protocol and were not evaluated at follow-up immediately after treatment. Sidik et al (2007a; 2007b) reported that 10 of 75 randomised patients did not complete the treatment protocol. Of the remaining 65 patients, clinical results were available for 46 at six month follow-up (16 patients died and three were lost to follow-up). Gothard et al (2010) reported that five of 58 randomised patients were not evaluated at baseline, and that seven of the remaining 53 patients were lost to follow-up after 12 months.

Non-randomised comparative studies

Non-neurological soft tissue radiation injuries

Summaries of the methodological quality of the two non-randomised comparative studies included for the assessment of HBOT for the treatment of non-neurological soft tissue radiation injuries (Carl et al 2001; Neovius et al 1997) are provided in Appendix H and described below.

Study design

Sample size

Sample sizes in the two non-randomised comparative studies were 30 (Neovius et al 1997) and 44 (Carl et al 2001). Neither study reported undertaking power calculations to determine the necessary sample sizes for detection of differences between groups.

Participants

Carl et al (2001) recruited patients with pain higher than grade 3 or with a total score of at least 8 points on their modified LENT-SOMA scale, but did not report any exclusion criteria. Neovius et al (1997) stated that for treatment with HBOT, patients with oral, pharyngeal or laryngeal cancer classified as T2-T4 and treated with a preoperative irradiation dose of 64 Gy were included, and that all patients had major infected wounds or chronic fistulas with no signs of healing at three weeks or longer after surgery; however, it is unclear as to whether these were prospective criteria for patient inclusion. Similar issues were found in the historical control group, with no prospective criteria for patient inclusion reported. No exclusion criteria were reported by Neovius et al (1997), although one patient was excluded from the study after refusing further HBOT treatment after two sessions.

Neovius et al (1997) reported comprehensive baseline characteristics of patients, with treatment groups well matched at baseline for demographic variables and clinical characteristics. Carl et al (2001) reported few demographic or clinical characteristics of patients; all patients in the study were female, and no significant differences were found between treatment groups in baseline LENT-SOMA scores. Neovius et al (1997) reported on radiation therapy received, with treatment groups appearing relatively well matched, while Carl et al (2001) reported only the maximum level of radiation dose received by included patients.

It should be noted that the use of historical control in the study by Neovius et al (1997) may introduce bias in their findings related to the selection of patients; although the authors reported that patients in the reference group 'had corresponding wounds, necrotic flaps, or fistulas treated without HBO' (p. 319), criteria for their recruitment was not reported, and identification and control for any confounding factors was not reported. Furthermore, any improvements in wound care practice or related technologies over time since the control group received treatment may also bias healing outcomes in favour of HBOT.

Interventions and outcomes

The HBOT intervention was well reported in both of the non-randomised comparative studies. The comparator intervention to HBOT was poorly described by Neovius et al (1997), who reported patients in the comparator group only as having been treated without HBOT. Carl et al (2001, p. 1030) stated that patients in the comparator group 'received no further treatment and served as controls, because they refused to undergo hyperbaric oxygen therapy.'

Neovius et al (1997) reported healing status of wounds as a major outcome. However, criteria for evaluation of healing were not defined, and it was unclear whether outcomes were assessed objectively using specific criteria. Carl et al (2001) utilised a modified version of the LENT-SOMA scale for late radiation-induced morbidity, developed by Pavy et al (1995); while the LENT-SOMA scale is a validated and commonly used measure, the validity and reliability of the modified version of the scale were not discussed by the authors.

Blinding

Blinding of outcome assessors to treatment group allocation was not reported in either of the non-randomised comparative studies, which may have led to biases in results. Carl et al (2001) acknowledged that the lack of randomisation in their study may have possibly resulted in biases in patient selection or symptom ratings.

Results reporting and analysis

Numbers analysed and statistical methods

Neither of the non-randomised comparative studies reported undertaking calculations to determine statistical power, or explicitly stated whether an intention-to-treat or per-protocol analysis had been conducted.

Neovius et al (1997) did not report any statistical comparison between treatment groups. Carl et al (2001) reported comparing LENT-SOMA scores using the Mann-Whitney test, an appropriate technique. Neither study prospectively identified an alpha level for statistical significance.

Outcomes and estimations

Neovius et al (1997) reported healing status of wounds in narrative form, and did not conduct statistical between-groups comparisons of healing outcomes. Carl et al (2001) tabulated LENT-SOMA scores pre- and post-treatment using median values and ranges; results from appropriate statistical comparisons were reported. Subgroup analyses were

not conducted in either of the studies. No measures of estimation were reported by either study.

Neovius et al (1997) briefly discussed individual adverse events after HBOT, while Carl et al (2001) reported that no adverse events occurred after HBOT.

Follow-up and losses to follow-up

Length of follow-up was five months in the study by Neovius et al (1997). It was not stated whether follow-up was of sufficient duration to observe wound healing end-points, although the authors acknowledged that some of the wounds in the control group may have healed without HBOT. This suggests that healing end-points may not have been fully reached at that stage. In the study by Carl et al (2001) HBOT and control patients were followed for a median of 11 and seven months, respectively; it was not reported by the authors whether LENT-SOMA scores may have been impacted if HBOT patients had been evaluated at later time points than patients in the control group.

Both non-randomised comparative studies reported that all patients allocated to treatment received follow-up evaluation.

Appraisal of case series studies

Appraisal of included case series evidence is available in Appendix I.

Is it safe?

All primary studies included in this assessment were reviewed for data related to adverse events occurring after treatment with HBOT. Adverse event rates have been reported in two manners, both of which may be at risk of bias. The rate has been presented as a proportion of patients in the studies that specifically reported that particular outcome, which may be an over-inflated representation of the outcome, particularly for rare events. The rate has also been presented as a proportion of the total patient number in all studies included for safety. This may also not be an accurate representation of more common outcomes such as barotrauma or vision change, which may not have been of interest in all studies, or where authors may have differed in their definition of what constituted an adverse event. For example, Feldmeier et al (1993, p. 333) stated that 'None of the patients had any lasting complications due to HBO, although several experienced a temporary change in visual acuity with a tendency toward myopia.' The authors reported no further data on this event, which other studies may have discussed in greater detail.

Mortalities

Fourteen studies encompassing 416 patients reported on mortalities occurring within their patient cohort during study follow-up (Abratt and Mills 1978; Bevers et al 1995; Chavez and Adkinson 2001; Clarke et al 2008; Feldmeier et al 1993; Feldmeier et al 1996; Filntisis et al 2000; Hart and Mainous 1976; Mayer et al 2001; Neheman et al 2005; Rijkmans et al 1989; Sidik et al 2007b; Williams et al 1992; Yoshida et al 2008). The indication in all studies was non-neurological soft tissue radiation injury; no studies examining chronic non-diabetic wounds reported patient mortalities during follow-up. It is important to note that patients with non-neurological soft tissue radiation injuries have generally received radical treatment for cancer; as such, there is a substantial rate of mortality associated with their underlying disease.

Of the 416 patients of interest, 64 were reported to have died during study follow-up (15.4%; see Table 14). This percentage figure is likely a considerable over-inflation of the outcome, as it does not include data from the majority of studies retrieved, for which no explicit statement regarding patient mortalities was made but it was implied that no patient mortality occurred. No reported deaths were attributed to HBOT treatment; patient mortalities were due to recurrence or progression of malignancies, progression of condition after treatment failure, or other unrelated causes. Reported mortalities usually occurred months or years after HBOT treatment. Hart and Mainous (1976) stated that 'One patient died during therapy of aspiration unrelated to [HBOT]' (p.2581); otherwise, minimum reported time of patient mortality after treatment with HBOT was one month (Bevers et al 1995).

Table 14 Summary of mortality events reported by studies included for assessment

Study	N	n	Rate where reported %	Rate across total number of patients %	Details
Clarke (2008)	120	5	4.2	1.2	No cause reported (5)
Sidik (2007)	65	16	24.6	3.8	HBOT group: died of cancer (6) Control group: died without explanation, most likely due to cancer (10)
Feldmeier (1996)	42	13	31.0	3.1	Recurrent cancer (3) General deterioration (1) Extensive sites of radiation necrosis (1) Cardiac disease (1) Drug overdose (1) Urosepsis (1) Stroke (1) Second malignancy (1) Cardiac deterioration and UGI bleed (1) Massive wound bleed (1) No cause reported (1)
Bevers (1995)	40	11	27.5	2.6	Cancer metastasis (4) Unrelated causes (3) Unknown (4)
Chavez (2001)	40	3	7.5	0.7	Recurrent tumour (3)
Filntisis (2000)	18	2	11.1	0.5	Lung cancer (1) Heart attack (1)
Mayer (2001)	18	2	11.1	0.5	Widespread prostate cancer (1) Myelodysplasia (1)
Hart (1976)	17	1	5.9	0.2	Aspiration unrelated to HBOT (1)
Williams (1992)	14	1	7.1	0.2	Progress of necrosis after treatment failure (1)
Rijkmans (1989)	10	2	20.0	0.5	Progressive local malignancy (1) Secondary malignancy (1)
Feldmeier (1993)	9	4	44.4	1.0	Secondary malignancies (2) Ethanol abuse (1) Respiratory arrest (1)
Abratt (1978)	8	2	25.0	0.5	Recurrent tumour (1) Unknown (1)
Yoshida (2008)	8	1	12.5	0.2	Pelvic abscess (1)
Neheman (2005)	7	1	14.3	0.2	Underlying malignancy (1)
TOTAL	416	64	-	15.4	-

-: not applicable; HBOT: hyperbaric oxygen therapy; UGI: upper gastrointestinal.

Adverse events

Although four studies reporting adverse events were comparative (Carl et al 2001; Clarke et al 2008; Gothard et al 2010; Neovius et al 1997), none reported on 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.

Twenty-five studies encompassing 634 patients made some quantification of safety outcomes or adverse events from HBOT treatment in their reporting of patient outcomes. Safety data was included from only one study where the treated condition was chronic non-diabetic wounds (Efrati et al 2007). Patient populations of interest within these studies ranged from four (Ashamalla et al 1996) to 120 (Clarke et al 2008). For convenience, the total adverse events reported across these 25 included studies were grouped and summarised, and are presented in Table 15. The full list of studies reporting on each category of adverse event is provided in Appendix J.

Table 15 Summary of adverse events reported by studies included for assessment

Adverse event	Studies	Patients N	Incidence n	Rate where reported (%)	Rate across total number of patients (%)
Ear barotrauma[a]	13	404	61	15.1	9.6
Transient vision change	9	329	38	11.6	6.0
Claustrophobia/anxiety	4	162	8	4.9	1.3
Oxygen toxicity of the central nervous system[b]	5	131	5	3.8	0.8
Sinus barotrauma	1	120	1	0.8	0.2
Angina episode	1	18	1	5.6	0.2
Exacerbation of aminodarone-induced pulmonary fibrosis	1	10	1	10.0	0.2
Hypertension	1	9	1	11.1	0.2
None[c]	9	187	-	-	-
TOTAL	25	634	-	-	-

[a] Also includes patients reporting significant ear equalisation problems, or requiring myringotomy and/or tympanostomy tubes; where reported, degree of ear barotrauma varied from mild to significant, with rupture of eardrum confirmed in one patient (0.2%).
[b] Includes patients described as experiencing 'oxygen toxicity seizure', 'hyperbaric oxygen-induced seizure', 'tonic-clonic seizure' and 'convulsions'.
[c] Authors stated explicitly that no patient in the study experienced an adverse event.
-: not applicable.

Nine studies with a total of 187 patients stated explicitly that no complications or adverse events associated with HBOT were experienced. The most common adverse events associated with HBOT were ear barotrauma and vision change, particularly myopia. Barotrauma and vision change were reported in 10 to 15 per cent of patients in studies that reported on those events, and between five and 10 per cent of all patients in studies included for evaluation of safety. Claustrophobia and anxiety in the treatment chamber was reported in a total of eight patients (4.9 per cent of patients in studies which reported this outcome; 1.3 per cent of patients in all studies included for evaluation of safety). Oxygen toxicity is a potentially more serious adverse event that manifests most commonly as neurologic changes such as seizures or convulsions. Some form of seizure or convulsion event due to oxygen toxicity of the central nervous system was found to occur in a total of five patients (3.8 per cent of patients in studies which reported this outcome; 0.8 per cent of patients in all studies included for evaluation of safety).

Safety data – other sources

The previous MSAC assessment of HBOT (MSAC 2004) reported a summary of side effects of HBOT following 21,033 sessions conducted in Australia between 1 July 2001 and 30 June 2002, presented at the 10th Annual Scientific Meeting of the Hyperbaric

Technicians and Nurses Association (HTNA) and the Australian and New Zealand Hyperbaric Medicine Group (ANZHMG) and shown below in Table 16 (HTNA and ANZHMG 2002). These sessions were conducted for a variety of indications, including those that are the focus of this review.

Table 16 Side effects associated with HBOT in Australia for financial year 2001–02

Side effect	Incidence per number of HBOT treatment sessions
Persistent ocular changes	1/112 (0.89%)
Significant ear barotrauma causing treatment interruption	1/170 (0.59%)
Claustrophobia	1/910 (0.11%)
CNS seizures (all treatment pressures)	1/1,548 (0.06%)
Sinus barotrauma	1/4,864 (0.02%)
Pulmonary oxygen toxicity	1/6,766 (0.01%)
Pulmonary barotrauma	0/15,475 (0.00%)
Deaths	0/21,033 (0.00%)

CNS: central nervous system; HBOT: hyperbaric oxygen therapy.
Source: HTNA and ANZHMG (2002).

Since the previous MSAC assessment, information on the incidence of side effects following 24,731 sessions of HBOT conducted in Australia between 1 July 2007 and 30 June 2008 was presented by the HTNA at the 16th Annual Scientific Meeting on Diving and Hyperbaric Medicine, shown in Table 17 (HTNA 2008).

Table 17 Side effects associated with HBOT in Australia for financial year 2007–08

Side effect	Incidence per number of HBOT treatment sessions
Minor grades of barotrauma to ears	1/274 (0.36%)
Persistent myopia	1/852 (0.12%)
Claustrophobia	1/1,902 (0.05%)
Sinus barotrauma	1/2,248 (0.04%)
Higher grades of barotrauma to the ears	1/6,182 (0.02%)
Oxygen toxicity seizures	1/8,243 (0.01%)
Lung barotrauma	1/24,731 (0.00%)
Staff decompression illness (minor, treatable)	1/6,636 (0.00%)

HBOT: hyperbaric oxygen therapy.
Source: HNTA (2008).

Consistent with the adverse events reported within the included primary evidence, the most common adverse events associated with HBOT were middle ear barotrauma and reversible myopia. Other reported adverse events were oxygen toxicity and claustrophobia, though these occurred considerably less frequently. It should be noted that the data presented by the HTNA is on a per-treatment session basis, while the data from the studies included in the current assessment is presented on a per-patient basis; it is common for patients to receive 20 of more HBOT sessions in a standard treatment regimen.

Is it effective?

Chronic non-diabetic wounds

Comparative studies

The primary outcome reported in the RCT by Hammarlund and Sundberg (1994) was the mean change in area of chronic non-diabetic leg ulcers. Through the course of 30 treatment sessions over a 6-week period, eight patients received HBOT and eight patients received hyperbaric air as a placebo, with the outcomes presented in Table 18. Significantly greater improvements in wound area were found in patients receiving 100 per cent oxygen compared to those receiving air at both four (p=0.009) and six weeks (p<0.001).

Table 18 Healing outcomes in patients with chronic non-diabetic wounds: comparative studies

Outcome	Follow-up	HBOT (N=8) mean (SD)	Placebo (N=8) mean (SD)	*p*-value
Percentage decrease in wound area compared to baseline (%)	2 weeks	6.6 (14)	2.8 (11)	0.556
	4 weeks	22.0 (13)	3.7 (11)	0.009
	6 weeks	35.7 (17)	2.7 (11)	<0.001

HBOT: hyperbaric oxygen therapy; SD: standard deviation.
Source: Hammarlund and Sundberg (1994).

At 18 weeks after treatment, six patients who received HBOT and five patients who received air as a placebo were available for follow-up. Mean decrease in wound size at 18 weeks was 60.5 per cent (standard deviation (SD)=40.2) amongst HBOT patients, compared to 26.2 per cent (SD=45.2) amongst those who received air. While no comparison between groups was reported by the authors at this follow-up point, this was found to be a statistically non-significant difference (p=0.216). The authors also reported that by 18 weeks two patients in the HBOT treatment group had complete healing of their ulcers, with another wound showing significant ongoing improvement. In the placebo group, no patient had complete healing, but one wound showed significant ongoing improvement. There was no significant difference between treatment groups as to the proportion of patients with wound healing at this stage (p=0.467).

Case series

Three case series reported on the use of HBOT for the treatment of chronic non-diabetic wounds (Efrati et al 2007; Hawkins et al 2006; Oubre et al 2007); each case series reported on some form of healing outcome. Efrati et al (2007) reported on the proportion of patients experiencing healing of vasculitis-induced non-healing skin ulcers at the end of a 4-week HBOT treatment regimen (five sessions per week). Of the 35 patients enrolled, 28 (80.0%) experienced complete ulcer healing, four (11.4%) had partial resolution (complete resolution of redness and oedema around the ulcer, with significant improvement in ulcer-related pain), while three (8.6%) had no response to HBOT. Oubre et al (2007) reported findings from 37 patients who had non-healing non-diabetic wounds with a mean size of 10 cm^2 (SD=2.5); after receiving six weeks of HBOT treatment (five sessions per week), patients reported an average reduction in wound area of 22.8 per cent (SD=12.7).

The case series by Hawkins et al (2006) reported the first-year results from the ANZHMG Wound Care study, an ongoing prospective cohort study of patients presenting to hyperbaric facilities across Australia with chronic wounds (>3 months duration), initiated in June 2004 as a recommendation of the previous MSAC assessment

(MSAC 2004). With respect to non-diabetic wounds, 48 patients (20 with wounds due to peripheral vascular (arterial) disease; 13 with wounds due to venous disease; 15 with miscellaneous non-diabetic aetiologies such as vasculitic and auto-immune diseases) were enrolled in the study and accepted for treatment with HBOT. Clinical healing outcomes reported in the study are shown in Table 19. The proportion of patients with complete or substantial healing of their wound at 12 months was reported to be 77.8 per cent in patients with peripheral vascular (arterial) disease and 100.0 per cent in patients with venous disease; results for patients with miscellaneous non-diabetic aetiologies were not reported. While the number of patients with healing responses by aetiological category was not reported in the publication, details were supplied by the authors.

Table 19 Healing outcomes in patients receiving HBOT for chronic non-diabetic wounds: published case series

Outcome	Wound aetiology	Follow-up	n (%)
Complete or substantial healing of wound	Peripheral vascular (arterial) disease	Immediately post-treatment	4/17 (23.5)
		1 month	4/15 (26.7)
		6 months	10/12 (83.3)
		12 months	7/9 (77.8)
	Venous disease	Immediately post-treatment	5/11 (45.5)
		1 month	6/10 (60.0)
		6 months	8/8 (100.0)
		12 months	6/6 (100.0)

HBOT: hyperbaric oxygen therapy; NR: not reported.
Source: Hawkins et al (2006).

Unpublished case series

The applicant and Advisory Panel brought to light two unpublished case series manuscripts (Hawkins and Bennett n.d.; Sidhom et al n.d.) that reported later results from the study by Hawkins et al (2006). As they provided updated results from the ongoing ANZHMG Wound Care study and provided further relevant information on the use of HBOT within the Australian healthcare context, the Advisory Panel's decision was to discuss these unpublished results in the assessment.

Hawkins and Bennett (n.d.) reported the sixth-year wound healing results of the ANZHMG Wound Care study. With respect to non-diabetic wounds, 223 patients (88 with wounds due to peripheral vascular (arterial) disease; 55 with wounds due to venous disease; and 80 with miscellaneous non-diabetic aetiologies such as vasculitic and auto-immune diseases) were enrolled in the study. Although healing rates and numbers of patients with healing responses were not stated by wound aetiological category in the draft manuscript, data was obtained from the authors, shown in Table 20. The proportion of patients with complete or substantial healing of their wound at 12 months was reported to be 65.8 per cent in patients with peripheral vascular (arterial) disease, 85.2 per cent in patients with venous insufficiency, and 79.5 per cent in patients with miscellaneous aetiologies.

Table 20 Healing outcomes in patients receiving HBOT for chronic non-diabetic wounds: unpublished case series

Outcome	Wound aetiology	Follow-up	n (%)
Complete or substantial healing of wound	Peripheral vascular (arterial) disease	Immediately post-treatment	35/87 (40.2)
		1 month	40/75 (53.3)
		6 months	33/54 (61.1)
		12 months	25/38 (65.8)
	Venous disease	Immediately post-treatment	30/55 (54.5)
		1 month	30/52 (57.7)
		6 months	28/41 (68.3)
		12 months	23/27 (85.2)
	Miscellaneous[a]	Immediately post-treatment	33/80 (41.3)
		1 month	38/73 (52.1)
		6 months	41/66 (62.1)
		12 months	35/44 (79.5)

a Includes wounds due to vasculitic and auto-immune diseases.
HBOT: hyperbaric oxygen therapy; NR: not reported.
Source: Hawkins and Bennett (n.d.).

Sidhom et al (n.d.) assessed the effect of HBOT on levels of pain in patients with chronic wounds enrolled in the ANZHMG Wound Care study. With respect to non-diabetic wounds, 119 patients (36 with wounds due to peripheral vascular disease; 32 with wounds due to venous disease; and 51 with miscellaneous non-diabetic aetiologies) had pain scores recorded on a visual analogue scale (VAS) at presentation and six months after receiving HBOT. The results showed a clinically significant improvement in median pain score after treatment with HBOT for all wound aetiologies (Table 21).

Table 21 Pain outcomes in patients receiving HBOT for chronic non-diabetic wounds: unpublished case series

Wound aetiology	VAS pain score		*p*-value (95% CI)
	Pre-HBOT median (IQR)	Post-HBOT median (IQR)	
Peripheral vascular disease (n=36)	6 (4–8)	0.5 (0–5)	<0.0001 (1.59–3.70)
Venous disease (n=37)	5 (3–8)	0 (0–3)	<0.0001 (2.53–5.40)
Miscellaneous (n=51)[a]	5 (4–8)	1 (0–4)	<0.0001 (1.88–4.00)

a Includes wounds due to vasculitic and auto-immune diseases.
CI: confidence interval; HBOT: hyperbaric oxygen therapy; IQR: interquartile range; VAS: visual analogue scale.
Source: Sidhom et al (n.d.).

Non-neurological soft tissue radiation injuries

Radiation proctitis and enteritis

Comparative studies

Two RCTs examined the effectiveness of HBOT for the treatment of radiation proctitis, reported across three publications (Clarke et al 2008; Sidik et al 2007a; Sidik et al 2007b). A range of outcomes were reported in the two studies, including clinical outcomes such as healing and resolution of radiation proctitis, scores for radiation-induced morbidity, and quality of life measures.

Clinical healing outcomes are presented in Table 22. The RCT by Clarke et al (2008) was a multi-centre, double-blind crossover trial examining 150 patients with problematic radiation proctitis. After completion of the initial treatment allocation (generally consisting of 30 sessions), 64 patients receiving HBOT and 56 patients receiving normobaric air as a placebo were available for evaluation. Of these patients, 56 (87.5%) patients receiving HBOT were assessed to have either healed or had some improvement in proctitis, compared to 35 (62.5%) patients receiving the placebo treatment. A significantly greater proportion of patients receiving HBOT experienced at least moderate improvement of proctitis than patients receiving placebo (p=0.0009), while logistic regression analysis showed that HBOT patients were approximately six times more likely to experience at least moderate improvement than patients receiving placebo (odds ratio: 5.93; 95% CI: 2.04–17.24; p=0.0011). A Jonckheere-Terpstra test for trend indicated that the HBOT group had significantly better clinical outcomes following completion of initial treatment allocation (p=0.0008). An absolute risk reduction of 0.32 was found, with the number needed to treat to achieve one extra case of healing being three. From an intention-to-treat perspective, patients receiving HBOT had a greater proportion of improvement than those receiving placebo treatment if all patients for whom there was no data had improvement (p=0.0057) or had no improvement (p=0.0007), or if one-half of those for whom there was no data had improvement (p=0.0036). While evaluation of clinical outcomes took place immediately after initial treatment allocation, these results significantly favour the use of HBOT.

In the RCT by Sidik et al (2007b), 32 patients received HBOT and 33 patients received only symptomatic treatment as a control. At six month follow-up, six of 32 of the HBOT group and 10 of 33 of the control group had died of their cancer. Two further patients in the control group were lost to follow-up. Of the remaining patients, 20 (76.9%) receiving HBOT were assessed to be free of radiation proctitis, compared to nine (42.9%) who received symptomatic treatment only. The authors concluded that that treatment with HBOT significantly decreased the prevalence of radiation proctitis compared to symptomatic treatment (p=0.026).

Table 22 Healing outcomes in patients with radiation proctitis: comparative studies

Study	Follow-up	Outcome	HBOT n (%)	Comparator n (%)	*p*-value
Clarke (2008)	Immediately post-treatment	Complete healing	5/64 (7.8)	0/56 (0.0)	
		Significant improvement	24/64 (37.5)	15/56 (26.8)	
		Moderate improvement	27/64 (42.2)	20/56 (35.7)	0.0008
		No improvement	7/64 (10.9)	21/56 (37.5)	
		Data not reported	1/64 (1.6)	0/56 (0.0)	
Sidik (2007b)	6 months	Healed	20/26 (76.9)	9/21 (42.9)	
		Not healed	6/26 (23.1)	11/21 (52.4)	0.026
		Data not reported	0/26 (0.0)	1/21 (4.8)	

HBOT: hyperbaric oxygen therapy.

Relative levels of radiation-induced morbidity recorded in the two RCTs were measured using the LENT-SOMA scale, and are presented in Table 23. Examination of the two studies shows that patients entered into the study by Clarke et al (2008) were symptomatically worse at baseline than those in the study by Sidik et al (2007a).

After adjusting for covariates, Clarke et al (2008) reported that both treatment groups had a statistically significant improvement in LENT-SOMA score from baseline levels after initial treatment (p<0.0001). However, the degree of improvement reported by

patients treated with HBOT was significantly greater than that of patients receiving the placebo (p=0.0019), and after completion of initial treatment LENT-SOMA scores were significantly lower (improved) in HBOT patients than in placebo patients (p=0.0150). When patients who initially received the placebo were crossed over to receive appropriate treatment with HBOT, they improved such that no difference in score was found between the treatment groups after both had received HBOT.

Sidik et al (2007a) reported that patients receiving HBOT had a greater level of improvement in LENT-SOMA score than patients receiving only symptomatic treatment, both at 1-to-2-month follow-up (p<0.001) and at 6-month follow-up (p=0.008).

Table 23 Radiation-induced morbidity in patients with radiation proctitis: comparative studies

Study	Outcome	Follow-up	HBOT mean (SD)	Comparator mean (SD)	*p*-value
Clarke (2008)	LENT-SOMA score	Baseline	12.55	12.84	0.5597
		Immediately post-treatment	7.48	10.23	0.0150
		After crossover to HBOT arm	-	6.92	0.6594[a]
Sidik (2007a)	LENT-SOMA score	Baseline	7.7 (2.0)	6.8 (2.3)	0.10
	Improvement from baseline (%)	1–2 months	44.12 (28.22)	0.71 (30.16)	<0.001
		6 months	33.64 (57.64)	-19.69 (69.44)	0.008

a Value represents comparator group score after treatment with HBOT following crossover, compared to HBOT group score immediately after treatment.
HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; SD: standard deviation.

Both RCTs reported on measures of patient quality of life, with results shown in Table 24. Clarke et al (2008) utilised the Bowel Bother and Bowel Function subscales of the EPIC questionnaire as well as the SF-12. Patients receiving HBOT showed statistically significant improvement on the Bowel Bother subscale immediately after treatment (p=0.0007). Patients receiving placebo treatment did not show a statistically significant improvement in Bowel Bother score after initial treatment (p=0.1521); however, they did show a significant improvement after crossover and completion of a course of HBOT treatment (p=0.0002). The authors did not provide any statistical comparisons or report any differences between treatment groups on the Bowel Function subscale (where baseline scores of treatment groups were more comparable) or the SF-12. The authors concluded that enhanced bowel-specific quality of life resulted from treatment with HBOT.

While the greater level of improvement reported by Clarke et al (2008) in the HBOT treatment group at the randomised analysis point may have been an indication of initial differences between the groups (the HBOT group had poorer Bowel Bother scores at baseline), no direct comparisons of Bowel Bother score were reported. The absolute values at follow-up immediately after initial treatment scores for both treatment groups appeared close to equal. The initial difference in Bowel Bother score indicates that the HBOT patients were symptomatically worse at entry to the trial.

Sidik et al (2007a) reported on patient quality of life via Karnofsky score, reporting that patients receiving HBOT had a greater level of improvement in quality of life than patients receiving only symptomatic treatment, both at 1-to-2-month follow-up (p<0.001) and at 6-month follow-up (p=0.007).

Table 24 Quality of life in patients with radiation proctitis: comparative studies

Study	Outcome	Follow-up	HBOT mean (SD)	Comparator mean (SD)	*p*-value
Clarke (2008)	EPIC Bowel Bother subscale score	Baseline	44.97	52.93	NR
		Immediately post-treatment	59.56	59.74	
		After crossover to HBOT arm	-	73.66	
	EPIC Bowel Function subscale score	Baseline	60.31	60.83	NR
		Immediately post-treatment	69.82	68.30	
		After crossover to HBOT arm	-	77.65	
Sidik (2007a)	Karnofsky score	Baseline	73.8 (6.0)	74.6 (8.3)	0.66
	Improvement from baseline (%)	1–2 months	19.67 (9.64)	4.53 (10.74)	<0.001
		6 months	15.27 (14.74)	2.47 (16.11)	0.007

-: not applicable; EPIC: Expanded Prostate cancer Index Composite questionnaire; HBOT: hyperbaric oxygen therapy; NR: not reported; SD: standard deviation.

Case series

Nine case series reported on patients with radiation-induced proctitis or enteritis; six of these studies included only patients with radiation proctitis or enteritis (Dall'Era et al 2006; Girnius et al 2006; Jones et al 2006; Marshall et al 2007; Warren et al 1997; Woo et al 1997) while three included patients with a variety of radiation injuries which included proctitis or enteritis (Fink et al 2006; Mayer et al 2001; Safra et al 2008). Four of the nine studies (Dall'Era et al 2006; Girnius et al 2006; Jones et al 2006; Mayer et al 2001) provided baseline assessments of the degree of radiation proctitis with a grading of the histological or symptomatic features, with each utilising a different grading scale. Administration of HBOT was generally comparable with most studies pressurising patients to 2.4 ATA for 60 to 90 minutes, although some studies used lower pressure (2.0 ATA) with slightly longer treatment sessions. A total of 25 to 30 sessions was common, although the nine patients in the study by Girnius et al (2006) underwent a median of 58 treatment sessions.

Outcomes reported in these case series incorporated clinical outcomes such as healing of radiation proctitis, resolution of symptoms, scores for radiation-induced morbidity and toxicity, and quality of life measures. Five of the nine case series reported on some form of overall response of radiation proctitis or enteritis to treatment with HBOT (Dall'Era et al 2006; Fink et al 2006; Marshall et al 2007; Warren et al 1997; Woo et al 1997). With regards to specific symptom outcomes, the most commonly reported outcome across the nine case series was rectal bleeding, reported across seven studies (Dall'Era et al 2006; Girnius et al 2006; Jones et al 2006; Mayer et al 2001; Safra et al 2008; Warren et al 1997; Woo et al 1997), while resolution of diarrhoea and pain was reported by four studies (Dall'Era et al 2006; Jones et al 2006; Warren et al 1997; Woo et al 1997). Assessment of response varied between studies, usually consisting of a description of the resolution of proctitis or symptoms, with some studies classifying responses by a percentage in wound or symptom healing. However, no study reported on a tangible scoring system that could

be used for statistical analysis. Duration of response was inconsistently reported, as it was often unclear at what time point clinical assessments of outcomes took place.

Due to the heterogeneity of these case studies, particularly in the reporting of outcomes, these reports were not amalgamated to produce an overall response rate for proctitis healing. The minimum overall proctitis response rate was reported in a study of 18 patients by Woo et al (1997), who reported that all symptoms resolved in two (11.1%) patients and partially resolved in eight (44.4%). In a relatively large case series of 65 patients with radiation proctitis and/or enteritis, Marshall et al (2007) reported a complete response rate (defined by the authors as a >90 per cent reduction in symptom frequency or subjective symptom complaints and endoscopic documentation of healing when available) of 43.1 per cent, with a partial response rate (defined as a 50–90 per cent reduction in symptom frequency or subjective measure of improvement and endoscopic documentation of improvement) of 24.6 per cent. In all, healing results from the case series were in accordance with the comparative studies by Clarke et al (2008) and Sidik et al (2007b), showing a substantial improvement in the majority of patients, with complete resolution in a smaller proportion. Results from individual case series can be seen in Table 66.

The RCT by Clarke et al (2008) also reported long-term healing outcomes after all patients had received treatment with HBOT (including those crossed over from placebo treatment), with up to five years of follow-up. This was treated as case series data and is shown in Table 25. While the majority of patients were lost to follow-up through the course of the study, the results tended towards improved radiation proctitis outcomes during the follow-up period.

Table 25 Healing outcomes in patients receiving HBOT for radiation proctitis: long-term follow-up

Outcome	Follow-up n (%)						
	3 months (n=103)	6 months (n=103)	1 year (n=105)	2 years (n=61)	3 years (n=38)	4 years (n=29)	5 years (n=13)
Complete proctitis healing	7 (6.8)	7 (6.8)	7 (6.7)	7 (11.5)	5 (13.2)	4 (13.8)	1 (7.7)
Proctitis improvement	57 (55.3)	54 (52.4)	62 (59.0)	33 (54.1)	27 (71.1)	22 (75.9)	10 (76.9)
Proctitis unchanged	36 (35.0)	36 (35.0)	33 (31.4)	19 (31.1)	6 (15.8)	3 (10.3)	1 (7.7)
Recurrence of cancer	3 (2.9)	6 (5.8)	3 (2.9)	2 (3.3)	0 (0.0)	0 (0.0)	1 (7.7)

HBOT: hyperbaric oxygen therapy.
Source: Clarke et al (2008).

Case series reporting on resolution of bleeding generally had very small sample sizes. Amongst 25 patients suffering from rectal bleeding, the study by Dall'Era et al (2006) reported complete resolution of bleeding symptoms in 12 (48.0%) patients, and improvement in a further seven (28.0%). The minimum bleeding response was reported in a study of 18 patients by Woo et al (1997), who reported that bleeding symptoms resolved in four of 17 (23.5%) patients and partially resolved in three of 17 (17.6%).

In addition to healing outcomes, two case series reported on radiation-induced morbidity outcomes before and after HBOT treatment (Table 26). Mayer et al (2001) measured patient morbidity using the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) gastrointestinal (GI) late morbidity criteria in 10 patients with radiation proctitis. Safra et al (2008) reported

radiation-induced toxicity results from six patients who had radiation proctitis and cystitis, measured using National Cancer Institute Common Toxicity Criteria. Both reported a statistically significant improvement in patients' degree of morbidity or toxicity after receiving treatment with HBOT, although both studies reported on small samples.

Table 26 Radiation-induced morbidity and toxicity in patients receiving HBOT for radiation proctitis: case series

Study	Morbidity/toxicity	Pre-HBOT n (%)	Post-HBOT n (%)	*p*-value
Mayer (2001)	RTOG/EORTC gastrointestinal late morbidity criteria			
	Grade 0	0/10 (0.0)	3/10 (30.0)	
	Grade 1	0/10 (0.0)	5/10 (50.0)	
	Grade 2	0/10 (0.0)	1/10 (10.0)	0.004
	Grade 3	4/10 (40.0)	0/10 (0.0)	
	Grade 4	6/10 (60.0)	0/10 (0.0)	
	Inadequate HBOT treatment	0/10 (0.0)	1/10 (10.0)	
Safra (2008)	Common Toxicity Criteria			
	Grade 0	0/6 (0.0)	5/6 (83.3)	
	Grade 1	0/6 (0.0)	0/6 (0.0)	0.031[a]
	Grade 2	0/6 (0.0)	1/6 (16.7)	
	Grade 3	4/6 (66.7)	0/6 (0.0)	
	Grade 4	2/6 (33.3)	0/6 (0.0)	

a Calculation based on data reported for patients suffering from radiation cystitis and proctitis only.
HBOT: hyperbaric oxygen therapy; RTOG/EORTC: Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer.

Clarke et al (2008) also reported long-term results regarding late radiation-induced morbidity, measured using LENT-SOMA score, and quality of life, measured using the Bowel Bother and Bowel Function subscales of the EPIC questionnaire (Table 27). Although a large proportion of patients were lost to follow-up through the course of the study, mean scores for morbidity and quality of life appeared to remain relatively stable through one year and showed some improvement through the remainder of the follow-up period.

Table 27 Radiation-induced morbidity and quality of life in patients receiving HBOT for radiation proctitis: long-term follow-up

Outcome	Follow-up						
	3 months	6 months	1 year	2 years	3 years	4 years	5 years
HBOT only group	(n=55)	(n=55)	(n=55)	(n=36)	(n=20)	(n=14)	(n=6)
LENT-SOMA score	5.96	6.85	5.29	3.61	3.55	4.21	3.71
EPIC Bowel Bother subscale score	58.16	64.49	69.12	73.16	83.33	79.63	85.71
EPIC Bowel Function subscale score	69.72	75.34	77.48	82.01	81.34	82.01	88.69
HBOT following placebo group	(n=48)	(n=48)	(n=50)	(n=25)	(n=18)	(n=15)	(n=7)
LENT-SOMA score	7.17	7.31	6.72	6.20	3.89	4.00	4.29
EPIC Bowel Bother subscale score	74.14	73.76	74.70	71.20	71.42	76.78	69.38
EPIC Bowel Function subscale score	80.33	77.50	75.35	73.36	77.29	78.38	76.53

EPIC: Expanded Prostate cancer Index Composite questionnaire; HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic.
Source: Clarke et al (2008).

Wounds in irradiated soft tissue of the head and neck region

Comparative studies

The primary outcome reported in the RCT by Marx et al (1985) was the clinical diagnosis of osteoradionecrosis after dental extractions in irradiated tissue. However, only those results related to the healing of soft tissue wounds were considered appropriate effectiveness outcomes for the present assessment (Table 28). Marx et al (1985) administered HBOT to 37 patients with 156 tooth socket wounds, while penicillin was given to 37 patients with 137 socket wounds. Six months after the completion of therapy four (2.6%) socket wounds treated with HBOT had failed to heal, significantly fewer than the 31 (22.6%) unhealed socket wounds found in patients receiving penicillin ($p<0.0001$). Of the patients receiving HBOT, 35 (94.6%) had healing of all socket wounds, compared to 26 (70.3%) who received penicillin.

Table 28 Healing of dental extraction wounds in irradiated soft tissue following treatment with HBOT or penicillin

Outcome	HBOT (N=37) n (%)	Penicillin (N=37) n (%)	*p*-value
Patients with healing of all tooth sockets	35 (94.6)	26 (70.3)	0.012
Healed tooth sockets	152/156 (97.4)	106/137 (77.4)	<0.0001

HBOT: hyperbaric oxygen therapy.
Source: Marx et al (1985).

The comparative study by Marx (1999) examined patients receiving soft tissue flaps introduced surgically into previously irradiated tissue of the head and neck. Three clinical outcomes related to flap healing were reported: wound infection, wound dehiscence and delayed healing. Wound infection and dehiscence were differentiated into major and

minor occurrences (Table 29). Patients receiving HBOT before and after surgery were significantly less likely to develop wound infections, both major (p=0.0028) and overall (p=0.0019), and wound dehiscence, both major (p<0.0001) and overall (p<0.0001), than those who did not. Patients receiving HBOT were also less likely to experience delayed wound healing than those who did not (p<0.0001).

Table 29 Healing of tissue flaps in irradiated soft tissue after receiving surgery with or without HBOT

Outcome	HBOT (N=80) n (%)	No HBOT (N=80) n (%)	*p*-value
Wound infection			
Minor[a]	3 (3.8)	6 (7.5)	0.3033
Major[b]	2 (2.5)	13 (16.3)	0.0028
Total	5 (6.3)	19 (23.8)	0.0019
Wound dehiscence			
Minor[c]	6 (7.5)	12 (15.0)	0.1333
Major[d]	3 (3.8)	26 (32.5)	<0.0001
Total	9 (11.3)	38 (47.5)	<0.0001
Delayed wound healing[e]	9 (11.3)	44 (55.0)	<0.0001

a Minor infection defined as responding to culture-specific antibiotics and wound irrigation.
b Major infection defined as requiring debridement surgery in addition to culture specific antibiotics and wound irrigation.
c Minor dehiscence defined as healing within three weeks with wound care and dressings.
d Major dehiscence defined as unhealed within three weeks and/or requiring secondary surgery/HBOT.
e Delayed wound healing defined as increase in inpatient hospital stay required to treat irradiated tissue wound.
HBOT: hyperbaric oxygen therapy.
Source: Marx (1999).

In the non-randomised comparative study by Neovius et al (1997), 15 patients received HBOT to treat wound complications such as necrosis, abscesses, dehiscence and fistulae that occurred after surgery in irradiated soft tissue of the head and neck; these patients were compared to a historical control group of 15 patients with corresponding injuries who had been treated without use of HBOT. After five months, 12 (80.0%) patients who received HBOT had complete healing of their wound, along with a further two (13.3%) patients with partial wound healing. In the control group, seven (46.7%) patients treated without HBOT had complete healing of their wound after five months, while two (13.3%) patients had massive postoperative haemorrhage, which in one case was fatal. Although the authors concluded that the healing processes seemed to be initiated and accelerated through the use of HBOT, no statistical between-groups comparison was reported by the authors.

Case series

Four case series reported on HBOT treatment of socket wounds after dental extractions from irradiated soft tissue (Ashamalla et al 1996; Chavez and Adkinson 2001; David et al 2001; Kaur et al 2009). All studies reported at least a mean number of teeth extracted per patient; Chavez and Adkinson (2001) reported a maximum of 32 extractions in at least one patient, while Kaur et al (2009) reported a maximum of 17 extractions in two patients. Three studies (Ashamalla et al 1996; Chavez and Adkinson 2001; Kaur et al 2009) used the Marx treatment protocol of 20 HBOT sessions prior to and 10 sessions after the dental extraction procedure, while David et al (2001) reported that patients received from six to 21 HBOT sessions before extraction and from two to 24 sessions after. HBOT was generally administered at 2.4 ATA or slightly higher for 60 or 90 minutes, although Ashamalla et al (1996) used 2 ATA for 120 minutes.

The primary outcome reported across these studies was the number of patients in whom the healing of all extraction sites occurred. Wound healing was generally poorly defined,

relating predominantly to the absence of osteoradionecrosis after treatment. Chavez and Adkinson (2001) were the only authors to explicitly describe mucosal coverage of extraction sites after treatment, and were the only authors to explicitly state time points at which follow-up assessments of patients took place. Across the four studies the minimum reported response for this intervention was reported by Chavez and Adkinson (2001), who found that 12 months after receiving HBOT, 31 of 35 (88.6%) patients had mucosal coverage of all extraction sites and 365 of 371 (98.4%) extraction sites had mucosal coverage at that point. It should be noted that the rates of healing reported across the four case series were all quite comparable to those reported by Marx et al (1985). Results from individual case series can be seen in Table 66.

Regarding radiation injury to other soft tissues of the head and neck region, five studies included patients in whom laryngeal radionecrosis was the primary indication for HBOT (Feldmeier et al 1993; Ferguson et al 1987; Filntisis et al 2000; Hart and Mainous 1976; Narozny et al 2005). All of these case series had very small sample sizes, with Filntisis et al (2000) the largest with 18 patients. With the exception of Hart and Mainous (1976), all studies reported baseline assessments of radiation injury severity, with patients presenting with either Chandler grade III or IV radionecrosis. Administration of HBOT was mixed, with the two most recent studies performing HBOT at 2.4 or 2.5 ATA for 60 to 90 minutes, and the two earlier studies using 2.0 ATA for 120 minutes.

Outcomes reported in these case series included requirement of laryngectomy, decannulation of existing tracheostomies, and overall improvement of symptoms, which generally included hoarseness with dyspnea, odynophagia, dysphagia, respiratory distress and pain. While length of follow-up was quite sufficient where reported, specific time points of clinical assessment were not stated. In three case series, response of radionecrosis to HBOT was sufficiently good in 29 of 35 (82.9%) patients that laryngectomy was not required (Feldmeier et al 1993; Ferguson et al 1987; Filntisis et al 2000). Across three studies that incorporated 32 patients with laryngeal radionecrosis, HBOT was reported to lead to resolution or substantial overall improvement of symptoms in 26 (81.3%) patients (Ferguson et al 1987; Filntisis et al 2000; Narozny et al 2005). In four studies, 22 patients were reported to have tracheostomies in place; after receiving HBOT decannulation was possible in 12 (54.5%) patients (Feldmeier et al 1993; Ferguson et al 1987; Filntisis et al 2000; Narozny et al 2005). Results from individual case series can be seen in Table 66.

Radiation-induced soft tissue oedema

Comparative studies

The RCT by Gothard et al (2010) and non-randomised comparative study by Carl et al (2001) reported on the effectiveness of HBOT for the resolution of soft tissue oedema induced by radiation treatment for breast cancer. Outcomes reported included physiological response measures, scores for radiation-induced morbidity, and quality of life measures.

In the RCT by Gothard et al (2010), 32 patients received HBOT for arm lymphoedema, while 20 control patients received no treatment for arm lymphoedema other than continued best standard care. The authors defined the primary endpoint as an absolute change of ≥ 8 per cent in the relative volume of the ipsilateral arm compared to the contralateral arm. When assessed at 12 months, nine of the 30 (30.0%) patients in the HBOT group met this criteria and were classified as responders, compared to three of 16 (18.8%) patients in the group which did not receive HBOT; this was found to be a non-

significant difference (p=0.50). As shown in Table 30, neither treatment group was found to have a statistically significant reduction in relative ipsilateral/contralateral arm volume after 12 months of follow-up (HBOT group: p=0.50; control group: p=0.64). No statistically significant difference was found between the two treatment groups with regards to change in arm volume over time (p=0.93).

Table 30 Arm volume in radiation-induced soft tissue oedema after receiving treatment with or without HBOT

Outcome	Follow-up	HBOT (n=30) median (IQR)	No HBOT (n=16) median (IQR)	*p*-value
Arm volume (mL)				
Ipsilateral arm	Baseline	3189 (2735–3971)	3350 (2659–4037)	
	12 months	3061 (2673–4066)	3350 (2581–3897)	
	Change (baseline to 12 months)	-41.0 (-166–59.5); p=0.14[a]	-3.5 (-243.5–76.7); p=0.44[a]	0.83
Contralateral arm	Baseline	2434 (1983–2821)	2550 (1921–2878)	
	12 months	2326 (2046–2661)	2435 (2072–2841)	
	Change (baseline to 12 months)	-20.5 (-82.5–65.5); p=0.55[a]	1.0 (-129.2–94.0); p=0.94[a]	0.75
Ipsilateral/contralateral arm volume (%)	Baseline	135.5 (126.5–146.0)	133.5 (126.0–152.3)	
	12 months	133.5 (122.3–144.9)	131.2 (122.7–151.5)	
	Change (baseline to 12 months)	-2.9 (-9.4–5.6); p=0.50[a]	-0.3 (-7.5–5.5); p=0.64[a]	0.93

a Denotes within-group comparison.
HBOT: hyperbaric oxygen therapy; IQR: interquartile range.
Source: Gothard et al (2010).

Although no statistical analyses were reported by Gothard et al (2010), the authors stated that neither treatment group showed a clear improvement in lymphatic clearance rates, and that rates were similar in both groups at baseline and after 12 months (Table 31).

Table 31 Lymphoscintigraphy results in radiation-induced soft tissue oedema after receiving treatment with or without HBOT

Outcome	Follow-up	HBOT (n=28) median (IQR)	No HBOT (n=12) median (IQR)	*p*-value
Lymphatic clearance rate (%/min)				
Ipsilateral forearm	Baseline	-0.040 (-0.056 to -0.014)	-0.013 (-0.035 to 0.006)	
	12 months	-0.050 (-0.069 to -0.020)	-0.023 (-0.073 to 0.005)	
	Change (baseline to 12 months)	-0.015 (-0.035 to 0.007)	-0.009 (-0.074 to 0.023)	NR
Contralateral forearm	Baseline	-0.064 (-0.079 to -0.027)	0.056 (-0.079 to -0.011)	
	12 months	-0.051 (-0.087 to -0.017)	-0.059 (-0.072 to -0.007)	
	Change (baseline to 12 months)	0.006 (-0.023 to 0.040)	0.007 (-0.032 to 0.075)	NR

HBOT: hyperbaric oxygen therapy; IQR: interquartile range; NR: not reported.
Source: Gothard et al (2010).

Gothard et al (2010) also stated that HBOT patients may have experienced greater reductions in extracellular water content in the upper arm compared to patients who did not receive HBOT (Table 32); however, no statistical analyses or comparisons were reported by the authors regarding this measure. The authors concluded that no evidence was found that showed a beneficial effect of HBOT for the treatment of arm lymphoedema following surgery with adjuvant radiotherapy for early breast cancer.

Table 32 Extracellular water content in radiation-induced soft tissue oedema after receiving treatment with or without HBOT

Outcome	Follow-up	HBOT (n=30) median (IQR)	No HBOT (n=13) median (IQR)	*p*-value
Arm fluid volume change – dielectric measurement (%)	Change (baseline to 12 months)			
Ipsilateral arm				
Upper arm (skin)		-2.0 (-4.2–1.7)	-0.7 (-2.5–4)	NR
Upper arm (subcutaneous)		-1.3 (-3.5–1.2)	0.3 (-0.7–2.5)	
Forearm (skin)		1.8 (-3.2–4.3)	0.7 (-3–2.7)	
Forearm (subcutaneous)		0.3 (-3.1–4.7)	-0.3 (-4.2 to 3.2)	
Contralateral arm				
Upper arm (skin)		0 (-1.4–0.7)	0 (-1.2–1.3)	NR
Upper arm (subcutaneous)		-0.3 (-1.4–0)	0 (-0.3 to 1)	
Forearm (skin)		1.3 (-0.7–2.4)	1 (-1–2.2)	
Forearm (subcutaneous)		1.0 (-0.7–2.1)	0.3 (-1.0–0.8)	

HBOT: hyperbaric oxygen therapy; IQR: interquartile range; NR: not reported.
Source: Gothard et al (2010).

Radiation-induced morbidity was reported in the non-randomised comparative study by Carl et al (2001), using a modified version of the LENT-SOMA scale (Pavy et al 1995); results are shown in Table 33. Thirty-two patients received HBOT for symptomatic breast oedema while 12 control patients received observation with no further treatment.

The authors reported statistically significant improvements in pain, oedema, erythema and total morbidity scores immediately post-treatment for patients who received HBOT compared to those who did not. Fibrosis and telangiectasia were not significantly affected by treatment with HBOT, with no significant difference found between the treatment groups on these two measures. Seven of the 32 patients who received HBOT were reported to be completely free of symptoms after treatment, whereas all 12 patients in the control group reported persisting complaints after observation alone.

Table 33 Radiation-induced morbidity in patients with radiation-induced soft tissue oedema after receiving treatment with or without HBOT

Outcome	Follow-up	HBOT (N=32) median (range)	No HBOT (N=12) median (range)	*p*-value
Modified LENT-SOMA scale				
Pain score	Pre-treatment	3 (1–4)	3 (1–3)	NS
	Post-treatment[a]	0 (0–2)	3 (1–4)	<0.001
Oedema score	Pre-treatment	3 (1–3)	2 (0–3)	NS
	Post-treatment	1 (0–2)	2 (0–3)	<0.001
Fibrosis score	Pre-treatment	0 (0–3)	0 (0–3)	NS
	Post-treatment	0 (0–3)	0 (0–3)	NS
Telangiectasia score	Pre-treatment	0 (0–3)	0 (0–2)	NS
	Post-treatment	0 (0–3)	0 (0–2)	NS
Erythema score	Pre-treatment	2 (0–3)	3 (0–3)	NS
	Post-treatment	0 (0–2)	0 (0–2)	<0.001
Total score	Pre-treatment	9 (6–14)	8 (3–12)	NS
	Post-treatment	2 (0–6)	7 (3–12)	<0.001

a Timing of post-treatment follow-up not specified, but implied to occur immediately upon completion of HBOT treatment.
HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; NS: not significant.
Source: Carl et al (2001).

Gothard et al (2010) reported on patient quality of life using two scales: an unpublished quality of life scale specifically for patients with upper limb lymphoedema, and the SF-36. The unpublished quality of life scale consisted of 12 questions designed to assess pain, self-awareness and restrictions to everyday activities (eg work, hobbies, bathing, sleep, shopping and choice of clothing) together in a similar format to the SF-36; results are shown in Table 34. The authors stated that patient ratings from the questionnaire were generally lower across the follow-up period in patients who received HBOT compared with those who did not, indicating fewer problems; however, no statistical analyses were reported to confirm this.

Table 34 Quality of life in patients with radiation-induced soft tissue oedema after receiving treatment with or without HBOT

Outcome	Follow-up	HBOT median (range)	No HBOT median (range)	*p*-value
Lymphoedema-specific quality of life score[a]	Baseline	(n=35) 50.0 (27.1–64.6)	(n=17) 47.9 (18.7–64.6)	NR
	3 months	(n=33) 33.3 (20.8–59.4)	(n=17) 58.3 (20.8–66.7)	
	6 months	(n=32) 32.3 (17.7–53.6)	(n=16) 47.9 (18.7–64.1)	
	9 months	(n=32) 43.7 (19.3–58.3)	(n=16) 33.3 (15.1–64.6)	
	12 months	(n=31) 37.5 (20.8–52.1)	(n=16) 45.8 (13.0–62.5)	

a Scale as yet unpublished; reflects pain, self-awareness, and impact of lymphoedema on everyday activities; scored 0 (best) to 100 (worst).
HBOT: hyperbaric oxygen therapy; NR: not reported.
Source: Gothard et al (2010).

Scores for functioning, general health and other subscales on the SF-36 were stated by Gothard et al (2010) to be very similar between the two treatment groups, though the authors reported no data on this measure.

Case series

The case series by Yu et al (2002) reported on patients with soft tissue oedema, with various degrees of pain and movement limitation, after irradiation for breast cancer. Amongst the four patients presenting with oedema of the breast/chest wall, complete resolution was achieved in all patients after treatment with HBOT. In five patients with axillary oedema, complaints were relieved in four (80.0%) after treatment with HBOT, with one (20.0%) patient continuing to have moderately limited arm lifting ability.

Radiation cystitis

Case series

Ten case series included patients treated with HBOT for radiation cystitis; seven of these studies reported exclusively on patients with radiation cystitis (Bevers et al 1995; Hampson and Corman 2007; Lee et al 1994; Neheman et al 2005; Rijkmans et al 1989; Waring and Oxer 2000; Yoshida et al 2008) three included patients with a variety of radiation injuries which included cystitis (Fink et al 2006; Mayer et al 2001; Safra et al 2008). In only one of these reports was there a baseline assessment of the degree of radiation cystitis with a score or a grade of the histological or symptomatic features (Mayer et al 2001). Administration of HBOT was generally 25 to 30 sessions of 90 to 100 minutes; approximately half of the studies used around 2.0 ATA, while the other half used 2.4 ATA or greater.

The primary outcome reported across these studies was the resolution of macroscopic haematuria, reported in nine case series (Bevers et al 1995; Hampson and Corman 2007; Lee et al 1994; Mayer et al 2001; Neheman et al 2005; Rijkmans et al 1989; Safra et al 2008; Waring and Oxer 2000; Yoshida et al 2008). Five studies also reported recurrence rates of haematuria or bleeding (Bevers et al 1995; Fink et al 2006; Neheman et al 2005; Waring and Oxer 2000; Yoshida et al 2008). Studies reporting on the resolution of haematuria all reported numbers of patients who had resolution or an absence of

symptoms after HBOT, but did not quantify outcomes in patients who had only partial resolution, using vague descriptors such as decreased, occasional, or intermittent haematuria. No system that could be scored and used for statistical analysis was reported. Haematuria recurrence was generally reported in terms of the number of patients who required retreatment with HBOT for recurrent bleeding. Mean length of patient follow-up was generally less than two years, and specific time points of clinical assessment were not stated.

Due primarily to the potential heterogeneity of patient characteristics and cystitis severity, these case series were not amalgamated to produce an overall response rate of haematuria resolution. The minimum reported rate of resolution was reported by Waring and Oxer (2000), who found complete haematuria resolution in six of 25 (24.0%) patients immediately after completion of HBOT treatment, with a 'marked reduction' reported in 11 (44.0%). In the largest case series, Hampson and Corman (2007) reported that haematuria was completely resolved in 38 of 94 (40.4%) patients, with 'marked improvement' of haematuria in a further 40 (42.6%). Recurrent haematuria requiring further HBOT treatment was generally reported in 10 to 25 per cent of patients. In the largest case series reporting on recurrence, Bevers et al (1995) reported severe macroscopic haematuria recurrence in seven of 37 (18.9%) patients who had at least a moderate initial response to HBOT, and that recurrence of severe haematuria occurred in 0.12 patients per year; in patients with a good initial response, recurrence occurred after a mean period of 13.3 months, while in patients with a moderate initial response, recurrence occurred after a mean of 2.3 months. Results from individual case series can be seen in Table 66.

Two case series also reported on radiation-induced morbidity in patients with radiation cystitis. Mayer et al (2001) reported on radiation-induced morbidity in 11 patients, measured using RTOG/EORTC genitourinary late morbidity criteria, reporting a statistically significant improvement in morbidity after treatment with HBOT (Table 35). Radiation-induced toxicity before and after treatment with HBOT in six patients with radiation cystitis and proctitis has been reported previously in Table 26, showing a statistically significant improvement in patients' toxicity after receiving treatment with HBOT (Safra et al 2008).

Table 35 Radiation-induced morbidity in patients receiving HBOT for radiation cystitis: case series

Morbidity	Pre-HBOT (N=11) n (%)	Post-HBOT (N=11) n (%)	*p*-value
RTOG/EORTC genitourinal late morbidity criteria			
Grade 0	0 (0.0)	2 (18.2)	
Grade 1	0 (0.0)	4 (36.4)	
Grade 2	3 (27.3)	2 (18.2)	0.004
Grade 3	6 (54.5)	1 (9.1)	
Grade 4	2 (18.2)	1 (9.1)	
Inadequate HBOT treatment	0 (0.0)	1 (9.1)	

HBOT: hyperbaric oxygen therapy; RTOG/EORTC: Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer.
Source: Mayer et al (2001).

Soft tissue radiation injury to the pelvis, abdomen, chest wall and extremities

Case series

A number of case series reported on radiation-induced ulceration, necrosis, fistulae, or wounds to other regions of the body. In general these studies were of relatively low methodological quality, were heterogeneous in their administration of HBOT, described severity of injury at baseline and length of follow-up inadequately, and had very small patient populations. Results from these individual case series can be seen in Table 66.

Six case series studies reported on the healing of radiation injuries to the abdomen or pelvis (Abratt and Mills 1978; Feldmeier et al 1996; Fink et al 2006; Hart and Mainous 1976; Safra et al 2008; Williams et al 1992). The most comprehensive result came from the study by Feldmeier et al (1996), who reported wound healing in 25 of 39 (64.1%) patients with soft tissue radiation injuries to the abdomen or pelvis who were available for follow-up. In a prospective observational study of 14 patients with pelvic soft tissue radiation injuries, Williams et al (1992) reported successful resolution of necrosis in 13 (92.9%) patients.

Three case series reported on the resolution of soft tissue wounds to the chest wall (Feldmeier et al 1995; Hart and Mainous 1976; Yu et al 2002). The largest patient group was reported in the study by Feldmeier et al (1995), who reported that six of eight (75.0%) patients with soft tissue radiation injury healed without requiring surgical debridement, although four patients of those patients did receive flaps or grafts to aid healing.

Feldmeier et al (2000) reported that 10 of 16 (62.5%) patients with soft tissue radiation injuries to the extremities experienced healing or significant improvement of their wounds after treatment with HBOT.

As well as healing outcomes, the case series by Safra et al (2008) reported on radiation-induced toxicity in seven patients who suffered from longstanding vaginal ulcers, vaginal fistulas or skin injuries to the pelvis, measured using Common Toxicity Criteria. Results are reported in Table 36, showing a statistically significant improvement in patients' degree of radiation-induced toxicity after receiving treatment with HBOT.

Table 36 Radiation-induced toxicity in patients receiving HBOT for radiation injury to soft tissue of the pelvis: case series

Toxicity	Pre-HBOT (N=7) n (%)	Post-HBOT (N=7) n (%)	*p*-value
Common Toxicity Criteria			
Grade 0	0 (0.0)	5 (71.4)	
Grade 1	0 (0.0)	2 (28.6)	
Grade 2	2 (28.6)	0 (0.0)	0.016[a]
Grade 3	1 (14.3)	0 (0.0)	
Grade 4	4 (57.1)	0 (0.0)	

a Calculation based on data reported for patients suffering from radiation injury to soft tissue of the pelvis only.
HBOT: hyperbaric oxygen therapy.
Source: Safra et al (2008).

Other relevant considerations

Clinical expert opinion

Expert opinion received from medical specialist members of the Advisory Panel has highlighted a number of issues related to the clinical utilisation of HBOT within the Australian healthcare context and its relation to the current assessment. These issues are summarised below:

- Clinical expert opinion is that HBOT is not a new technology, but an established therapeutic modality for a range of health conditions. It is approved for 13 indications by the UHMS, while in 1998 the ANZHMG developed a heavily restricted list of conditions for which there is an adequate base of clinical evidence to support routine clinical use. Both of these lists include chronic non-diabetic wounds and soft tissue radiation injuries. The members of the ANZHMG and the Australian and New Zealand College of Anaesthetists do not support the use of HBOT as a routine treatment outside this list of conditions. Prior to MSAC assessment 1018-1020, the use of HBOT for the treatment of these indications had received full funding on the MBS (previously under MBS Items 13012 and 13020).
- HBOT is not advocated as a primary treatment for the treatment of chronic non-diabetic wounds and soft tissue radiation injuries. The place of HBOT is as a secondary intervention introduced after the exhaustion of simpler, often cheaper primary treatment options with little or no improvement in patient outcomes. The applicant requested that HBOT be considered as an intervention for chronic non-diabetic problem wounds only after three months of failed standard care.
- The overall number of HBOT treatments across all MBS Items has not seen a significant increase over the last decade of use. Clinical expert opinion is that this relatively stable base of utilisation for HBOT, since the introduction of MBS Item 13015 is largely a reflection of the self-regulation regarding treatment indications within the field in Australia, and that there is no evidence of an impending increase in utilisation, or financial threat through inappropriate overservicing.
- While outside the scope of the current assessment, clinical expert opinion is that the overall evidence base for other treatment options for both indications of interest is relatively poor, including some treatments which currently receive MBS funding. Clinical expert opinion is that the evidence in support of the use of HBOT is at least as good as that available for alternative treatments and therapies.
- The determination of the relative clinical and economic effectiveness of HBOT is confounded by a number of issues:
  - HBOT is an adjunctive treatment option that is generally added to a regime after the failure of conventional treatment to provide healing, and does not have a clear and direct comparator intervention.
  - There are no definitive 'gold standard' treatments available for the two indications covered in the current assessment when conventional care is

shown to be ineffectual. In many cases, patients have exhausted all available conventional treatment options.

  - Ethical issues related to therapeutic beneficence and the offering of optimal medical care render it difficult to randomise patients to a placebo arm in a methodologically rigorous study, due to potential exposure of patients to risks associated with denial of treatment. This is especially significant due to the limited treatment options available for the indications of interest.
  - The established nature of HBOT as a therapeutic modality means there has been little impetus to conduct further large clinical trials.

- Clinical expert opinion is that the current assessment process may not be appropriate for an existing and widely-used therapeutic intervention such as HBOT. Instead, a patient-centred approach where all options for the treatment of the nominated conditions are examined would be optimal. Clinical expert opinion is that the current assessment should determine the relative merits of the treatment options available, rather than simply examining a single, existing treatment option in isolation. The application included 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, this was deemed to be outside the remit of the current assessment.
- Data on the impact of HBOT on chronic non-diabetic wounds in the Australian healthcare context continues to be collected from the ongoing ANZHMG Wound Care study, a multi-centre prospective cohort study initiated following recommendations arising from MSAC assessment 1054. Resources and funding were insufficient to conduct an RCT, and it was decided that the most feasible approach was to conduct the multi-centre database study currently in progress.

Consumer implications and other considerations

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. Treatment for chronic wounds generally involves conservative measures such as wound dressings and compression therapy, while treatment of soft tissue radiation injuries generally involves management of symptoms. 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. While this has quantifiable economic ramifications, the associated psychological consequences such as loss of self-esteem, continued pain and possible depression are more difficult to quantify.

In many patients, these conditions do not respond to conventional and symptomatic treatment. Chronic wounds can lead to complications such as infection, pain and, if

unsuccessfully treated, limb loss or even death. Soft tissue radiation injury can also be life-threatening and may significantly reduce quality of life; patients with such injuries frequently face serious complications such as intractable pain, nutritional deficiencies, pathologic fractures, oral and cutaneous fistulas, and symptoms such as bleeding, diarrhoea and urinary urgency. 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.

The rationale for treatment is that HBOT enhances delivery of oxygen to injured tissues, which promotes wound and injury healing. It is beneficial as both a stand-alone treatment, or as an adjunct to assist healing in support of surgical treatments. The procedure involves the patient sitting in a hyperbaric chamber breathing pure oxygen after the chamber is pressurised to 2 to 3 ATA. A course of HBOT may entail 20 or more individual treatment sessions which are generally delivered daily, five to seven days per week; each session will generally last from one to two hours. During a course of treatment, best conventional treatment (eg wound management and dressing, symptomatic treatment is generally continued, with HBOT acting as an adjunct. There are some adverse events associated with HBOT related to the high oxygen concentration and pressurisation; however, these are generally infrequent, minor and self-limiting, and resolve after cessation of HBOT treatment. The treatment is usually well tolerated by patients, even those in their 80s.

In summary, HBOT offers a viable, safe and non-invasive treatment to promote healing in patients where conventional treatment therapies have been found to be ineffective. Indeed there may be a good argument to introduce HBOT earlier in the treatment pathway to potentially significantly improve patients' clinical outcomes and quality of life significantly, and avoid the more radical and invasive treatment strategies otherwise used for these conditions.

What are the economic considerations?

Economic evaluation of new healthcare technologies is important when determining whether the new initiative offers additional benefits and at what cost. Economic evaluations are able to determine whether the new initiative is dominated by (or dominates) the existing technology, such that the costs are higher (lower) and the effectiveness is less (greater). Economic evaluation is particularly important where the new initiative offers health benefits at additional costs. Within a constrained healthcare budget, determining the additional cost that would be paid for a given health gain is important when ascertaining whether such incremental costs represent value for money.

The usual process for an economic evaluation is first to determine the incremental effectiveness, which is the additional benefits associated with the new technology relative to current practice. The second step is to determine the incremental costs, which is the difference in costs between the new initiative and current practice. Finally the incremental cost-effectiveness ratio (ICER) can be calculated using the following ratio:

$$ICER = \frac{Cost_{New} - Cost_{Comparator}}{Effectiveness_{New} - Effectiveness_{Comparator}}$$

To allow comparison of effectiveness across interventions and/or across settings, it is preferable for an economic evaluation to take the form of a cost-utility analysis. This analysis generates an ICER as described which can then be compared to a threshold, or range of thresholds, to determine whether the health system should invest in the new technology. The most common generic outcome measure is the quality-adjusted life year (QALY). This is a measure of effectiveness that combines morbidity and mortality dimensions into one composite measure of outcome. The use of cost-utility analysis, while preferable to disease-specific outcome measure, is reliant on the existence of appropriate published data.

Where the new technology demonstrates equal effectiveness to the existing technology (ie it is non-inferior) then a cost-minimisation approach is warranted.

Objective

The objectives of this section were to conduct economic evaluations of the therapeutic use of HBOT in the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries. The treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries are be considered separately.

For chronic non-diabetic wounds the most appropriate comparator is usual care. As there are multiple conditions for non-diabetic wounds the focus of this evaluation is on venous ulcers, the most common chronic non-diabetic wound.

For soft tissue radiation injuries the most appropriate comparator is usual care. Usual care is defined as the patient's usual treatment pathway, should HBOT not be available. As there are multiple conditions for soft tissue radiation injuries the focus of this evaluation is on radiation proctitis, the condition with the highest level of clinical

evidence. This forms the basis of cost-effectiveness analysis for all soft tissue radiation injuries.

Search strategies

As described in the 'approach to assessment', a search strategy was developed to systematically identify studies in which HBOT was used.

Databases of peer-reviewed literature including Medline, PubMed, CINAHL and Cochrane were searched. The bibliographies of all retrieved publications were hand-searched for any relevant references missing in the database search. Web-based searches included the Internet engines 'Google' and 'Google scholar'.

In addition to the search terms described in the 'approach to assessment' section, Cost$ or Econ$ were added. This was to identify any published cost-effectiveness analyses. The inclusion and exclusion criteria remained the same.

Background – evidence of cost-effectiveness

There are a limited number of published cost-effectiveness analyses of HBOT for the management of patients with soft tissue radiation injuries and chronic non-diabetic wounds.

A cost analysis conducted by Gomez-Castillo and Bennett (2005) reported the cost per treatment and cost per patient of a number of different conditions for patients from The Prince of Wales Hospital in 2003–04. The average cost per treatment for soft tissue radiation injuries was $311 per treatment and $7,153 per patient (equivalent to $273,838 per year based on 881 treatment sessions). The average cost per treatment for chronic wounds was $311 per treatment and $3,732 per patient ($188,010 per year based on 605 treatment sessions). There are some limitations to the comparability of this study. The extra healthcare costs of patients with soft tissue radiation injuries or chronic wounds (ie costs of complications) were not considered in this analysis and the patients treated with HBOT included diabetic and non-diabetic patients.

A previous MSAC assessment report assessed the use of HBOT for chronic non-diabetic wounds (MSAC 2001). The ICER of providing HBOT for chronic wounds was $6,941 per one third reduction in wound area. There are a number of limitations to this study. The effectiveness data was based on an RCT by Hammarlund and Sundberg (1994) (N=16) and the reported outcome was a reduction in wound size, which does not easily extrapolate to a clinically meaningful end-point. There was no statistically significant difference in the proportion of ulcers healed in the HBOT group (RR=1.33; 95% CI: 0.89–1.99).

A supportive study by Dempsey et al (1997) reported a Canadian based model that focused on the treatment of osteoradionecrosis, with and without HBOT. Based on a sample of 42 patients Dempsey et al (1997) reported the cost of HBOT to equate to$9,797[1] per patient healed (range $9,352–$10,688 per patient healed) and the cost of conservative treatment to equate to $61,530 per patient (range $60,414–$63,755 per

[1] Based on exchange rate of 1.03 as at July 2011.

patient healed). Although this study focused on a radiation injury of the bone rather than soft tissue, the authors concluded that HBOT was both clinically and cost effective as a treatment for osteoradionecrosis of the mandible compared with conservative therapy.

A number of other cost analyses were identified (Abidia et al 2003; Guo et al 2003; Treweek and James 2006; Ward et al 2000). However, they were excluded from the analysis because either there was no comparator identified or they reported on diabetic ulcers.

Transforming quality of life scores into utility values

As seen in Table 24, there are a number of published quality of life studies of HBOT for soft tissue radiation injuries. Notably, one RCT of patients with radiation proctitis reported the mean LENT-SOMA and Bowel Bother scores of patients (N=120) treated with HBOT and sham HBOT (Clarke et al 2008). The study found that patients' quality of life was improved in the HBOT group at three months (2.61 versus 5.00 p=0.0019; lower values represent higher quality of life) respectively, when compared with patients with usual care.

Sidik et al (2007a) reported significant differences in LENT-SOMA and Karnofsky quality of life measures, finding a 33.64 per cent improvement from baseline LENT-SOMA scores in the HBOT group, compared to 19.69 per cent deterioration from baseline scores in the comparator group (p=0.008) at six months.

Similarly Carl et al (2001), in a prospective comparative study of 47 patients with soft tissue radiation injuries after breast cancer showed that patients' quality of life post-treatment was improved in the HBOT group (2 versus 7, p<0.001; lower values represent higher quality of life) for patients treated with HBOT and usual care, respectively.

While there appears to be evidence of quality of life gains with HBOT, there are limitations to the use of these data in an economic model. The scores are most often reported as a LENT-SOMA scale, which reports on symptomatic presentation of the specific condition. Consequently, it is not possible to transform these scores into the meaningful QALY estimates required to inform a cost-utility analysis.

No studies examining use of HBOT for chronic non-diabetic wounds with suitable quality of life data were found.

Rationale for the cost-effectiveness analysis

There was insufficient comparative evidence to support a full cost-effectiveness analysis of HBOT for the treatment of chronic non-diabetic wounds. Therefore the aim of the economic evaluation was to calculate the annual cost of providing HBOT compared to usual care for the treatment of patients with chronic non-diabetic wounds.

There was sufficient evidence to conduct a cost-effectiveness analysis, but insufficient evidence to conduct a cost-utility analysis, of HBOT for the treatment of soft tissue radiation injuries. A decision analytic model was developed that provides a framework for decision-making under conditions of uncertainty. Therefore the aim of the economic evaluation was to estimate the incremental cost-effectiveness of HBOT compared to usual care. A healthcare perspective is adopted to capture total resource usage.

Chronic non-diabetic wounds

Economic model

As previously mentioned, there were insufficient data to support the superior effectiveness of HBOT over usual care for chronic non-diabetic wounds. A cost analysis was conducted to compare the annual cost of treating chronic non-diabetic wounds (venous ulcers) with HBOT and usual care.

Estimate of effectiveness

Hawkins and Bennett (n.d.) recently reported the results of six years of the AHZHMG Wound Care study. They demonstrated complete or substantial healing in 57.6 per cent (30/52) of patients with venous ulcers one month post-treatment, which increased to 68.3 per cent (28/41) at six months and 85.2 per cent (23/27) at 12 months. The results indicate an incremental improvement of 10.6 per cent at six months and 16.9 per cent at 12 months. The results are confounded somewhat by the losses to follow-up during this time period. For the purposes of the economic evaluation it was assumed that losses to follow up were independent of wound healing.

An additional RCT by Gordon et al (2006) compared community wound care with a wound care clinic in 56 venous ulcer patients in Queensland. This study demonstrated that at six months a total of 13.9 per cent of ulcers (5/36) were healed in both groups.

A comparison of these two studies suggests that HBOT is more effective than wound care clinics for the treatment of chronic wounds. However since there is no common comparator it is not possible to undertake an indirect comparison of the data from Hawkins and Bennett (n.d.) and Gordon et al (2006). As a result the data from Hawkins and Bennett (n.d.) formed the basis of the effectiveness of HBOT and usual care for the economic analysis.

Estimate of costs

The estimated costs were taken from a number of sources, including the MBS, AR-DRG (version 5.1 round 12—Private and Public), manufacturers' costs, the average charged Medicare fee (Commonwealth Department of Health and Ageing 2011a; Commonwealth Department of Health and Ageing 2011c), Gomez-Castillo and Bennett (2005) and Gordon et al (2006). Resource use and MBS Item numbers were determined by the Advisory Panel.

Community wound care costs

The average community wound care per patient costs over one year were based on the following assumptions: a level 4 registered nurse (NSW Health 2010) completing home visits for one hour per visit, two times per week, 52 weeks per year; bandaging and dressing costs as defined by the Advisory Panel, mileage defined as $0.74 per kilometre[2] for 20 km per visit. Consumables were based on estimates from Gordon et al (2006) ($0.35 per session). It was assumed that bandaging and dressings are a consumable cost whilst the patient is undergoing HBOT and an out-of-pocket cost once the patient enters community wound care.

[2] Australian Tax Office mileage rates

Surgical procedures

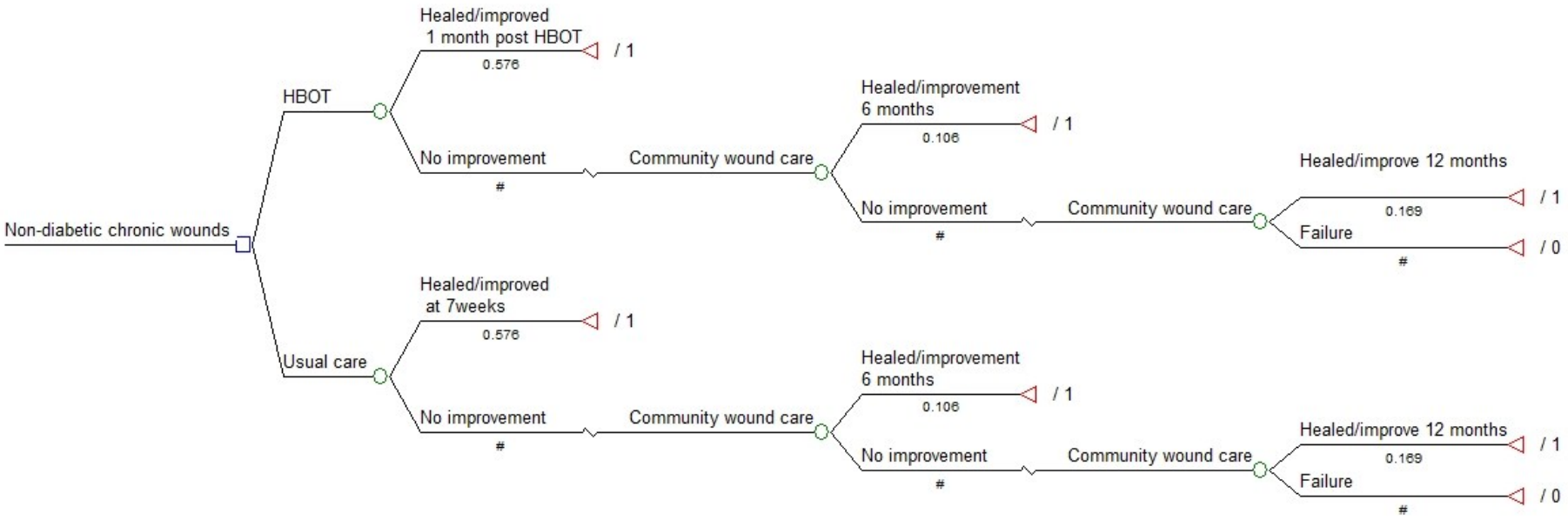
It was assumed that patients receive one skin graft if treatment is successful and two skin grafts if treatment is not successful over the 12 month period, as defined by the Advisory Panel. The average per diem cost for hospitalisation for skin grafts was derived from the AR-DRG information for DRG IJ13A (version 5.1 round 13—Private). This DRG is for Lower limb—Ulcer with cellulitis plus graft with catastrophic severe complications. The estimated hospital stay for a patient would be approximately 10.47 days (version 5.1 round 13—Private). The hospital stay was estimated as the total cost (including pharmacy, pathology, allied health, intensive care, emergency department, supplies and hotel) divided by the average length of stay.

Complications

It was assumed that patients who fail either HBOT or usual care have two emergency visits for sepsis, as defined by Advisory Panel. The average per diem cost for hospitalisation for sepsis was derived from the AR-DRG information for DRG T60B (version 5.1 round 13—Private). This DRG is for Septicaemia without catastrophic severe complications. The estimated hospital stay for a patient would be approximately 6.23 days per episode (version 5.1 round 13—Private). The hospital stay was estimated as the total cost (including pharmacy, pathology, allied health, intensive care, emergency department, supplies and hotel and capital costs) divided by the average length of stay.

Costs were incorporated into the model as average per-person per year costs. Expected values were calculated by adding the costs across treatment pathways and weighting these according to the proportion of patients expected to follow each pathway. The proportion of patients in each arm was determined by the effectiveness of HBOT or usual care. The structure of the model is shown in Figure 9.

Figure 9 Decision tree: chronic non-diabetic wounds



HBOT: hyperbaric oxygen therapy.

Main assumptions in the model

- The model follows a cohort of patients with chronic non-diabetic wounds from the point of HBOT commencement for one year of treatment.
- Eight potential patient pathways are possible:
    1. Patients treated successfully with HBOT at one month post-HBOT: these patients receive 12 sessions of HBOT treatment (0.5 months) + one skin graft + bandaging costs during HBOT treatment and for six weeks of follow-up + ongoing management.
    2. Patients treated successfully with HBOT at six months post-HBOT: these patients receive 12 sessions of HBOT treatment (0.5 months) + one skin graft + bandaging costs during HBOT treatment and for six weeks of follow-up + ongoing management + 18 weeks of community wound care.
    3. Patients treated successfully with HBOT at 12 months post-HBOT: these patients receive 12 sessions of HBOT treatment (0.5 months) + one skin graft + bandaging costs during HBOT treatment and for six weeks of follow-up + ongoing management + 44 weeks of community wound care.
    4. Patients treated successfully with usual care at one month post-HBOT: these patients receive eight weeks of community wound care + one skin graft + ongoing management.
    5. Patients treated successfully with usual care at six months: these patients receive six months of community wound care + one skin graft + ongoing management.
    6. Patients treated successfully with usual care at 12 months: these patients receive 12 months of community wound care + one skin graft + ongoing management.
    7. Patients who fail HBOT: these patients receive 12 sessions of HBOT treatment + bandaging costs during HBOT treatment + two skin grafts + ongoing management + 44 weeks of community wound care + complications.
    8. Patients who fail HBOT: these patients receive ongoing management + two skin grafts + 12 months community wound care + complications.
- HBOT and usual care are assumed to be not significantly different, with effectiveness based on data reported in Hawkins and Bennett (n.d.).
- A healthcare perspective is adopted.

Table 37 Average cost per patient for HBOT and ongoing management: chronic non-diabetic wounds

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Operational					
HBOT (outpatient)	$208.34	12	$2,500.02		
MBS 13015 co-payment (outpatient)	$59.89	12	$718.63		
Bandaging[a]	$79.90	4	$319.60		
Dressing (Biatain)[a]	$12.60	16	$201.60		
Dressing (Aquacel)[a]	$21.90	4	$87.60		
Ongoing management					
MBS 105	$35.15	3	$105.44	3	$105.44
MBS 105 co-payment	$36.00	3	$108.00	3	$108.00
Ultrasound MBS 55223	$72.05	1	$72.05	1	$72.05
MBS 55223 co-payment	$12.71	1	$12.71	1	$12.71
Support stocking	$40.00	3	$120.00	3	$120.00
Total consumables			$728.80		$120.00
Total MBS fees			$2,677.51		$177.49
Total patient out-of-pocket			$839.34		$120.71
Subtotal HBOT plus ongoing management			**$4,245.65**		**$418.21**

a Bandaging: 4-layer bandage, one per fortnight (26 per year); Biatain: one per dressing, two dressings per week; and Aquacel: ¼ dressing, two dressings per week (all advised by the Advisory Panel). Patient out-of-pocket for these items assumed to be 0.
HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 38 Average cost per patient for community wound care (12 months): chronic non-diabetic wounds

	Unit cost	HBOT (once discharged from HBOT treatment) (44 weeks)		Usual care (full year)	
		Units	Total	Units	Total
Community wound care					
GP consult (MBS 23)	$34.30	10.15	$348.28	12	$411.60
MBS 23 co-payment	$24.00	10.15	$243.69	12	$288.00
Consumables (medical gloves etc)[a]	$0.35	88	$30.90	104	$36.52
Bandaging[b]	$79.90	22	$1,757.80	26	$2,077.40
Dressing (Biatain)[b]	$12.60	88	$1,108.80	104	$1,310.40
Dressing (Aquacel)[b]	$21.90	22	$481.80	26	$569.40
RN time[c]	$44.85	88	$3,946.69	104	$4,664.28
Mileage[d]	$0.74	1760	$1,302.40	2080	$1,539.20
Total consumables			$5,279.99		$6,239.99
Total MBS fees			$348.28		$411.60
Total patient out-of-pocket			$3,592.09		$4,245.20
Subtotal community wound care			**$9,220.36**		**$10,896.79**

a Sourced from: Gordon et al (2006).
b Bandaging: 4-layer bandage, one per fortnight (26 per year); Biatain: one per dressing, two dressings per week; Aquacel: ¼ dressing, two dressings per week (all advised by the Advisory Panel).
c Sourced from NSW Health (2010).
d RN travel assumes that patients travel 10km each way to wound clinic, three times per week, 48 weeks per year. The per kilometre mileage was based on estimate from Australian Tax Office (0.74c/km).
HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 39 Average cost per patient with surgical procedures: chronic non-diabetic wounds

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Surgical procedures					
Skin graft (MBS 45442)	$423.20	1	$423.20	1	$423.20
MBS 45442 co-payment	$354.81	1	$354.81	1	$354.81
Debridement of wound (MBS 30023)	$235.30	1	$235.30	1	$235.30
MBS 30023 co-payment	$161.95	1	$161.95	1	$161.95
Surgery consult (MBS 104)	$69.96	1	$69.96	1	$69.96
MBS 104 co-payment	$66.00	1	$66.00	1	$66.00
Specialist visits (MBS 105)	$36.00	2	$72.00	2	$72.00
MBS 105 co-payment	$36.00	2	$72.00	2	$72.00
Surgery assist (MBS 51300)	$62.29	1	$62.29	1	$62.29
MBS 51300 co-payment	$64.00	1	$64.00	1	$64.00
Initiation of anaesthesia (MBS 21270)	$129.55	1	$129.55	1	$129.55
MBS 21270 co-payment	$19.43	1	$19.43	1	$19.43
Anaesthesia (1.5 hours) MBS 23063	$56.10	1	$56.10	1	$56.10
MBS 23063 co-payment	$0.00	1	$0.00	1	$0.00
Pre-anaesthetic consult (10 minute)	$31.05	1	$31.05	1	$31.05
MBS 17610 co-payment	$44.00	1	$44.00	1	$44.00
Hospital stay for skin graft (AR-DRG J13A)	$744.13	10.47	$7,791.00	10.47	$7,791.00
Total consumables			$7,791.00		$7,791.00
Total MBS fees			$1,079.44		$1,079.44
Total patient out-of-pocket			$782.19		$782.19
Subtotal surgical procedures			**$9,652.64**		**$9,652.64**

AR-DRG: Australian Refined Diagnosis Related Groups; HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 40 Average cost per patient with complications: chronic non-diabetic wounds

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Emergency admissions					
Emergency admissions due to sepsis (AR-DRG T60B)	$666.99	12.54	$8,364.00	12.54	$8,364.00
Specialist consult (MBS 104)	$69.96	6	$419.73	6	$419.73
MBS 104 co-payment	$66.00	6	$396.00	6	$396.00
Specialist visits (MBS 105)	$36.00	6	$216.00	6	$216.00
MBS 105 co-payment	$36.00	6	$216.00	6	$216.00
Total consumables			$8,364.00		$8,364.00
Total MBS fees			$635.73		$635.73
Total patient out-of-pocket			$612.00		$612.00
Subtotal complications			**$9,611.73**		**$9,611.73**

AR-DRG: Australian Refined Diagnosis Related Groups; HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 41 provides an estimate of the average costs used in the costing model. All costs represent the total average cost for a patient treated for one year. The costs vary depending upon success or failure with HBOT or usual care. For example, an individual who is successfully treated with HBOT at one month will receive one skin graft plus ongoing monitoring costs plus bandaging for the period of HBOT and six weeks follow-up plus the costs of HBOT ($4,246 + $9,612 = $13,898). In the case of successful usual care treatment, an individual will accrue one skin graft plus ongoing monitoring costs (equivalent to HBOT) and eight weeks of usual care ($418 + ($10,897/52*8) + $9,612 = $11,747). An individual who fails HBOT will incur two skin grafts + ongoing management costs + the costs of HBOT + 44 weeks of usual care + bandaging during HBOT and six weeks follow-up + complications ($4,246 + $9,220 + ($9,653*2) + $9612 = $42,383).

Table 41 Costs of clinical pathways: chronic non-diabetic wounds

Description	Treatment	Cost
HBOT success (1 month)	1 year	$13,898
HBOT success (6 months)	1 year	$17,670
HBOT success (12 months)	1 year	$23,119
Usual care success (1 month)	1 year	$11,747
Usual care success (6 months)	1 year	$15,519
Usual care success (12 months)	1 year	$20,968
HBOT failure	1 year	$42,383
Usual care failure	1 year	$40,232

HBOT: hyperbaric oxygen therapy.

Average costs per year

The total estimated one year cost of HBOT and usual care versus usual care only is $24,365.60 and $22,214.74, respectively. This represents an incremental cost of $2,151 ($2,437 MBS plus $65 out-of-pocket items, minus incremental gain of $351 consumables).

Implication to the Extended Medicare Safety Net

According to the department's Medicare co-payment data 42 per cent of HBOT services are performed in the outpatient setting. The total out-of-pocket costs for these items are $3,510 per patient per year for usual care and $3,576 per patient per year for HBOT. For some patients these costs will contribute towards the EMSN. The HBOT and usual care costs are above the $1,126 threshold ($562.90 for concession card holders). Consequently, out-of-pocket contributions relating to HBOT are likely to impact upon the EMSN.

Other cost considerations

The analysis assumed 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 the analysis did 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 patients' quality of life may be substantial (Carl et al 2001; Clarke et al 2008). Consequently the actual benefit to the patient of providing HBOT is likely to have been underestimated.

Additionally, the model was restricted to patient costs that were 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.

Financial implications

To estimate the cost per annum of providing HBOT instead of usual care, the number of patients with soft tissue radiation injuries was estimated from two different sources. The first method used the number of separations for MBS Item 13015 in the year July 2010 to June 2011. This Item included 8910 individual separations for the treatment of soft tissue radionecrosis or chronic or recurring non-diabetic wounds where hypoxia can be demonstrated. The application estimates that 45 per cent of patients from Item 13015 were treated for chronic non-diabetic wounds. However it is not possible to estimate the total number of patients per year, as each of the indications listed under MBS Item 13015 is treated with a different number of overall sessions.

A second estimate was derived from the Australian hyperbaric treatment statistics (HTNA 2008). According to the application, 1435 patients were treated with a total of 24,731 sessions of HBOT in the year July 2007 to June 2008. Of these, 154 patients (10%) were treated for soft tissue radiation injuries. As this is likely to be nationally representative this estimate formed the basis for the financial implications.

Table 42 Financial implications of chronic non-diabetic wounds per annum

	HBOT	Usual care
Total cost per patient	$24,366	$22,215
Number of patients	154	154
Breakdown of financial implications		
Consumables	$2,509,378	$2,563,463
MBS Items	$692,317	$317,066
Patient out-of-pocket	$550,631	$540,542
Total financial implications	**$3,752,327**	**$3,421,071**
Incremental costs		
Consumables	-$54,085	
MBS Items	$375,251	
Patient out-of-pocket	$10,090	
Total cost	**$331,256**	

HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

As can be seen in Table 42 if direct replacement of usual care occurred for chronic non-diabetic wounds, the overall cost would be $3,752,326. If HBOT was used to treat 154 patients instead of usual care, there would be an incremental cost of $331,256 per annum.

It is important to note that the MBS separations data will only pick up patient treatment that has been billed under the MBS. Any HBOT procedures charged as part of a public hospital budget (public inpatient) will not be captured.
Additionally, there has been an increasing trend of HBOT utilisation since 2007. Table 43 details the total number of separations for MBS Item 13015 since 2007 and shows that there has been a 77 per cent increase over this time period, from5035 to 8910. As a result this may underestimate the overall financial implications.

Table 43 Total MBS separations for Item 13015

Financial year	MBS Item	Total separations
2007-08	13015	5,035
2008-09	13015	4,803
2009-10	13015	6,124
2010-11	13015	8,910

MBS: Medicare Benefits Schedule.

Non-neurological radiation injuries: radiation proctitis

Clinical pathway

Radiation proctitis is a complex condition that can result in multiple problems. According to the literature (Gilinsky et al 1983; Tagkalidis and Tjandra 2001) and in conjunction with Advisory Panel advice, the clinical classification of radiation proctitis falls broadly into three distinct groups:

1. patients who have low-grade bleeding not requiring transfusion and minimal bowel dysfunction and are most commonly treated with enemas (steroid, butyrate and 5-Aminosalicylates);
2. patients who require frequent blood transfusion for rectal bleeding but have minimal bowel dysfunction;
3. patients who in addition to rectal bleeding have significant alteration in bowel habit, particularly fistula, rectal strictures and ulceration. These complications tend to develop after a longer latency than rectal bleeding.

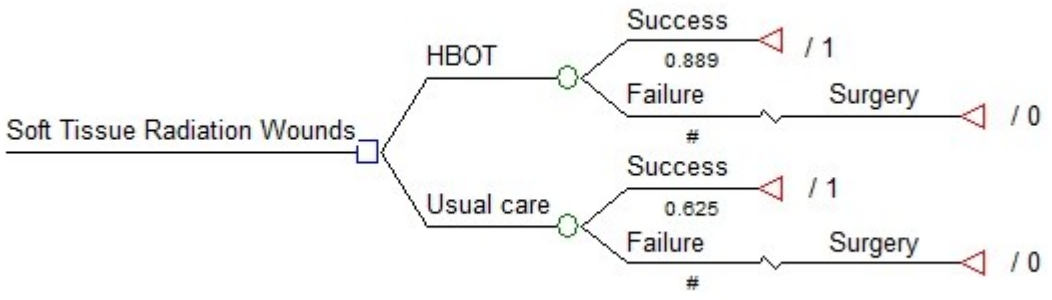
Given that the population of interest in the RCT by Clarke et al (2008) is defined by having a diagnosis present for ≥ 3 months and not responding sufficiently to other therapies, the group two treatment pathway was identified as being the most appropriate for HBOT, and consequently these patients formed the base case for this evaluation.

Economic model

A decision tree was developed for estimating the costs and effectiveness of using HBOT compared to usual care for the treatment of soft tissue radiation injuries.

Costs were incorporated into the model as average per-person per year costs. Expected values were calculated by adding the costs across treatment pathways and weighting these according to the proportion of patients expected to follow each pathway. The proportion of patients in each arm was determined by the effectiveness of HBOT or usual care. The structure of the model is shown in Figure 10.

Figure 10 Decision tree: non-neurological soft tissue radiation injuries (radiation proctitis)



HBOT: hyperbaric oxygen therapy.

Main assumptions in the model

- The model follows a cohort of patients with soft tissue radiation injuries from the point of HBOT commencement, which is usually the point of standard treatment failure, for one year of treatment.
- Four potential patient pathways are possible:
    1. Patients treated successfully with HBOT: these patients receive three months of HBOT treatment + 12 months of ongoing monitoring + four months of medications.
    2. Patients treated successfully with usual care: these patients receive three formalin treatments + six general practitioner (GP) visits + 12 months of ongoing monitoring + four months of medications.
    3. Patients with failed HBOT who subsequently undergo surgery: these patients receive three months of HBOT + three emergency visits + 12 months ongoing management + 12 months medications + colostomy surgery.
    4. Patients with failed usual care who subsequently undergo surgery: these patients receive three usual care visits + three emergency visits + six GP visits + 12 months ongoing management + 12 months medications + colostomy surgery.
- It is assumed that all patients who are not successfully treated with HBOT or usual care undergo surgery. Due to the lack of evidence the effectiveness of surgery is assumed to be 0.
- A healthcare perspective is adopted.

Estimate of effectiveness

The estimate of effectiveness of HBOT that was used in the model was taken from a study by Clarke et al (2008) (discussed previously in the effectiveness section). This RCT compared HBOT to a sham procedure in patients with radiation proctitis. Patients were randomised to either to active treatment (hyperbaric oxygen at 2.0 ATA; n=64) or sham procedure (air at 1.1 ATA; n=56). For the purposes of the economic model, it was assumed that the sham procedure would be equivalent to usual care. The results demonstrated that complete healing or improvement (defined as significant or moderate) occurred in 88.9 per cent of those in the HBOT group, compared to 62.5 per cent of those in the control group, at three months ($p<0.0008$).

There were limitations to this study. Patients underwent HBOT treatment for 90 minutes, once daily, five times per week. This is consistent with Gomez-Castillo and Bennett (2005). However, Clarke et al (2008) provided between 30 and 40 treatment sessions, whereas Gomez-Castillo and Bennett (2005) suggested that the average number of sessions provided in Australia is 23. In addition, the inclusion criteria required ≤ 3 months of 'standard conservative therapy' with persisting symptoms before patients were treated with HBOT. This indicates that the population in the Clarke et al (2008) trial may be healthier than the population for whom this treatment is targeted. For the basis of the

economic model this effectiveness data is assumed to be generalisable to the Australian population.

A further study by Sidik et al (2007b) provides additional supportive evidence of the effectiveness on HBOT when compared to usual care. This study demonstrated that 76.9 per cent (20/26) of patients receiving HBOT were free of radiation proctitis at six months, compared to 45 per cent (9/20) who received symptomatic treatment only (p=0.026). This study has been used as part of a meta-analysis in the sensitivity analysis.

Estimate of costs

The estimated costs of HBOT and usual care were taken from a number of sources, including the MBS, AR-DRG (version 5.1 round 13—Private and Public) (Commonwealth Department of Health and Ageing 2011a), manufacturers' costs and the average charged Medicare fee. Resource use and MBS Item numbers were determined by the Advisory Panel.

Average costs per procedure

MBS Items

The MBS Item fees, which represent the Australian Government contribution to each procedure, were obtained from MBS online (Commonwealth Department of Health and Ageing 2011c). The patient usually receives a reimbursement of 75 per cent of the schedule fee for inpatient services and 85 per cent for outpatient services. Consequently the benefit amount and not the full Medicare schedule fee were used in the model. Using the full fee would double count some of the co-payment contribution.

It was assumed that the MBS Items for HBOT include capital costs, technical and nursing support, irrespective of the level of reimbursement.

Average co-payments

Average co-payments were provided by the department. The co-payment component was calculated as the MBS fee charged minus the MBS benefit paid. The co-payment may not be the exact patient contribution, since it may also include some insurance contribution (up to 25 per cent of the MBS fee). To avoid double counting, the 25 per cent insurance contribution was not included as a separate cost. The co-payments were calculated as averages of all procedures claimed under the Item number. Consequently, there may be a degree of heterogeneity; therefore the accuracy of the co-payment is dependent on the other procedures that are also claimed under the same Item number.

Table 44 MBS Items, numbers, fees and co-payments: non-neurological soft tissue radiation injuries

MBS Item	Item number	MBS fee	MBS schedule[a]	Co-payment
Pre-anaesthesia consultation	20745	$114.30	$85.73	$221.00
HBOT[a]	13015	$245.10	$208.34	$59.89

a Items billed as outpatient procedures, therefore 85% of the scheduled fee is reimbursable.
HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

HBOT treatment

The model assumed that HBOT treatment involves 23 sessions for soft tissue radiation injuries (Gomez-Castillo and Bennett 2005). It was assumed that all patients undergo HBOT in an outpatient setting. Although MBS data shows that only 42 per cent of

patients are outpatients, Advisory Panel input suggested that those who are inpatients are likely to be already admitted. The number of sessions of HBOT has been explored further in the sensitivity analysis.

Usual care

The model assumed that usual care includes formalin treatment. According to Tagkalidis and Tjandra (2001) the endoscopic therapies available for treatment of problematic rectal bleeding are most commonly argon plasma coagulation (APC) and formalin. Clinical expert opinion suggests that these therapies in addition to HBOT remain the current clinical practice. A recent unpublished randomised trial (Botten et al 2011) found no difference in the efficacy of formalin and APC and this finding was supported by the Advisory Panel, who considered that the two treatments are interchangeable (ie patients would trial one and if failure occurs, they would try repeated applications or trial the other). For the purposes of the model it was assumed that patients undergo repeated formalin treatments and that this treatment is no less or more expensive than APC.

MBS data show that formalin treatment is primarily conducted in an inpatient setting. The Advisory Panel estimated that patients would also present in emergency for rectal bleeding if treatment was unsuccessful. As a result the treatment has been defined in two ways: prospective treatment (usual care) (Table 45) and emergency presentations for complications (Table 47). Patients who undergo prospective treatment were assumed to have a shorter hospital stay than those patients who present in emergency (one day versus 1.5 days) and patients are assumed to undergo conscious sedation, rather than anaesthesia, which is captured in the MBS Item 32212. This is consistent with the clinical practice outlined by Tagkalidis and Tjandra (2001). The average per diem cost for hospitalisation due to complications arising from radiation proctitis was derived from the AR-DRG information for Diagnosis Related Group (DRG) H40Z (version 5.1 round 13—Private). This DRG is for Endoscopic procedure—Bleeding. The hospital stay was estimated as the total cost (including pathology, pharmacy, allied health, intensive care, emergency department, supplies and hotel) divided by the average length of stay. The average per diem cost for hospitalisation for prospective radiation proctitis treatment was derived from the AR-DRG information for DRG H40Z (version 5.1 round 13—Private). This DRG is for Endoscopic procedure—Bleeding. The hospital stay was estimated as the total cost (including hotel and pathology) divided by the average length of stay. In addition, it was assumed that usual care patients will continue to visit their GP for ongoing management of proctitis (Table 45).

Blood transfusions

The Advisory Panel indicated that patients with chronic radiation proctitis have been found to undergo numerous blood transfusions and that this is considered to be an indicator for surgical intervention. The average per diem cost for hospitalisation for blood transfusion was derived from the AR-DRG information for DRG F21B (version 5.1 round 13—Private). This DRG is for other circulatory system procedures without catastrophic severe complications. The Advisory Panel indicated that the estimated hospital stay for a patient would be one day. The hospital stay was estimated as the total cost (including pathology, pharmacy, allied health, intensive care, emergency department, supplies and hotel) divided by the average length of stay.

Colostomy

Surgery (colostomy) is considered a viable option for patients who fail usual care or HBOT (Clarke et al 2008; Tagkalidis and Tjandra 2001). However, the effectiveness of

surgery for cessation of bleeding is uncertain. As a result the model assumed no success at the end of one year and no additional costs were assumed.

It is assumed patients undergo pelvic ultrasound, anal manometry and pudendal nerve terminal motor latency testing prior to surgery (MSAC 2008). Clinical expert advice has indicated that patients may have, on average, two to three consultations with the specialist prior to the surgical procedure; for the purposes of this assessment, it was assumed that patients will have one prior consultation and two follow-up consultations.

The average per diem cost for hospitalisation for colostomy (surgery) was derived from the AR-DRG information for DRG H40Z (version 5.1 round 13—Private). This DRG is for Endoscopic procedures—Bleeding. The estimated hospital stay for a patient would be approximately 10.5 days (version 5.1 round 13—Private). The hospital stay was estimated as the total cost (including pathology, pharmacy, allied health, intensive care, emergency department, supplies and hotel) divided by the average length of stay. The unit costs involved in the pre-procedural and post-procedural work-up colostomy are presented in Table 39.

Follow-up and endoscopy

It was assumed that all patients, irrespective of treatment, undergo follow-up and endoscopy. The average per diem cost for hospitalisation for endoscopy was derived from the AR-DRG information for DRG Z50Z (version 5.1 round 13—Private). This DRG is for follow-up and endoscopy. The hospital stay was estimated as the total cost (including pathology, pharmacy, allied health, intensive care, emergency department, supplies and hotel) divided by the average length of stay (one day).

Cost of treatment of radiation proctitis (HBOT versus usual treatment)

The estimated average costs of HBOT compared with usual treatment can be seen in Table 45 through Table 49.

Table 45 Average cost per patient for ongoing management: non-neurological soft tissue radiation injuries

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Operational costs					
HBOT (outpatient)	$208.34	23	$4,791.71		
MBS 13015 co-payment (outpatient)	$59.89	23	$1,377.37		
GP consult (MBS 23)	$34.30			6	$205.80
MBS 23 co-payment	$24.00			6	$144.00
Formalin (MBS 32212)	$98.33			3	$294.98
MBS 32212 co-payment	$68.07			3	$204.21
Hospital stay (AR-DRG H40Z) for prospective formalin	$88.12			3	$264.35
Specialist visits (MBS 105)	$36.00			3	$108.00
MBS 105 co-payment	$36.00			3	$108.00
Ongoing monitoring costs					
GI endoscopy/proctoscopy (MBS 31456)	$177.19	1	$177.19	1	$177.19
MBS 31456 co-payment	$144.00	1	$144.00	1	$144.00
Initiation of anaesthesia (MBS 20745)	$85.73	1	$85.73	1	$85.73
MBS 20745 co-payment	$221.00	1	$221.00	1	$221.00
Anaesthesia (15 minutes) (MBS 23010)	$14.05	1	$14.05	1	$14.05
MBS 23010 co-payment	$0.00	1	$0.00	1	$0.00
Hospital stay (AR-DRG H40Z)	$823.57	1	$823.57	1	$823.57
FBC (pathology) MBS 65070	$14.49	3	$43.48	3	$43.48
MBS 65070 co-payment	$8.00	3	$24.00	3	$24.00
Microbiology swabs MBS 69317	$30.69	1	$30.69	1	$30.69
MBS 69317 co-payment	$4.60	1	$4.60	1	$4.60
Additional specialist visits MBS 105	$35.15	2	$70.30	2	$70.30
MBS 105 co-payment	$36.00	2	$72.00	2	$72.00
Total consumables			$823.57		$1,087.93
Total MBS fees			$5,213.13		$1,030.20
Total patient out-of-pocket			$1,842.97		$921.81
Subtotal HBOT plus ongoing monitoring			**$7,879.67**		**$3,039.94**

NOTE: 42 per cent of HBOT services are conducted in outpatient setting; 58 per cent of HBOT services are conducted in inpatient setting (Commonwealth Department of Health and Ageing Medicare co-payments 2007-2011). The MBS schedule is 75 per cent of the MBS fee for inpatient services and 85 per cent for outpatient services; those MBS Items undertaken in the outpatient setting will contribute to the Extended Medicare Safety Net.

AR-DRG: Australian Refined Diagnosis Related Groups; FBC: full blood count; GI: gastrointestinal; GP: general practitioner; HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 46 Average cost per patient for other medications (12 months): non-neurological soft tissue radiation injuries

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Antispasmodics, antidiarrhoeals, 1 pack per 3 days[a]	$16.95	122	$2,067.90	122	$2,067.90
Iron tablets pack 30, 2 per day[a]	$6.56	24	$157.44	24	$157.44
Pain killers[a]	$15.60	52	$811.20	52	$811.20
Adult incontinence nappies (14 pack)	$30.00	52	$1,560.00	52	$1,560.00
Total consumables			$4,596.54		$4,596.54
Total MBS fees			$0.00		$0.00
Total patient out-of-pocket			$0.00		$0.00
Subtotal 12 months ongoing treatment			**$4,596.54**		**$4,596.54**

a Other medications derived from Advisory Panel input.
HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 47 Average cost per patient requiring emergency admissions: non-neurological soft tissue radiation injuries

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Emergency admissions due to complications for proctitis (Cost per night based on AR-DRG (G11A)[a]	$823.57	1.5	$1,235.36	1.5	$1,235.36
Formalin (MBS 32212)	$98.33	1	$98.33	1	$98.33
MBS 32212 co-payment	$68.07	1	$68.07	1	$68.07
Specialist visits (MBS 105)	$36.00	1	$36.00	1	$36.00
MBS 105 co-payment	$36.00	1	$36.00	1	$36.00
Total consumables			$1,235.36		$1,235.36
Total MBS fees			$134.33		$134.33
Total patient out-of-pocket			$104.07		$104.07
Subtotal formalin			**$1,473.76**		**$1,473.76**

a Hospital stay for transfusion based on (AR-DRG H40Z) and includes ward medical and nursing, pharmacy, operating, intensive care unit, emergency, allied health, supplies and hotel (derived from Advisory Panel input).
AR-DRG: Australian Refined Diagnosis Related Groups; HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 48 Average cost per usual care (12 months): non-neurological soft tissue radiation injuries

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Blood transfusion					
Blood transfusion (MBS 13309)	$205.55	1	$205.55	1	$205.55
MBS 13309 co-payment	$93.45	1	$93.45	1	$93.45
Hospital stay for transfusion (1 day) (AR-DRG G11A)[a]	$841.94	1	$841.94	1	$841.94
Specialist visit (MBS 105)[b]	$35.15	1	$35.15	1	$35.15
MBS 105 co-payment	$36.00	1	$36.00	1	$36.00
Total consumables			$841.94		$841.94
Total MBS fees			$240.70		$240.70
Total patient out-of-pocket			$129.45		$129.45
Subtotal blood transfusion			**$1,212.08**		**$1,212.08**

a Hospital stay for emergency admission based on (AR-DRG F21B)and includes ward medical and nursing, pharmacy, operating, intensive care unit, emergency, allied health, supplies and hotel.
b Number of specialist consults, pathology and investigations based on data from application document
AR-DRG: Australian Refined Diagnosis Related Groups; HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 49 Average cost per patient requiring surgery: non-neurological soft tissue radiation injuries

	Unit cost	HBOT		Usual care	
		Units	Total	Units	Total
Surgery					
Colostomy (MBS 32030)	$376.13	1	$376.13	1	$376.13
MBS 32030 co-payment	$94.03	1	$94.03	1	$94.03
Initiation of anaesthesia (MBS 20745)	$85.73	1	$85.73	1	$85.73
MBS 20745 co-payment	$221.00	1	$221.00	1	$221.00
Anaesthesia (2 hours) (MBS 23083)	$112.20	1	$112.20	1	$112.20
MBS 23083 co-payment	$0.00	1	$0.00	1	$0.00
Pre-anaesthetic consult (10 minutes) (MBS 17610)	$84.15	1	$84.15	1	$84.15
MBS 17610 co-payment	$56.10	1	$56.10	1	$56.10
Pelvic ultrasound (MBS 55044)	$41.75	1	$41.75	1	$41.75
MBS 55044 co-payment	$10.44	1	$10.44	1	$10.44
Anal manometry (MBS 11830)	$134.80	1	$134.80	1	$134.80
MBS 11830 co-payment	$12.71	1	$12.71	1	$12.71
Pudendal nerve terminal motor latency (MBS 11833)	$180.25	1	$180.25	1	$180.25
MBS 11833 co-payment	$20.16	1	$20.16	1	$20.16
Colonoscopy MBS 32090	$241.25	1	$241.25	1	$241.25
MBS 32090 co-payment	$60.31	1	$60.31	1	$60.31
Surgery consult (MBS 104)[a]	$69.96	1	$69.96	1	$69.96
MBS 104 co-payment	$66.00	1	$66.00	1	$66.00
Surgery consult (MBS 105)[a]	$61.73	2	$123.45	2	$123.45
MBS 105 co-payment	$66.00	2	$132.00	2	$132.00
Assist (MBS 51300)[b]	$198.45	1	$198.45	1	$198.45
MBS 51303 co-payment	$197.00	1	$197.00	1	$197.00
Hospital stay (AR-DRG H40Z)[c]	$823.57	10.52	$8,664.00	10.52	$8,664.00
Total consumables			$8,664.00		$8,664.00
Total MBS fees			$1,648.11		$1,648.11
Total patient out-of-pocket			$869.75		$869.75
Subtotal surgery			**$11,181.86**		**$11,181.86**

a Surgery costs derived from MSAC 2008.
b Assist MBS 51300 =$83.05, if surgery < $537.15.
c Hospital stay based on (AR-DRG H40Z) and includes ward medical and nursing, pharmacy, operating, intensive care unit, emergency, allied health, supplies and hotel.
AR-DRG: Australian Refined Diagnosis Related Groups; HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

Table 50 provides an estimate of the average costs used in the cost-effectiveness model. All costs are the total average cost for a patient treated for one year. The costs vary depending upon success or failure with HBOT or usual care. For example, an individual who is successfully treated with HBOT will receive only ongoing monitoring costs (this includes: three full blood counts, one microbiology swab, two additional specialist visits and the hospital costs associated with endoscopy) plus the costs of HBOT and four months of other medications ($7,880 + ($4,597/12*4) = $9,085). In the case of successful usual care treatment, an individual will accrue ongoing monitoring costs (this includes: three full blood counts, one microbiology swab, two additional specialist visits, GP visits and the hospital costs associated with endoscopy) plus four months of other medications ($3,040 + ($4,597/12*4) = $4,572). An individual who fails HBOT and undergoes surgery incurs ongoing management costs plus the costs of HBOT, 12 months of other medications, three emergency visits, two blood transfusions and surgery ($7,880 + $4,597 + ($1,474*3) + ($1,212*2) + $11,182 = $30,504).

Table 50 Costs of clinical pathways: non-neurological soft tissue radiation injuries

Description	Treatment	Cost
HBOT success	1 year	$9,412
HBOT failure with surgery	1 year	$30,504
Usual care success	1 year	$4,572
Usual care failure with surgery	1 year	$25,664

HBOT: hyperbaric oxygen therapy.

Cost-effectiveness results

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

Table 51 Summary of cost-effectiveness analysis for HBOT: non-neurological soft tissue radiation injuries

Procedure	Total cost ($)	Total WH	Incremental cost	Incremental WH	ICER ($/WH)
Usual care	$12,482	0.625	$728		Dominated
HBOT	$11,753	0.889		0.264	

HBOT: hyperbaric oxygen therapy; ICER: incremental cost-effectiveness ratio; WH: wound significantly improved/healed.

HBOT is less expensive than usual care because the additional cost of providing HBOT is more than offset by the costs of surgery for the additional patients who fail usual care.

Sensitivity analysis

Effectiveness of HBOT

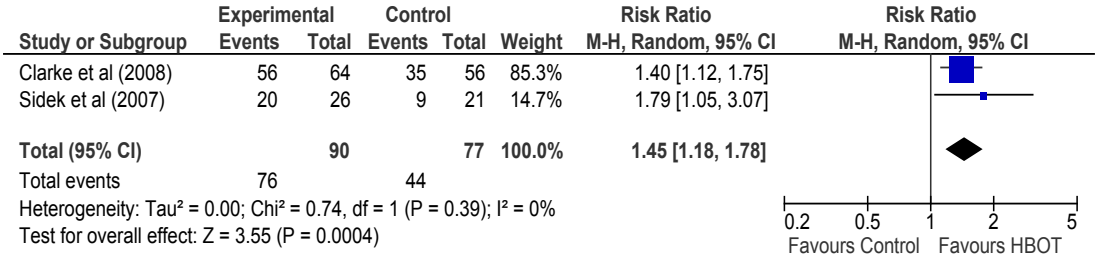
In the base case scenario, it was assumed that the effectiveness of HBOT is 0.889, relative to the effectiveness of usual care (0.625), based on results from Clarke et al (2008). A number of different scenarios were explored in the sensitivity analysis.

Scenario one

A meta-analysis was undertaken to consider the RCT by Clarke et al (2008) in addition to a supporting RCT by Sidik et al (2007b). The meta-analysis is summarised in Figure 11 below. Based on the RR of 1.45 the resulting ICER was dominant.

The impact of effectiveness was tested by applying the confidence intervals to the model. Applying the +/- 95% CI around the RR, the resulting ICER is dominant (highest 95% CI) and $14,599 per wound healed/improved respectively (lowest 95% CI).

Figure 11 Meta-analysis of the effectiveness of HBOT versus usual care: non-neurological soft tissue radiation injuries



CI: confidence interval; HBOT: hyperbaric oxygen therapy; M-H: Mantel-Haenszel.
Source: Clarke et al (2008); Sidik et al (2007b).

Scenario two – definition of success

The base case model defined 'success' as healed, significant improvement or moderate improvement, as defined in Clarke et al (2008). The underlying assumption was that moderate improvement is clinically equivalent to healed and significant improvement. This assumption was relaxed and in this scenario it was assumed that patient with only moderate improvements continue to surgery. Using the effectiveness data based on 'healed' and 'significant' improvement only, the ICER increased to $4,052 per wound healed/significantly improved.

Cost of usual care pathway

In the base case scenario, the usual care costs were based on a number of assumptions determined by the available evidence (clinical expert opinion, case study analysis and the literature). There is considerable uncertainty around the estimates of usual care due to the complexity of the treatment pathway. Three prospective formalin treatments were included in the base model. By assuming +/-20% around the number of prospective formalin session in the sensitivity analysis, the resulting ICER is dominant at the +95% CI and increases the ICER to $14,599/wound healed/improved at the -95% CI.

Cost of complications

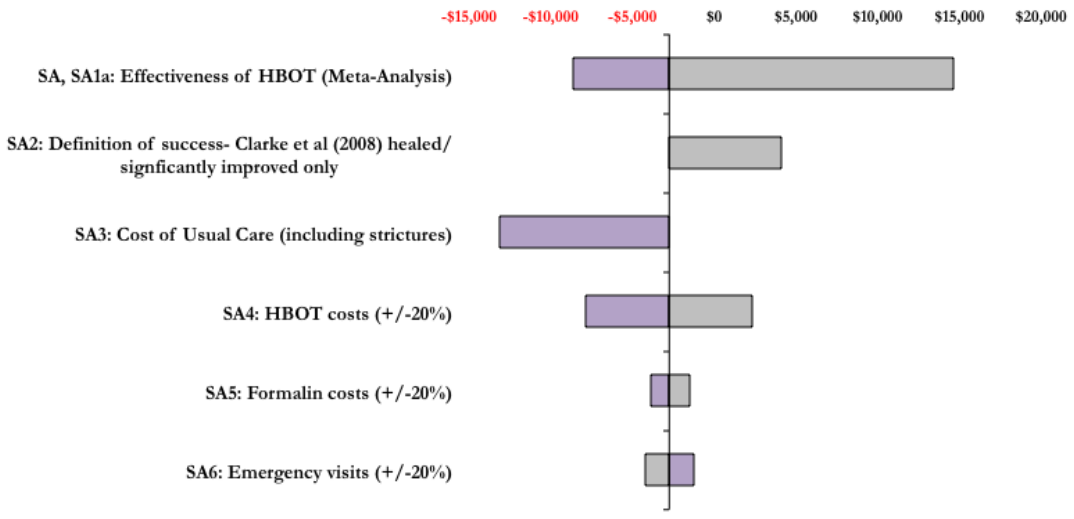
The base case model assumes three emergency presentations for patients who have failed usual care or HBOT. By assuming +/-20% around the number of emergency visits the resulting ICER remains dominant (favours HBOT). Additionally, no costs were assumed in the model for additional complications of radiation proctitis, namely fibrous strictures. If the cost of treating strictures (dilation of stricture) is assumed in the patients who fail usual care and HBOT, this favours HBOT (remains dominant).

The sensitivity analysis was conducted on the following parameters:

- SA1: effectiveness data—meta-analysis +95% CI
- SA1a: effectiveness data—meta-analysis -95% CI
- SA2: definition of success—based on healed and significant improvement only
- SA3: cost of usual care (including strictures)
- SA4: number of sessions of HBOT +/-20%
- SA5: number of sessions of formalin +/-20%
- SA6: number of emergency visits +/-20%.

The results of this analysis are presented as a tornado diagram in Figure 12. The vertical axis on the graph represents the base case ICER of HBOT versus usual care which is -$2,759 (HBOT dominant). The bars to the left of the vertical axis represent a reduction in the ICER and the bars to the right represent an increase in the ICER. The model is most sensitive to fluctuations in the effectiveness of HBOT.

Figure 12 Sensitivity analysis: non-neurological soft tissue radiation injuries



HBOT: hyperbaric oxygen therapy; SA: sensitivity analysis.

Implication to the Extended Medicare Safety Net

According to the MBS separations data 42 per cent of services for HBOT are performed in the outpatient setting. Therefore any out-of-pocket cost associated with these items will contribute towards the EMSN. The total out-of-pocket costs for these items are $2,002 per patient per year for HBOT and $1,462 per patient per year for usual care.

These costs are approximately $900 and $500, respectively, above the $1,126 threshold ($562.90 for concession card holders). Consequently, out-of-pocket contributions relating to HBOT are likely to impact upon the EMSN.

Financial implications

To estimate the cost per annum of providing HBOT instead of usual care the number of patients with soft tissue radiation injuries was estimated from two different sources. The first method used the number of separations for MBS Item 13015 (July 2010 to June 2011). This Item included 8910 individual separations for the treatment of soft tissue radionecrosis or chronic or recurring wounds where hypoxia can be demonstrated. The application estimates that 55 per cent of patients from Item 13015 are treated for soft tissue radiation injuries. However it is not possible to estimate the total numbers of patients per year as each of the indications listed under Item 13015 is treated with a different number of overall sessions.

A second estimate was derived from the Australian hyperbaric treatment statistics (HTNA 2008). According to the application, it is reported that 1435 patients were treated with a total of 24,731 sessions of HBOT in the year July 2007 to June 2008. Of these 189 patients (13%) were treated for soft tissue radiation injuries. As this is likely to be nationally representative, this estimate formed the basis for the financial implications.

As can be seen in Table 52, if direct replacement of usual care occurred for soft tissue radiation injuries, the overall cost would be $2,221,321. If HBOT was used to treat 189 patients instead of usual care, there would be a cost savings of $137,679 per annum.

Table 52 Financial implications of non-neurological soft tissue radiation injuries per annum

	HBOT	Usual care
Total cost per patient	$11,753	$12,482
Number of patients	189	189
Breakdown of financial implications		
Consumables	$804,362	$1,708,461
MBS Items	$1,038,410	$374,197
Patient out-of-pocket	$378,549	$276,343
Total financial implications	**$2,221,321**	**$2,359,001**
Incremental costs		
Consumables	-$904,099	
MBS Items	$664,214	
Patient out-of-pocket	$102,206	
Total cost	**-$137,679**	

HBOT: hyperbaric oxygen therapy; MBS: Medicare Benefits Schedule.

It is important to note that the MBS separations data will only pick up patient treatment that has been billed under the MBS. Any HBOT procedures charged as part of a public hospital budget (public inpatient) will not be captured.

Additionally, there has been an increasing trend of HBOT utilisation since 2007. Table 43 details the total number of separations for MBS Item 13015 since 2007 and shows that there has been a 77 per cent increase over this time period, from 5035 to 8910. As a result this may underestimate the overall financial implications.

Other cost considerations

The analysis assumed that HBOT is superior to usual care in terms of clinical effectiveness. However, the analysis did 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 patients' quality of life may be substantial (Carl et al 2001; Clarke et al 2008; Sidik et al 2007a). Consequently the actual benefit to the patient of providing HBOT may be underestimated.

Additionally, the model was 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 had healed wounds in the HBOT group at 12 months compared to usual care. For this reason the model is likely to have underestimated overall costs in the usual care group.

Discussion

Limitations of the evidence

Primary evidence for the use of HBOT for the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries included higher level study designs such as RCTs and non-randomised comparative studies. Well-conducted secondary studies (systematic reviews and HTAs) that generally identified the same body of primary source studies that was retrieved by the current assessment were used to provide summary supporting data on the effectiveness of HBOT. The majority of studies retrieved were case series which were used to supplement and support available comparative study evidence. The limitations of the evidence base retrieved are discussed below.

While HBOT is widely regarded to be a 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. Adverse events associated with the majority of conservative and symptomatic therapies for chronic wounds and soft tissue radiation injuries (eg wound dressings and irrigation, stool softeners and bladder lavage) are expected to be relatively minor or negligible.

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 generally of limited value in determining the effectiveness of an intervention due to their proneness to bias.

With respect to non-neurological soft tissue radiation injuries, the conclusions regarding the effectiveness of HBOT are not limited by quantity but rather the quality of the included studies. Six of the seven retrieved comparative studies related to soft tissue radiation injuries; however, the majority of these studies were of mediocre to poor methodological quality, an issue acknowledged in the previous MSAC assessment (MSAC 2004) and a number of included secondary studies. This requires that results from particular studies be interpreted with caution, as it is known that effect sizes in RCTs are overestimated if particular methodological parameters such as description of the randomisation process, allocation concealment procedures or blinding are not met (Schulz et al 1995). It should be acknowledged that 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 not conducted consistently or reported at a high standard. Furthermore, the validity of reported patient outcomes in almost all case series and a small number of comparative studies was difficult to ascertain due to a lack of blinded assessment or objective assessment with validated outcome assessment tools, failure to report explicit outcome measurement criteria, and a possible reporting bias towards significant positive outcomes.

An overall evaluation of the body of evidence for HBOT as an adjunct to conventional treatment for the management of chronic non-diabetic wounds is presented in Table 53.

An evaluation of the body of evidence for HBOT as an adjunct to conventional treatment for the management of non-neurological soft tissue radiation injuries is presented in Table 54.

Table 53 Body of evidence assessment matrix for HBOT: chronic non-diabetic wounds

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base[a]			Level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	
Consistency			Some inconsistency reflecting genuine uncertainty around clinical question	
Clinical impact			Moderate	
Generalisability		Population/s studied in the body of evidence are similar to the target population		
Applicability		Applicable to Australian healthcare context with few caveats		

a Level of evidence determined from the NHMRC evidence hierarchy (Table 12).
HBOT: hyperbaric oxygen therapy

Table 54 Body of evidence assessment matrix for HBOT: non-neurological soft tissue radiation injuries

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base[a]		Level II studies with low risk of bias or a systematic review/several level III studies with low risk of bias		
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact		Substantial		
Generalisability		Population/s studied in the body of evidence are similar to the target population		
Applicability		Applicable to Australian healthcare context with few caveats		

a Level of evidence determined from the NHMRC evidence hierarchy (Table 12).
HBOT: hyperbaric oxygen therapy.

Is it safe?

As was found in the previous MSAC assessments (MSAC 2001; 2004), adverse events related to treatment with HBOT were barotraumas, visual changes, claustrophobia and oxygen toxicity. The most common adverse events associated with HBOT were barotraumas and visual changes, particularly myopia, which were reported in five to 10 per cent of all patients in studies included for evaluation of safety. Claustrophobia and anxiety in the treatment chamber was reported in just over one 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 one per cent of patients in all studies included for evaluation of safety. It should be noted that the requirement for patients to undergo multiple treatment sessions in a course of HBOT, often 20 or more, increases the potential for adverse event occurrence. The rate of adverse events reported within the included primary evidence was generally in accordance with data on adverse events related to HBOT within the Australian healthcare context reported by the HTNA (HTNA 2008; HTNA and ANZHMG 2002).

Ear barotrauma and vision changes associated with HBOT are both are considered to be relatively minor, transient events, with myopia usually reversing between three to four weeks after treatment. As discussed in the previous MSAC assessments of HBOT (MSAC 2001; 2004), progressive myopia is associated with prolonged, daily exposure to HBOT and is more common at higher pressures. However, in Australian clinical practice it is uncommon for the number of treatment sessions to exceed 60, with the length of these sessions generally lasting 90 minutes at 2.4 ATA (MSAC 2004). Psychological discomfort or anxiety due to confinement (ie claustrophobia) is recognised to be a possible complication of HBOT. Treatment in large multiplace hyperbaric chambers may reduce the incidence of patients who experience this discomfort, while mild sedatives can also assist in the continuation of therapy. Oxygen toxicity is a potentially more serious adverse event that can manifest as pulmonary changes, albeit rarely, or more commonly as neurologic changes such as seizures or convulsions. However, these seizures do not produce residual effects, and rarely lead to discontinuation of treatment.

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.

Is it effective?

Chronic non-diabetic wounds

No new comparative studies examining HBOT for chronic non-diabetic wounds have been published since MSAC assessment 1054. The one comparative study identified that met the inclusion criteria, a small RCT, was included and discussed in MSAC assessment 1054 and 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.

Three published and two unpublished case series on chronic non-diabetic wounds met the inclusion criteria; all demonstrated beneficial outcomes from the use of HBOT in wound healing or pain relief. Three of these reports were derived from the ongoing ANZHMG Wound Care study, a multi-centre Australian prospective cohort study initiated following recommendations arising from MSAC assessment 1054. Although uncontrolled, this study represents a sizeable body of collective clinical data from Australian hyperbaric facilities measuring the response to HBOT of chronic problem wounds that have failed three months of standard treatment.

In summary, while low-level evidence was found within the Australian healthcare context indicating a healing benefit 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.

Non-neurological soft tissue radiation injuries

Two RCTs examined the use of HBOT for the treatment of radiation proctitis; both RCTs were published subsequent to MSAC assessment 1054, and one was a placebo-controlled trial. Both showed a significantly higher probability of proctitis healing outcomes, improvement in radiation-induced morbidity (measured via LENT-SOMA score) and quality of life in patients receiving HBOT as an adjunct to conventional treatment compared to conventional treatment without HBOT, up to six months post-intervention. Data from these controlled studies were supported by nine case series which, despite heterogeneity in outcome reporting, generally showed marked healing and symptom response in over half of patients treated, in accordance with the results of the two RCTs. The pathology of radiation injury suggests that tissues similar to those affected by radiation proctitis (ie colon and rectum), such as the bladder, may respond similarly to HBOT. While no comparative studies were identified in the assessment regarding radiation injury to the bladder (radiation cystitis), the use of HBOT in ten case series examining this indication showed rates of haematuria resolution similar to those for healing of radiation proctitis.

Regarding radiation injuries to the head and neck region, one RCT evaluated the effect of HBOT in promoting mucosal healing of socket wounds after dental extraction from irradiated soft tissue; this study reported significantly better healing outcomes in HBOT patients six months after treatment compared to a group receiving antibiotic therapy. Four case series demonstrated similarly high rates of wound healing in patients receiving HBOT after dental extraction from irradiated soft tissue. One RCT with potential methodological quality issues showed that 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, compared to patients treated without HBOT. The authors of a non-randomised comparative study examining post-surgery wound complications in irradiated soft tissue of the head and neck stated that treatment with HBOT seemed 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. Data from five small case series showed some beneficial effect of HBOT for the treatment of laryngeal radionecrosis.

With respect to other soft tissue radiation injuries, two comparative studies were identified that investigated the effect of HBOT on soft tissue oedema following

irradiation for breast cancer. One of these was an RCT published subsequent to MSAC assessment 1054 that did not demonstrate any statistically significant improvement in arm lymphoedema or quality of life at 12 month follow-up in patients who received HBOT as an adjunct to conventional treatment, compared to those who received conventional treatment without HBOT. The second study, a 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. While no comparative studies were identified in the review for soft tissue radiation injuries to tissues of the pelvis, abdomen, chest wall and extremities, limited case series evidence reported some beneficial healing effect of HBOT for the treatment of these injuries.

In summary, 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 beneficial effect on wound and mucosal healing across a range of tissue types. Good quality evidence demonstrated a benefit in healing and quality of life in patients receiving HBOT as an adjunct to conventional treatment for radiation proctitis. Additional evidence, qualified to some degree by methodological issues, demonstrated a benefit for HBOT as an adjunct to conventional treatment in patients requiring surgery to irradiated soft tissue of the head and neck, including mucosal healing of dental extraction wounds to prevent development of osteoradionecrosis. Case series evidence identified was relatively extensive and generally supported comparative study evidence in reporting patient outcome improvements following treatment with HBOT. From these results, HBOT as an adjunct to conventional treatment appears to provide significantly greater clinical benefit to patients, compared to conventional treatment without HBOT, for the treatment of non-neurological soft tissue radiation injuries. However, it should be noted that available studies do not support the use of HBOT for radiation-induced soft tissue lymphoedema of the arm after treatment for breast cancer.

What are the economic considerations?

The objectives of this section were to conduct economic evaluations of the therapeutic use of HBOT in the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries. Following advice from the Advisory Panel, it was decided that the treatment of chronic non-diabetic wounds and non-neurological soft tissue radiation injuries would be considered separately.

Chronic non-diabetic wounds

There was insufficient comparative evidence to undertake a full cost-effectiveness analysis of HBOT for the treatment of chronic non-diabetic wounds. A cost analysis was conducted to compare the annual cost of treating chronic non-diabetic wounds (venous ulcers) with HBOT and usual care.

The average treatment cost per patient is $24,366 and $22,215 for HBOT and usual care, respectively. Based on an estimated 154 cases of chronic non-diabetic wounds per annum, the overall cost of providing HBOT to these patients would be approximately $3.7 million per year. This represents an incremental cost of $331,256 relative to usual care, or $2,151 per patient. The majority of this cost is related to MBS Items. The analysis assumed that HBOT and usual care are identical in terms of effectiveness. This is likely to underestimate the costs of usual care. Additionally, comparison of these treatments did not take into account any reduction in quality of life that may occur and as

a result the benefit to the patient of proving HBOT may be underestimated. Individual patient characteristics may also impact on the suitability of each treatment option.

Non-neurological soft tissue radiation injuries: radiation proctitis

There was sufficient comparative evidence to undertake a cost-effectiveness analysis of HBOT for the treatment of soft tissue radiation injuries. A decision analytic model was developed to compare the treatment of radiation proctitis (a soft tissue radiation injury) with HBOT or usual care (ie without HBOT). The model considered the demonstrated clinical superior effectiveness of HBOT treatment to provide an estimate of the cost per wound healed.

For radiation proctitis, an estimated additional 26.4 per cent of patients would be treated successfully if HBOT was provided. There is an estimated cost savings of $2,759 per patient treated, therefore HBOT is dominant (ie HBOT is less expensive and is more effective). HBOT is less expensive than usual care 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.

The main driver of the cost-effectiveness result is the effectiveness of HBOT relative to usual care and the costs associated with usual care and HBOT. In the sensitivity analysis, if the RR was reduced to 1.18 (lower 95% CI), the resulting ICER is $14,599 per wound healed/improved. The other driver of the cost-effectiveness results is the definition of treatment success. Using the effectiveness data based on 'healed' and 'significant' improvement only, the ICER is increased to $4,052 per wound healed/significantly improved.

The average treatment cost per patient is $11,753 and $12,482 for HBOT and usual care, respectively. Based on an estimated 189 cases of radiation proctitis per annum, the overall cost of providing HBOT to these patients would be approximately $2.2 million per year. This represents a cost savings of $137,679 relative to usual care. The majority of this cost savings is related to surgery avoided.

The analysis assumed that HBOT is superior to usual care in terms of clinical effectiveness. However, the analysis did 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 patients' quality of life may be substantial (Carl et al 2001; Clarke et al 2008). Consequently the actual benefit to the patient of providing HBOT may be underestimated.

Conclusions

Safety

As was reported in previous MSAC assessments of HBOT (MSAC 2001; 2004), 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 were 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.

Effectiveness

While low-level evidence was found within the Australian healthcare context indicating a healing benefit 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.

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 beneficial effect on wound and mucosal healing across a range of tissue types. Good quality evidence demonstrated a benefit in healing and quality of life in patients receiving HBOT as an adjunct to conventional treatment for radiation proctitis. Additional evidence, qualified to some degree by methodological issues, demonstrated a benefit for HBOT as an adjunct to conventional treatment in patients requiring surgery to irradiated soft tissue of the head and neck, including mucosal healing of dental extraction wounds to prevent development of osteoradionecrosis. Case series evidence identified was relatively extensive and generally supported comparative study evidence in reporting improvements in patient outcome following treatment with HBOT. From these results, HBOT as an adjunct to conventional treatment appears to provide significantly greater clinical benefit to patients, compared to conventional treatment without HBOT, for the treatment of non-neurological soft tissue radiation injuries. However, it should be noted that available studies generally do not support the use of HBOT for radiation-induced soft tissue lymphoedema of the arm after treatment for breast cancer.

Economic considerations

Chronic non-diabetic wounds

There was insufficient comparative evidence to undertake a full cost-effectiveness analysis of HBOT for the treatment of chronic non-diabetic wounds; hence a cost analysis was conducted to compare the annual cost of treating chronic non-diabetic wounds (venous ulcers) with HBOT and usual care.

The average treatment cost per patient is $24,366 and $22,215 for HBOT and usual care, respectively. Based on an estimated 154 cases of chronic non-diabetic wounds per annum, the overall cost of providing HBOT to these patients would be approximately

$3.7 million per year. This represents an incremental cost of $331,256 relative to usual care, or $2,151 per patient. The majority of this cost is related to MBS Items. The analysis assumed that HBOT and usual care are identical in terms of effectiveness, which is likely to underestimate the costs of usual care. Additionally, comparison of these treatments did not take into account any reduction in quality of life that may occur and as a result the benefit to the patient of proving HBOT may be underestimated. Individual patient characteristics may impact on the suitability of each treatment option.

Non-neurological soft tissue radiation injuries: radiation proctitis

There was sufficient comparative evidence to undertake a cost-effectiveness analysis of HBOT for the treatment of soft tissue radiation injuries. A decision analytic model was developed to compare the treatment of radiation proctitis (a soft tissue radiation injury) with HBOT or usual care (ie without HBOT). The model considered the demonstrated clinical superior effectiveness of HBOT treatment to provide an estimate of the cost per wound healed.

For radiation proctitis, an estimated additional 26.4 per cent of patients would be treated successfully if HBOT was provided. There is an estimated cost savings of $2,759 per patient treated, therefore HBOT is dominant (ie HBOT is less expensive and is more effective). HBOT is less expensive than usual care 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

The main driver of the cost-effectiveness result is the effectiveness of HBOT relative to usual care and the costs associated with usual care and HBOT. In the sensitivity analysis, if the RR was reduced to 1.18 (lower 95% CI), the resulting ICER is $14,599 per wound healed/improved. The other driver of the cost-effectiveness results is the definition of treatment success. Using the effectiveness data based on 'healed' and 'significant' improvement only, the ICER is increased to $4,052 per wound healed/significantly improved.

The average treatment cost per patient is $11,753 and $12,482 for HBOT and usual care, respectively. Based on an estimated 189 cases of radiation proctitis per annum, the overall cost of providing HBOT to these patients would be approximately $2.2 million per year. This represents a cost savings of $137,679 relative to usual care. The majority of this cost savings is related to surgery avoided.

The analysis assumed that HBOT is superior to usual care in terms of clinical effectiveness. However, the analysis did 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 patients' quality of life may be substantial and consequently the actual benefit to the patient of providing HBOT may be underestimated (Carl et al 2001; Clarke et al 2008).

Appendix A MSAC terms of reference and membership

The Medical Services Advisory Committee (MSAC) is an independent scientific committee comprising individuals with expertise in clinical medicine, health economics and consumer matters. It advises the Minister for Health and Ageing on whether a new medical service should be publicly funded based on an assessment of its comparative safety, effectiveness, cost-effectiveness and total cost, using the best available evidence. In providing this advice, MSAC may also take other relevant factors into account. This process ensures that Australians have access to medical services that have been shown to be safe and clinically effective, as well as representing value for money for the Australian healthcare system.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services including those 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.

The membership of MSAC at the 54th meeting held November 2011 comprised a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member *(Executive listed first followed by members in alphabetical order)*	**Expertise or affiliation**
Professor Robyn Ward (Chair)	Medical oncology
Dr Frederick Khafagi (Deputy Chair)	Nuclear medicine
Professor Jim Butler (Chair, Evaluation Sub-committee)	Health economics
Associate Professor John Atherton	Cardiology
Professor Chris Baggoley	Commonwealth Chief Medical Officer
Associate Professor Michael Bilous	Anatomical pathology
Associate Professor Kirsty Douglas	General practice/research
Professor Kwun Fong	Thoracic medicine
Professor Paul Glasziou	Evidence-based health care
Mr Scott Jansson	Pathology
Professor David Little	Orthopaedics
Mr Russell McGowan	Consumer health representative
Professor David Roder	Health medicine/epidemiology
Associate Professor Bev Rowbotham	Haematology
Dr Graeme Suthers	Genetics/pathology
Professor Ken Thomson	Cardiovascular/interventional radiology
Dr Christine Tippett	Obstetrics/gynaecology
Dr Simon Towler	AHMAC representative
Associate Professor David Winlaw	Paediatric cardiothoracic surgery
Dr Caroline Wright	Colorectal cancer/surgery

Appendix B Advisory Panel and evaluators

Advisory Panel – MSAC application 1054.1

Member	Nomination/expertise or affiliation
Professor John Horvath (Chair until 22 March 2011)	MSAC Member (until 31 December 2010) Renal medicine/health workforce
Dr Christine Tippett (Deputy Chair until 30 March 2011, Chair from 30 March 2011)	MSAC Member Obstetrics/gynaecology
Associate Professor David Smart*	Hyperbaric medicine
Associate Professor Michael Bennett*	Hyperbaric medicine
Dr Lizbeth Kenny	Radiation oncology
Associate Professor Michael Leung	Plastic and reconstructive surgery
Mr Malcolm Wells	Consumer Health Forum nominee

*** Associate Professors David Smart and Michael Bennett of the 1054.1 Advisory Panel did not agree that their views were reflected in the final MSAC Assessment Report: Review of Interim Funded Service: Hyperbaric Oxygen Therapy (HBOT) for the Treatment of Chronic Non-Diabetic Wounds and Non-Neurological Soft Tissue Radiation Injuries.**

The statement of their dissent is that the analysis of clinical outcomes and cost for Hyperbaric Oxygen treatment on non-diabetic problem wounds was flawed, in that an incorrect clinical pathway was used and the results of a prospective multicentre national study of Hyperbaric Oxygen treatment of non-diabetic wounds, was dismissed by MSAC.

Evaluation Sub-committee input – MSAC application 1054.1

Member	Nomination/expertise or affiliation
Professor Justin Beilby	Member of MSAC Evaluation Sub-committee General practice

Evaluators – MSAC application 1054.1

Name	Organisation
Mr Ben Hoggan	ASERNIP-S
Dr Alun Cameron	ASERNIP-S
Ms Paula Cronin	CHERE
Dr Stephen Goodall	CHERE

Appendix C Search strategies

Databases and websites searched

Table 55 Bibliographic databases searched

Database	Period covered
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database, and the NHS Economic Evaluation Database	Inception–12/2010
PubMed (incorporating Medline)	Inception–12/2010
CINAHL	Inception–12/2010
EMBASE	Inception–12/2010
The University of York Centre for Reviews and Dissemination – including NHS Economic Evaluation Database (NHS EED)/Database of Abstracts of Reviews of Effect (DARE)/Heath Technology Assessment (HTA) Database	Inception–12/2010

Table 56 Electronic internet databases searched

Database	Internet location
National Health and Medical Research Council (NHMRC) (Australia)	http://www.nhmrc.gov.au
Australian Department of Health and Ageing	http://www.health.gov.au/
Scirus – for Scientific Information Only	http://www.scirus.com
TRIP database	http://www.tripdatabase.com
National Health Service (NHS) Evidence	http://www.evidence.nhs.uk/
Current Controlled Trials metaRegister	http://controlled-trials.com/
Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/
ClinicalTrials.gov	http://clinicaltrials.gov/
World Health Organization International Clinical Trials Registry Platform	http://apps.who.int/trialsearch/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/pages/grey_literature_report

Table 57 Health technology assessment Internet sites

Argentina
Institute for Clinical Effectiveness and Health Policy (IECS) http://www.iecs.org.ar/iecs-visor-publicaciones-ing.php
Australia
Adelaide Health Technology Assessment (AHTA) http://www.health.adelaide.edu.au/ahta
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/asernip-s.htm
Centre for Clinical Effectiveness, Monash University http://www.mihsr.monash.org/cce/
Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au
Medical Services Advisory Committee (MSAC) http://www.msac.gov.au
Austria
Institute of Technology Assessment (ITA) http://www.oeaw.ac.at/ita/e1-3.htm
Brazil
Departamento de Ciência e Tecnologia (DECIT) http://portal.saude.gov.br/portal/saude/area.cfm?id_area=1088
Canada
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?home
Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications/

Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
Institute of Health Economics (IHE) http://www.ihe.ca/
Ministry of Health and Long-Term Care – Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html
Denmark
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) http://www.dacehta.dk
Finland
Finnish Office for Health Technology Assessment (FinOHTA) http://finohta.stakes.fi/EN/index.htm
France
Committee for Evaluation and Diffusion of Innovative Techniques (CEDIT) http://cedit.aphp.fr/english/index_present.html
French National Authority for Health (HAS) http://www.has-sante.fr
Germany
German Agency for Health Technology Assessment (DAHTA) http://www.dimdi.de/dynamic/en/hta/db/index.htm
Hungary
Unit of Health Economics and Technology Research Assessment (HunHTA) http://hecon.uni-corvinus.hu/corvinus.php?lng=en
The Netherlands
Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php?phpLang=en
Netherlands Organisation for Health Research and Development (ZonMw) http://www.zonmw.nl/en/home.html
New Zealand
New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/
Norway
Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/index.php?show=84&expand=14,38,84
Spain
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud Carlos III/Health Technology Assessment Agency (AETS) http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
Andalusian Agency for Health Technology Assessment (AETSA) http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp?V=EN
Sweden
Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp
Center for Medical Health Technology Assessment http://www.cmt.liu.se/english/publications
Switzerland
Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/
United Kingdom
National Health Service Health Technology Assessment (UK)/National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.ncchta.org/
University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/index.htm
United States
Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/
US Blue Cross/Blue Shield Association Technology Evaluation Centre (TEC) http://www.bcbs.com/betterknowledge/tec/
Veterans' Affairs Technology Assessment Program (VATAP) http://www.va.gov/vatap/publications.htm

Search strategy (MEDLINE)

#1 Wounds and Injuries [MeSH]

#2 Ulcer [MeSH]

#3 Skin Ulcer [MeSH]

#4 Radiotherapy [MeSH]

#5 (#1 OR #2 OR #3 OR #4)

#6 wound* (textword)

#7 ulcer* (textword)

#8 (#6 OR #7)

#9 leg (textword)

#10 foot (textword)

#11 skin (textword)

#12 varicose (textword)

#13 venous (textword)

#14 chronic (textword)

#15 stasis (textword)

#16 arterial (textword)

#17 decubitus (textword)

#18 pressure (textword)

#19 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

#20 (#8 AND #19)

#21 bedsore (textword)

#22 (#20 OR #21)

#23 radiation* (textword)

#24 radiotherap* (textword)

#25 (#23 OR #24)

#26 damage* (textword)

#27 injur* (textword)

#28 wound* (textword)

#29 destruction (textword)

#30 necrosis (textword)

#31 oedema (textword)

#32 edema (textword)

#33 proctitis (textword)

#34 enteritis (textword)

#35 cystitis (textword)

#36 (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)

#37 (#25 AND #36)

#38 radionecrosis (textword)

#39 (#37 OR #38)

#40 (#5 OR #22 OR #39)

#41 Hyperbaric Oxygenation [MeSH]

#42 hyperbar* (textword)

#43 "high pressure" (textword)

#44 (#42 OR #43)

#45 oxygen* (textword)

#46 (#44 AND #45)

#47 HBO* (textword)

#48 "multiplace chamber" (textword)

#49 "monoplace chamber" (textword)

#50 (#41 OR #46 OR #47 OR #48 OR #49)

#51 (#40 AND #50)

Appendix D Included studies

Health technology assessments and systematic reviews

Bennett, M. H., Feldmeier, J., et al, 2005. 'Hyperbaric oxygen therapy for late radiation tissue injury', *Cochrane Database of Systematic Reviews,* Issue 3, Art. No.: CD005005.

Denton, A., Forbes, A., et al, 2002. 'Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis', *Cochrane Database of Systematic Reviews,* Issue 1, Art. No.: CD003455.

Denton, A. S., Clarke, N., et al, 2002. 'Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis', *Cochrane Database of Systematic Reviews,* Issue 3, Art. No.: CD001773.

Goldman, R. J. 2009. 'Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review', *PM&R,* 1 (5), 471-489.

Kranke, P., Bennett, M., et al, 2004. 'Hyperbaric oxygen therapy for chronic wounds.' *Cochrane Database of Systematic Reviews,* Issue 2, Art. No.: CD004123.

Ritchie, K., Baxter, S., et al, 2008. NHS Quality Improvement Scotland (NHS QIS). *The clinical and cost effectiveness of hyperbaric oxygen therapy*. Glasgow, Scotland.

Chronic non-diabetic wounds

Level II studies

Hammarlund, C. and Sundberg, T. 1994. 'Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study', *Plastic and Reconstructive Surgery,* 93 (4), 829–833.

Level IV studies

Efrati, S., Bergan, J., et al, 2007. 'Hyperbaric oxygen therapy for nonhealing vasculitic ulcers', *Clinical and Experimental Dermatology,* 32 (1), 12–17.

Hawkins, G. C., Bennett, M. H., et al, 2006. 'The outcome of chronic wounds following hyperbaric oxygen therapy: a prospective cohort study - the first year interim report,' *Diving and Hyperbaric Medicine,* 36 (2), 94–98.

Oubre, C. M., Roy, A., et al, 2007. 'Retrospective study of factors affecting non-healing of wounds during hyperbaric oxygen therapy', *Journal of Wound Care,* 16 (6), 245–250.

Unpublished case series

Hawkins, G. C. and Bennett, M. n.d.. 'The outcome of chronic wounds following hyperbaric oxygen therapy: a prospective cohort study – the sixth year report.'

Sidhom, M. B., Bennett, M. H., et al, n.d.. 'Ulcer pain in a cohort of chronic ulcer patients referred for hyperbaric oxygen therapy.'

Non-neurological radiation injuries

Level II studies

Clarke, R. E., Tenorio, L. M., et al, 2008. 'Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up', *International Journal of Radiation Oncology, Biology and Physics,* 72 (1), 134–143.

Gothard, L., Haviland, J., et al, 2010. 'Randomised phase II trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema after radiotherapy for cancer', *Radiotherapy and Oncology,* 97 (1), 101–107.

Marx, R. E. 1999. 'Radiation injury to tissue', In: E. P. Kindwall and H. T. Whelan (eds)., *Hyperbaric Medicine Practice*, Flagstaff, Best Publishing Company, 682-687.

Marx, R. E., Johnson, R. P., et al, 1985. 'Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin', *Journal of the American Dental Association,* 111 (1), 49–54.

Sidik, S., Hardjodisastro, D., et al, 2007a. 'Does hyperbaric oxygen administration decrease side effect and improve quality of life after pelvic radiation?', *Acta Medica Indonesiana,* 39 (4), 169–173.

Sidik, S., Hardjodisastro, D., et al, 2007b. 'Oxygen hyperbaric therapy in patients with radiation proctitis', *The Indonesian Journal of Gastroenterology, Hepatology and Digestive Endoscopy,* 8 (1), 1–4.

Level III-2 studies

Carl, U. M., Feldmeier, J. J., et al, 2001. 'Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery', *International Journal of Radiation Oncology, Biology and Physics,* 49 (4), 1029–1031.

Level III-3 studies

Neovius, E. B., Lind, M. G., et al, 1997. 'Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck: a review of the literature and a report of 15 consecutive patients', *Head & Neck,* 19 (4), 315–322.

Level IV studies

Abratt, R. P. and Mills, E. E. 1978. 'The use of hyperbaric oxygen as an adjunct in the treatment of radionecrosis', *South African Medical Journal,* 54 (17), 697–699.

Ashamalla, H. L., Thom, S. R., et al, 1996. 'Hyperbaric oxygen therapy for the treatment of radiation-induced sequelae in children. The University of Pennsylvania experience', *Cancer,* 77 (11), 2407–2412.

Bevers, R. F., Bakker, D. J., et al, 1995. 'Hyperbaric oxygen treatment for haemorrhagic radiation cystitis', *Lancet,* 346 (8978), 803–805.

Chavez, J. A. and Adkinson, C. D. 2001. 'Adjunctive hyperbaric oxygen in irradiated patients requiring dental extractions: outcomes and complications', *Journal of Oral and Maxillofacial Surgery,* 59 (5), 518–522.

Dall'Era, M. A., Hampson, N. B., et al, 2006. 'Hyperbaric oxygen therapy for radiation induced proctopathy in men treated for prostate cancer', *Journal of Urology,* 176 (1), 87–90.

David, L. A., Sandor, G. K., et al, 2001. 'Hyperbaric oxygen therapy and mandibular osteoradionecrosis: a retrospective study and analysis of treatment outcomes', *Journal of the Canadian Dental Association,* 67 (7), 384.

Feldmeier, J. J., Heimbach, R. D., et al, 1993. 'Hyperbaric oxygen as an adjunctive treatment for severe laryngeal necrosis: a report of nine consecutive cases', *Undersea & Hyperbaric Medicine,* 20 (4), 329–335.

Feldmeier, J. J., Heimbach, R. D., et al, 1995. 'Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: a retrospective review of twenty-three cases', *Undersea & Hyperbaric Medicine,* 22 (4), 383–393.

Feldmeier, J. J., Heimbach, R. D., et al, 1996. 'Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis.' *Undersea & Hyperbaric Medicine,* 23 (4), 205–213.

Feldmeier, J. J., Heimbach, R. D., et al, 2000. 'Hyperbaric oxygen in the treatment of delayed radiation injuries of the extremities', *Undersea & Hyperbaric Medicine,* 27 (1), 15–19.

Ferguson, B. J., Hudson, W. R., et al, 1987. 'Hyperbaric oxygen therapy for laryngeal radionecrosis', *Annals of Otology, Rhinology and Laryngology,* 96 (1 Pt 1), 1–6.

Filntisis, G. A., Moon, R. E., et al, 2000. 'Laryngeal radionecrosis and hyperbaric oxygen therapy: report of 18 cases and review of the literature', *Annals of Otology, Rhinology and Laryngology,* 109 (6), 554–562.

Fink, D., Chetty, N., et al, 2006. 'Hyperbaric oxygen therapy for delayed radiation injuries in gynecological cancers', *International Journal of Gynecological Cancer,* 16 (2), 638–642.

Girnius, S., Cersonsky, N., et al, 2006. 'Treatment of refractory radiation-induced hemorrhagic proctitis with hyperbaric oxygen therapy', *American Journal of Clinical Oncology,* 29 (6), 588–592.

Hampson, N. B. and Corman, J. M. 2007. 'Rate of delivery of hyperbaric oxygen treatments does not affect response in soft tissue radionecrosis', *Undersea & Hyperbaric Medicine,* 34 (5), 329–334.

Hart, G. B. and Mainous, E. G. 1976. 'The treatment of radiation necrosis with hyperbaric oxygen (OHP)', *Cancer,* 37 (6), 2580–2585.

Jones, K., Evans, A. W., et al, 2006. 'Treatment of radiation proctitis with hyperbaric oxygen', *Radiotherapy and Oncology,* 78 (1), 91–94.

Kaur, J., Hay, K. D., et al, 2009. 'Retrospective audit of the use of the Marx Protocol for prophylactic hyperbaric oxygen therapy in managing patients requiring dental extractions following radiotherapy to the head and neck', *New Zealand Dental Journal,* 105 (2), 47–50.

Lee, H. C., Liu, C. S., et al, 1994. 'Hyperbaric oxygen therapy in hemorrhagic radiation cystitis: a report of 20 cases', *Undersea & Hyperbaric Medicine,* 21 (3), 321–327.

Marshall, G. T., Thirlby, R. C., et al, 2007. 'Treatment of gastrointestinal radiation injury with hyperbaric oxygen', *Undersea & Hyperbaric Medicine,* 34 (1), 35–42.

Mayer, R., Klemen, H., et al, 2001. 'Hyperbaric oxygen--an effective tool to treat radiation morbidity in prostate cancer', *Radiotherapy and Oncology,* 61 (2), 151–156.

Narozny, W., Sicko, Z., et al, 2005. 'Hyperbaric oxygen therapy in the treatment of complications of irradiation in head and neck area', *Undersea & Hyperbaric Medicine,* 32 (2), 103–110.

Neheman, A., Nativ, O., et al, 2005. 'Hyperbaric oxygen therapy for radiation-induced haemorrhagic cystitis', *British Journal of Urology International,* 96 (1), 107–109.

Rijkmans, B. G., Bakker, D. J., et al, 1989. 'Successful treatment of radiation cystitis with hyperbaric oxygen', *European Urology,* 16 (5), 354–356.

Safra, T., Gutman, G., et al, 2008. 'Improved quality of life with hyperbaric oxygen therapy in patients with persistent pelvic radiation-induced toxicity', *Clinical Oncology (Royal College of Radiologists),* 20 (4), 284–287.

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Study could not be obtained

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Appendix F Current clinical trials for hyperbaric oxygen therapy

Completed

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Yarnold, J.R. (study contact), Royal Marsden NHS Foundation Trust, Sutton, United Kingdom. 'Randomized double-blind controlled phase III trial of hyperbaric oxygen therapy in patients suffering long-term adverse effects of radiotherapy for pelvic cancer.' Reported completion August 2011. See controlled-trials.com for more information, identifier ISRCTN86894066.

Ongoing

Clarke, R. (study contact), Baromedical Research Foundation, Columbia, USA. 'Hyperbaric oxygen radiation tissue injury study – I (soft tissue radionecrosis).' Expected completion July 2012. See controlled-trials.com for more information, identifier ISRCTN02327449.

Clarke, R. (study contact), Baromedical Research Foundation, Columbia, USA. 'Hyperbaric oxygen radiation tissue injury study – III (radiation cystitis).' Expected completion July 2012. See controlled-trials.com for more information, identifier ISRCTN19501634.

Clarke, R. (study contact), Baromedical Research Foundation, Columbia, USA. 'Hyperbaric oxygen radiation tissue injury study – VII (laryngeal radionecrosis).' Expected completion July 2012. See controlled-trials.com for more information, identifier ISRCTN01022468.

Kuhnt, T. (study contact), Martin-Luther-Universität, Halle-Wittenberg, Germany. 'Randomized phase II trial of hyperbaric oxygen for the treatment of radiation-induced xerostomia.' Expected completion October 2009. See clinicaltrials.gov for more information, identifier NCT00682747.

Shaw, R. (study contact), University of Liverpool, Liverpool, United Kingdom. 'A randomised controlled trial of hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible.' Expected completion May 2014. See controlled-trials.com for more information, identifier ISRCTN39634732.

Not yet recruiting

Thistlethwaite, K. (study contact), Wesley Centre for Hyperbaric Medicine, Brisbane, Australia. 'The effectiveness of hyperbaric oxygen therapy (HBOT) for healing chronic venous leg ulcers: A randomised, double blind, placebo-controlled trial.' Anticipated date of participant enrolment June 2011. See anzctr.org.au for more information, identifier ACTRN12611000505909.

Appendix G Critical appraisal of randomised controlled trials

Table 58 Critical appraisal summary of randomised controlled trials – study design details: non-neurological soft tissue radiation injuries

Study	Sample size	Participants	Randomisation	Blinding	Interventions and outcomes
Radiation proctitis					
Clarke (2008) Columbia, USA Note: More information on this study can be found in Table 62, Table 64 and Table 66.	Total: 150 HBOT: 76 Comparator: 74 Enrolment dates not reported. No sample size or power calculations reported.	Inclusion criteria: Development of rectal late radiation tissue injury after undergoing pelvic radiation therapy; diagnosis to have been present for at least 3 months and to not have responded sufficiently to other therapies (eg antibiotics, anti-inflammatory agents, antispasmodic agents, anticholinergic agents, antidiarrheal agents, intestinal bypass, intestinal resection, fistula repair, colostomy, ileostomy, fulguration). Exclusion criteria: Patient refusal to participate (eg socio-economic reasons, unknown reasons); concomitant medical conditions (eg cerebrovascular incident, obstructive jaundice, tumour activity/recurrence, continuous bleeding, extremely ill health); receiving definitive surgery; 'other reasons' (unspecified). Treatment groups were well matched at baseline for gender as well as clinical characteristics such as interval between radiotherapy and symptoms, tumour location, cancer treatments received, symptomatic treatments received, blood transfusion requirements, hypertension, diabetes and tobacco use. Baseline scores for radiation-induced morbidity were not statistically different between treatment groups. Baseline scores for the Bowel Function subscale of the EPIC quality of life questionnaire appeared comparable between treatment groups. However, patients in the HBOT treatment group appeared to have considerably poorer baseline scores on the Bowel Bother quality of life subscale; this was not discussed by the authors. The authors stated that 'Baseline comparisons of the covariates for the two groups resulted in no significant differences.' These were: gender; tobacco use; external beam radiotherapy/brachytherapy; interval between radiotherapy and symptoms; interval between symptoms and treatment; and country of residence.	Randomisation sequence generated by external biostatisticians and concealed within the study database software. Patients were randomly assigned (1:1) to HBOT or placebo using a blocking process. The block size was four, equally stratified with two of each treatment option. Randomisation sequence became available to the unblinded local principal investigator only on irretrievable entry of each patient's demographic information, medical history and clinical characteristics.	A double-blind design was used. Patients in both treatment groups experienced compression of the hyperbaric chamber to blind them to treatment; in the placebo group, the chamber was slowly decompressed after a brief initial compression. Patients were unblinded after treatment and assessment, with 72 (33 HBOT, 39 placebo) surveyed to determine their opinion on which allocation they had received; no relationship was found between patient opinion and treatment received (p=0.9058). Patients' referring physicians acted as assessors, and were blinded to treatment allocation.	HBOT intervention described; number of sessions not reported. Comparator intervention (placebo) described; number of sessions not reported. Outcome measures were: late radiation-induced morbidity (measured using LENT-SOMA criteria); quality of life (measured using Bowel Function and Bowel Bother subscales of EPIC, and physical and mental components of the SF-12); and proctitis healing (criteria for healing not defined). All outcomes were measured by patient's referring physician shortly after completion of treatment.

Study	Sample size	Participants	Randomisation	Blinding	Interventions and outcomes
Sidik (2007a & 2007b) Jakarta, INDONESIA	Total: 65 HBOT: 32 Comparator: 33 Enrolment dates: July 2004 – January 2006 No sample size or power calculations reported.	Inclusion criteria: Patients aged 55 years or younger diagnosed with radiation proctitis after receiving pelvic radiation therapy for cervical cancer (stage I-IIIB). Exclusion criteria: Pneumothorax; metabolic diseases; diabetes mellitus, malnutrition; other chronic diseases; depression; refusal to partake in study. Patients were excluded from analysis if they were unwilling or unable to complete an adequate course of 20 HBOT sessions. Treatment groups were well matched at baseline for age, weight, height, total radiation dose received and haemoglobin level, with the authors finding no statistically significant differences. Baseline scores for radiation-induced morbidity and quality of life appeared comparable between treatment groups.	Initially, a total of 75 patients randomised to HBOT (n=35) or control (n=40) groups through 'block randomisation' process (no further details reported) after providing written consent. No details of concealment reported.	The authors acknowledged that one limitation of the study was that patients were not blinded to treatment received, which may introduce subjective bias. No other details on blinding were reported.	HBOT intervention poorly described; length, number or frequency of sessions not reported. Comparative intervention poorly described; reported only as 'symptomatic treatment as well as vitamin B and C as necessary.' Outcome measures were: late radiation-induced morbidity (measured using LENT-SOMA criteria); quality of life (measured using Karnofsky score); and proctitis healing (criteria for healing not defined). Radiation-induced morbidity and quality of life measures were assessed 1–2 and 6 months post-treatment, with proctitis healing assessed 6 months post-treatment.
Wounds in irradiated soft tissue of the head and neck region					
Marx (1985) Miami, USA	Total: 74 (291 wounds) HBOT: 37 (156 wounds) Comparator: 37 (135 wounds) Enrolment dates not reported. No sample size or power calculations reported.	Inclusion criteria: Indication for removal of one or more teeth in a segment of the mandible that had received a documented absorbed radiation dose of 6,000 rads of irradiation or greater. Exclusion criteria: Received irradiation less than 6 months or more than 15 years before treatment; received chemotherapy (including any steroid drugs) less than 6 months before treatment; evidence of persistent tumour or new primary malignant disease; known contraindications to treatment; concomitant systemic disease expected to affect wound healing. Treatment groups could not be compared for equivalence at baseline, as no patient characteristics were reported.	No details of randomisation reported. No details of concealment reported.	The authors stated that the study was not a double-blind design. No other details on blinding were reported.	HBOT intervention well described. Comparator intervention (treatment with penicillin) well described. Outcome measure was healing of dental extraction socket wounds (defined as absence of exposed bone in the socket), assessed 6 months post-treatment.

Study	Sample size	Participants	Randomisation	Blinding	Interventions and outcomes
Soft tissue oedema following irradiation for breast cancer					
Gothard (2010) Sutton, UK	Total: 58 HBOT: 38 Comparator: 20 Enrolment dates not reported. Calculation of power and required sample size described. Sample size of 63 (42 treatment: 21 control) provided 90% power to detect 8% absolute difference between groups in reduction of volume in the affected arm.	Inclusion criteria: Ipsilateral arm lymphoedema (15% or greater increase in arm volume) following supraclavicular (with or without axillary) radiation treatment for cancer; freedom from cancer recurrence; physical and psychological fitness for HBOT. Exclusion criteria: Patients randomised to HBOT group were withdrawn from the study in the event of cancer recurrence. HBOT group was twice the size of control group due to method of randomisation. Treatment groups were well matched for age, timing of treatment and previous cancer treatments received, although more HBOT patients had received lymphatic radiotherapy of the supraclavicular fossa alone than control patients (52.6% versus 25.0%). Patient quality of life and physiological measures of arm volume and lymphatic clearance rate also comparable at baseline. The authors reported that 'baseline characteristics for the two randomised groups were very similar', except for a higher rate of sampling rather than clearance amongst HBOT patients who had received axillary surgery as part of their cancer treatment.	Participants were randomised with a ratio of 2:1 (HBOT:control) after confirmation of eligibility and consent procedure by a telephone call to the randomisation service of The Institute of Cancer Research Clinical Trials & Statistics Unit. No details of concealment reported.	No details of blinding reported.	HBOT intervention well described. Comparator intervention poorly described; reported only as 'best standard care for lymphoedema', with provision or adjustment of hosiery if appropriate. Outcome measures were: arm volume (measured via perometer); lymphatic clearance rate (measured through lymphoscintigraphy); arm fluid volume change (measured through via dielectric constant meter); and patient quality of life (measured using unpublished upper limb lymphoedema quality of life scale, and the SF-36). Outcome measurement methodology was described in detail.
Soft tissue flaps introduced into irradiated tissue					
Marx (1999) Miami, USA	Total: 160 HBOT: 80 Comparator: 80 Enrolment dates not reported. No sample size or power calculations reported.	Inclusion criteria not reported. Exclusion criteria not reported. Treatment groups could not be compared for equivalence at baseline, as no patient characteristics were reported.	No details of randomisation reported. No details of concealment reported.	No details of blinding reported.	HBOT intervention described as adjunct treatment to major soft tissue surgery or introduction of soft tissue flap. Comparator intervention described as major soft tissue surgery or introduction of soft tissue flap. Outcome measures were: wound infection (minor: responding to culture-specific antibiotics and local wound irrigations; major: requiring debridement surgery in addition to culture-specific antibiotics and wound irrigations); wound dehiscence (minor: healing within 3 weeks with wound care and dressings; major: unhealed within 3 weeks and/or requiring secondary surgery or HBOT); and delayed wound healing (increase in in-patient hospital stay specifically to treat wound).

EPIC: Expanded Prostate cancer Index Composite questionnaire; HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; SF-12: Short Form 12 General Health Function Survey; SF-36: UK Short Form 36 Health Survey; UK: United Kingdom; USA: United States of America.

Table 59 Critical appraisal summary of randomised controlled trials – results details: non-neurological soft tissue radiation injuries

Study	Numbers analysed	Statistical methods	Outcomes and estimation	Ancillary analyses	Adverse events	Follow-up
Radiation proctitis						
Clarke (2008) Note: More information on this study can be found in Table 62, Table 64 and Table 66.	Some intention-to-treat analysis reported. The authors compared healing results if: all patients for whom they had no results had shown improvement; all patients for whom they had no results had not shown improvement; and for both groups, half of those for whom they had no results had shown improvement and half had not. Analysis conducted primarily for patients who did not meet exclusion criteria (eg recurrence of cancer), completed the therapy protocol (30 treatment sessions), and were available at follow-up.	Outcomes were compared using Fisher's exact test and logistic regression analysis containing covariate variables. A Jonckheere-Terpstra test for trend was also used. Exact *p*-values were reported. Level of significance was not defined.	Healing of proctitis: Tabular data reported displaying frequency of healing outcomes; *p*-values and 95% CI reported for between-groups differences. LENT-SOMA: Mean scores displayed via chart (no range or SD provided). Mean changes in score reported in text (no range or SD provided); *p*-values and 95% CI reported for between-groups differences in mean changes in score. EPIC: Mean scores displayed via chart (no range or SD provided). Mean changes in score reported in text (no range or SD provided). *P*-values reported for within-group changes in score on Bowel Bother subscale; no statistical comparison reported for within-group changes in score on Bowel Function subscale, or for between-groups differences in score. SF-12: No results reported.	No subgroup analyses performed.	Adverse events: discussion of individual incidents only, with no comparison of treatment groups.	Evaluation took place after patient received 30 treatment sessions (10 additional treatment sessions were provided to selected patients, depending on individual responses); patients in placebo group were crossed over to receive HBOT at that time. Losses to follow-up: HBOT: 11 of 75 randomised patients did not complete treatment protocol, and had no results reported (1 definitive surgery; 2 lost before start of study; 1 socioeconomic reasons; 1 cerebrovascular incident; 1 obstructive jaundice; 1 lung metastasis; 1 refusal to start treatment). Placebo: 19 of 75 randomised patients did not complete treatment protocol, and had no results reported (6 definitive surgery; 6 lost before start of study; 3 tumour activity/recurrence; 2 socioeconomic reasons; 1 continuous bleeding; 1 extremely ill health).

Study	Numbers analysed	Statistical methods	Outcomes and estimation	Ancillary analyses	Adverse events	Follow-up
Sidik (2007a & 2007b)	Intention-to-treat analysis not reported. Analysis conducted for patients who completed the therapy protocol (20 treatment sessions), and were available at follow-up.	Data was analysed using statistical analysis software. Continuous outcomes were compared using unpaired t-tests, while categorical outcomes were compared using chi-square tests for independent groups. Exact *p*-values were reported. Level of significance was not defined.	Prevalence of proctitis: Tabular data reported displaying frequency of proctitis; *p*-values reported for between-groups differences. LENT-SOMA: Tabular data reported displaying mean scores at baseline (SD provided, range not provided). Tabular data displaying mean changes in score reported (SD provided, range not provided); *p*-values reported for between-groups differences in mean changes in score. Karnofsky score: Tabular data reported displaying mean scores at baseline (SD provided, range not provided). Tabular data displaying mean changes in score reported (SD provided, range not provided); *p*-values reported for between-groups differences in mean changes in score.	No subgroup analyses performed.	Adverse events were not reported.	First evaluation took place 1 to 2 months post-treatment. Second evaluation took place 6 months post-treatment. Losses to follow-up: HBOT: 3 of 35 randomised patients did not complete treatment protocol, and had no results reported (3 unable to complete 20 sessions). At 6 months, 6 of 32 patients were lost to follow-up (6 died at home of their illness). Placebo: 7 of 40 randomised patients did not complete treatment protocol, and had no results reported (4 unable to make follow-up visits; 3 withdrew without explanation). At 6 months, 13 of 33 patients were lost to follow-up (10 died at home without explanation, likely due to their illness; 2 relocated and could not attend follow-up).
Wounds in irradiated soft tissue of the head and neck region						
Marx (1985)	Intention-to-treat analysis not reported. Per-protocol analysis not defined.	Statistical tests were not explicitly defined, but chi-square tests were used for comparison. Exact *p*-values were reported. Level of significance was not defined.	Healing of wounds: Tabular data reported displaying frequency of wound healing (patients and individual sites); *p*-values reported for between-groups differences.	No subgroup analyses performed.	Adverse events were not reported.	Evaluation took place at 6 months post-treatment. Losses to follow-up: none reported.

Study	Numbers analysed	Statistical methods	Outcomes and estimation	Ancillary analyses	Adverse events	Follow-up
Soft tissue oedema following irradiation for breast cancer						
Gothard (2010)	Intention-to-treat analysis not reported. Analysis conducted for patients who did not meet exclusion criteria (eg recurrence of cancer) and were available at follow-up. Analysis did include patients who did not complete the therapy protocol (30 treatment sessions). The authors acknowledged that the small sample size reduced the size of treatment effect that could be reliably detected.	Outcomes were compared using nonparametric methods as data distributions were skewed and no suitable transformation could be found. Wilcoxon signed rank test was used to investigate within-patient change from baseline to 12 months for each treatment group. Change over time was compared between treatment groups using the Mann-Whitney test. Groups were compared for RR of response using Fisher's exact test. Exact *p*-values were reported. Level of significance was defined as $p<0.05$.	Arm volume: Frequency of patients responding to treatment reported in text; *p*-values and 95% CI reported for between-groups differences in response to treatment. Tabular data reported displaying median arm volume (IQR provided, mean, SD and range not provided); *p*-values reported for within-group changes and between-groups differences in arm volume. Lymphatic clearance rate: Tabular data reported displaying median clearance rate (IQR provided, mean, SD and range not provided); no statistical comparison made for between-groups differences. Arm fluid volume change: Tabular data reported displaying median fluid volume change (IQR provided, mean, SD and range not provided); no statistical comparison made for between-groups differences. Lymphoedema quality of life scale: Tabular data reported displaying median score (IQR provided, mean, SD and range not provided); no statistical comparison made for between-groups differences. SF-36: No results reported.	No subgroup analyses performed.	Adverse events: discussion of individual incidents only, with no comparison of treatment groups.	Evaluation took place 12 months after baseline assessment. Losses to follow-up: HBOT: At baseline, 2 of 38 patients had no results reported (2 diagnosed with metastases). At 12 months, 6 of 36 patients lost to follow-up (2 diagnosed with metastases, 2 withdrew as treatment was 'too much to cope with', 1 unwilling to travel). Control: At baseline, 3 of 20 patients had no results reported (1 hospitalised at time of assessment with pain in back and legs, 1 diagnosed with new primary tumour, 1unwilling to travel). At 12 months, 1 of 17 patients lost to follow-up (1 diagnosed with metastases).
Soft tissue flaps introduced into irradiated tissue						
Marx (1999)	Intention-to-treat analysis not reported. Per-protocol analysis not defined.	Statistical tests were not explicitly defined, but chi-square tests were used for comparison. Exact *p*-values were reported. Level of significance was not defined.	Wound infection, wound dehiscence and delayed wound healing: Tabular data reporting frequency of wound infection (major and minor), wound dehiscence (major and minor) and delayed wound healing reported; *p*-values reported for between-groups differences.	No subgroup analyses performed.	Adverse events were not reported.	Duration of follow-up not reported. Losses to follow-up not reported.

CI: confidence interval; EPIC: Expanded Prostate cancer Index Composite questionnaire; HBOT: hyperbaric oxygen therapy; IQR: interquartile range; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; RR: relative risk; SD: standard deviation; SF-12: Short Form 12 General Health Function Survey; SF-36: UK Short Form 36 Health Survey

Appendix H Critical appraisal of non-randomised comparative studies

Table 60 Critical appraisal summary of non-randomised comparative studies: non-neurological soft tissue radiation injuries

Study	Sample size	Study design (NHMRC level of evidence)	Participants	Interventions and outcomes	Numbers analysed and statistical methods	Outcomes and estimations	Follow-up
Wounds in irradiated soft tissue of the head and neck region							
Neovius (1997) Stockholm, SWEDEN	Total: 30 HBOT: 15 Comparator: 15 Enrolment dates (HBOT group): October 1993 – August 1995 No sample size or power calculations reported.	Retrospective comparative study with historical controls (Level III-3)	Inclusion criteria not reported. Exclusion criteria not reported; one patient who refused further HBOT treatment after 2 sessions was excluded from the study. The authors reported that patients with corresponding wounds treated without HBOT constituted the comparator group. Treatment groups were well matched at baseline for age and gender as well as clinical characteristics such as timing of surgery after irradiation, cancer location and stage, presence of neck metastases, and radiation dose received.	HBOT intervention well described. Comparator intervention described only as treatment without HBOT. Outcome measure was healing status of wounds measured up to 5 months post-treatment (criteria for evaluation not defined). Adverse events after treatment with HBOT were reported and discussed as individual incidents only, with no comparison of treatment groups.	Intention-to-treat analysis not reported. Analysis conducted for patients who completed the therapy protocol (30 treatment sessions). Statistical comparisons were not described or conducted.	Healing of wounds: Frequency of healing outcomes reported narratively in text; no statistical comparison made for between-groups differences.	Evaluation took place at 5 months post-treatment. Losses to follow-up: none reported.

Study	Sample size	Study design (NHMRC level of evidence)	Participants	Interventions and outcomes	Numbers analysed and statistical methods	Outcomes and estimations	Follow-up
Soft tissue oedema following irradiation for breast cancer							
Carl (2001) Dusseldorf, GERMANY	Total: 44 HBOT: 32 Comparator: 12 Enrolment dates: July 1996 – March 1999 No sample size or power calculations reported.	Prospective comparative study with concurrent controls (Level III-2)	Inclusion criteria: Symptomatic breast oedema with subjective pain of grade III or total score of 8 points or greater on LENT-SOMA scale. Exclusion criteria not reported. HBOT group was significantly larger than control group, as patients were only allocated to control if they refused to undergo HBOT. No baseline demographic or clinical characteristics were reported; however, no significant differences in pre-treatment LENT-SOMA scores were found between treatment groups.	HBOT intervention well described. Comparator intervention described as observation with no further treatment. Outcome measure was late radiation-induced morbidity (subscales of a modified LENT-SOMA scale, developed by Pavy et al (1995)) scored by the physician in charge. Adverse events after treatment with HBOT: none reported.	Intention-to-treat analysis not reported. Per-protocol analysis not defined. Data was analysed using statistical analysis software. Between-groups comparison of post-treatment LENT-SOMA score was conducted using the Mann-Whitney test. Exact *p*-values were not reported. Level of significance was not defined.	LENT-SOMA: Median scores displayed via chart (range provided, SD not provided); *p*-values reported for between-groups differences in score.	HBOT: Median follow-up 11 months (range 1–32) Control: Median follow-up 7 months (range 2–38) Losses to follow-up: none reported.

HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; NHMRC: National Health and Medical Research Council; SD: standard deviation

Appendix I Critical appraisal of case series

Table 61 Descriptive characteristics of HBOT case series: chronic non-diabetic wounds

First author (year)	Study location	Dates of enrolment	Number of patients included	No. of males	Mean age (years ± SD)	Co-morbidities[a]	Inclusion/exclusion criteria
Efrati (2007)	Israel	Jan 2001 to May 2005	35	9	53.5 ± 17.8	Diabetes mellitus (7) Hypertension (4) Chronic renal failure (3) Congestive heart failure (2)	Inclusion: Patients with vasculitis-induced severe non-healing ulcers who were admitted to the Institute of Hyperbaric Medicine and Wound Care Clinic at Assaf Harofeh Medical Center, Israel. Patients were included if they had histologically or serologically proven vasculitis, were aged 18 years or older and had received immunosuppressive treatment for at least 3 months. Exclusion: Patients having chest pathology incompatible with pressure changes, inner ear disease, or suffering from claustrophobia were excluded from the study.
Hawkins (n.d.)	Australia	June 2004 onwards	223 (non-diabetic wound patients only)	NR	NR	NR	Inclusion: All patients presenting to a participating hyperbaric unit for assessment of a chronic wound (greater than 3 months duration) were eligible for inclusion regardless of wound aetiology or prior therapy. Exclusion: Patient refusal, acute wounds (less than 3 months duration), wounds that had surgical intervention within the last 3 months and wounds associated with exposure to therapeutic radiation.
Hawkins (2006)	Australia	June 2004 onwards	48 (non-diabetic wound patients only)	NR	NR	NR	Inclusion: All patients presenting to a participating hyperbaric unit for assessment of a chronic wound (greater than 3 months duration) were eligible for inclusion regardless of wound aetiology or prior therapy. Exclusion: Patient refusal, acute wounds (less than 3 months duration), wounds that had surgical intervention within the last three months and wounds associated with exposure to therapeutic radiation.
Oubre (2007)	USA	December 1997 to May 2004	NR (37 wounds) (non-diabetic wounds only)	NR	65.6 ± 11.2	NR	Inclusion: Review of patients presenting to the Davis Hyperbaric Wound Healing Center, Brooks City-Base, Texas. Patients were treated and included if they could clear their sinuses during initial pressurisation, were not claustrophobic, completed 6 weeks of treatment, had at least 3 digital images of their wound available for assessment, and had a wound in an area permitting a reasonable estimation of wound area. Exclusion: Patients who received treatment to demark margins before amputation.

First author (year)	Study location	Dates of enrolment	Number of patients included	No. of males	Mean age (years ± SD)	Co-morbidities[a]	Inclusion/exclusion criteria
Sidhom (n.d.)	Australia	June 2004 onwards	119 (non-diabetic wound patients only)	NR	Peripheral vascular disease: 69.4 (Range: 39–88) Venous disease: 69.7 (Range: 42–88) Miscellaneous non-diabetic aetiologies: 65.8 (Range: 29–95)	NR	Inclusion: All patients presenting to a participating hyperbaric unit for assessment of a chronic wound (greater than 3 months duration) were eligible for inclusion regardless of wound aetiology or prior therapy. Exclusion: Patient refusal, acute wounds (less than 3 months duration), wounds that had surgical intervention within the last 3 months and wounds associated with exposure to therapeutic radiation.

NR: not reported; SD: standard deviation; USA: United States of America.

Table 62 Descriptive characteristics of HBOT case series: non-neurological soft tissue radiation injuries

First author (year)	Study location	Dates of enrolment	Number of patients included	No. of males	Mean age (years ± SD)	Co-morbidities[a]	Inclusion/exclusion criteria
Abratt (1978)	South Africa	Jan 1975 to Feb 1977	5 of 8 (soft tissue radiation injury patients only)	NR	53.6 ± 9.95 Range: 43–68	NR	Inclusion: Patients with radionecrosis confirmed on histological examination treated at Groote Schuur Hospital. Exclusion: Patients in whom response of HBOT could not be assessed (ie lost to follow-up, onset of rapidly progressing cancer, HBOT discontinued due to convulsions during initial stages of therapy).
Ashamalla (1996)	USA	1989 to 1994	4 of 10 (dental extraction patients only)	1	17.1 ± 5.32 Range: 12–26	NR	Inclusion: Patients treated with irradiation as children referred for HBOT for prophylaxis or treatment of osteoradionecrosis at the Institute for Environmental Medicine at the University of Pennsylvania, Philadelphia.
Bevers (1995)	Netherlands	Jan 1986 to Jan 1994	40	27	71.4 Range: 56–86	NR	Inclusion: Patients with severe haemorrhagic cystitis due to radiotherapy not responding to other treatments. Exclusion: Tumour recurrence in the bladder at cystoscopy before treatment, concomitant bleeding disorders, severe pulmonary disease with pulmonary bullae.
Chavez (2001)	USA	1990 to 1997	40	26	57.6 Range: 37–76	Malnutrition (14) Tobacco use (8) Heavy alcohol use (6) Infection (4) Poor compliance (4) Thyroid disease (3) COPD (2) Congestive heart failure (1) History of seizures (1) Optic neuritis (1) Middle ear surgery (1)	Inclusion: Consecutive patients treated at a single institution with HBOT before and after dental extractions in a previously irradiated field. Exclusion: Active tumour, chronic obstructive pulmonary disease with blebs or uncontrolled wheezing, poorly controlled prior pneumothorax or chronic heart failure.
Clarke (2008)	USA	NR	150	16	NR	Hypertension (31) Diabetes mellitus (19) Tobacco use – past (11) Tobacco use – current (8)	Inclusion: Patients were eligible for enrolment if they had undergone pelvic radiotherapy and had subsequently developed evidence of rectal late radiation tissue injury. The diagnosis had to have been present for ≥3 months and to not have responded sufficiently to other therapies. Exclusion: Patients not meeting inclusion criteria, refusing to participate, or unspecified 'other reasons'.
Dall'Era (2006)	USA	Oct 1988 to Dec 2003	27	27	71.8 Range: 53–82	NR	Inclusion: Patients with radiation induced proctitis secondary to brachytherapy, external beam radiation therapy or combined treatment for prostate cancer, treated with HBOT at Virginia Mason Medical Center in Seattle, Washington.

First author (year)	Study location	Dates of enrolment	Number of patients included	No. of males	Mean age (years ± SD)	Co-morbidities[a]	Inclusion/exclusion criteria
David (2001)	Canada	1985 to Jun 1997	24 of 75 (dental extraction patients only)	13	61 Range: 35–78	NR	Inclusion: Review of all patients who had HBOT prophylactically for the extraction of teeth, who had been followed up for a minimum of 6 months. Exclusion: Patients were deemed medically compromised if they had peripheral vascular disease or diabetes.
Feldmeier (1993)	USA	1980 to 1985	9	9	64.8 ± 7.84 Range: 56–82	NR	Inclusion: Review of all patients referred for HBO and treated for laryngeal necrosis at the hyperbaric medicine facility at Southwest Methodist Hospital, San Antonio, Texas, who had not had a total laryngectomy before referral.
Feldmeier (1995)	USA	1980 onwards	8 of 23, with 9 soft tissue injuries (soft tissue radiation injury patients only)	1	55.3 ± 13.44 Range: 30–71	NR	Inclusion: Review of patients with chest wall radiation necrosis referred to the hyperbaric medicine departments of Southwest Texas Methodist and Nix Hospitals, San Antonio, Texas.
Feldmeier (1996)	USA	1979 onwards	42 of 44 (soft tissue radiation injury patients only)	8	62.5 ± 12.56 Range: 33–84	NR	Inclusion: Review of all patients referred to Southwest Texas Methodist and Nix Hospitals, San Antonio, Texas for HBOT due to diagnosis of radiation-induced delayed injury to tissues of the abdomen and pelvis.
Feldmeier (2000)	USA	1979 to 1997	16 of 17, with 17 soft tissue injuries (soft tissue radiation injury patients only)	8	62.9 ± 17.47 Range: 21–87	NR	Inclusion: Review of all patients treated at Southwest Texas Methodist and Nix Hospitals, San Antonio, Texas for non-healing necrotic wounds of the extremities within previously irradiated fields.
Ferguson (1987)	USA	1979 onwards	8	7	59.3 ± 6.34 Range: 48–68	NR	Inclusion: Patients with severe radionecrosis of the larynx treated with adjunctive HBOT.
Filntisis (2000)	USA	1990 to 1996	18	11	61 ± 9.75 Range: 41–77	Tobacco use (12) COPD (3) Hypertension (3) Diabetes (3) Hyponatraemia (1) Chronic renal failure (1) Lung carcinoma (1) Basal cell carcinoma (1) Angina (1) Rheumatoid arthritis (1) Steroid therapy (1) Alcohol abuse (1)	Inclusion: All patients referred for HBO therapy to the FG Hall Hyperbaric Center at Duke University Medical Center Durham, North Carolina with the diagnosis of radiation-induced laryngeal damage. Exclusion: Patients who had already undergone total laryngectomy.

First author (year)	Study location	Dates of enrolment	Number of patients included	No. of males	Mean age (years ± SD)	Co-morbidities[a]	Inclusion/exclusion criteria
Fink (2006)	Australia	Nov 1997 to Oct 2003	14, with 15 soft tissue injuries (soft tissue radiation injuries only)	0	52.9 ± 12.84 Range: 34–77	NR	Inclusion: Review of all patients with delayed radiation injuries after treatment of a gynaecological cancer referred to the Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital, Sydney. Exclusion: Patients did not receive HBOT due to poor general medical condition, failed test compression, or refusal to undergo HBOT.
Girnius (2006)	USA	1997 to 2005	9	NR	74.2 ± 5.14 Range: 66–83	NR	Inclusion: Review of patients diagnosed with haemorrhagic radiation proctitis treated with HBOT at The University Hospital in Cincinnati, Ohio. Patients were eligible for inclusion if their prostate cancer was treated definitively with external beam radiotherapy and/or brachytherapy, had been diagnosed with haemorrhagic radiation proctitis by endoscopy and experienced at least twice-weekly rectal bleeding.
Hampson (2007)	USA	May 1988 to 2006	94 of 159 (radiation cystitis patients only)	NR	Median: 74 Range: 15–91	NR	Inclusion: Review of consecutive patients with haemorrhagic radiation cystitis treated with HBOT at Virginia Mason Medical Center in Seattle, Washington.
Hart (1976)	USA	Jan 1969 to Aug 1975	17 of 69 (soft tissue radiation injury patients only)	5	57	Obvious remaining tumour (3)	Inclusion: All patients with radiation necrosis who were failures to accepted therapy routines. Exclusion: Continuing malignancy at site of radiation (except when necrotising process involves a vital part of the body), congenital spherocytosis, concurrent acute viral infection, user of nicotine products unable to refrain from use during treatment, chronic obstructive pulmonary disease with a PCO_2 above 55mmHg, uncontrollable claustrophobia, failure to complete therapy.
Jones (2006)	Canada	Aug 2000 to early 2004	10	3	65 Range: 39–79	All patients were free of diabetes mellitus, inflammatory bowel disease, hypertension and peripheral vascular disease	Inclusion: Review of patients with chronic radiation proctitis who failed to respond to oral or topical conventional treatments referred to the Adult Radiation Late Effects Clinic at the Princess Margaret Hospital.
Kaur (2009)	New Zealand	2003 to 2006	26	16	60 ± 14.98 Range: 17–85	NR	Inclusion: Review of patients with tumours of the head and neck region treated with radiotherapy referred to Oxygen Therapies Ltd prior to undergoing dental extraction.
Lee (1994)	Republic of China (Taiwan)	Nov 1989 to Oct 1992	20	0	63 ± 9.38 Range: 42–79	NR	Inclusion: Patients with haemorrhagic radiation cystitis.
Marshall (2007)	USA	Jul 1991 to Jun 2003	65	37	65 Range: 36–84	NR	Inclusion: Consecutive patients with endoscopically-confirmed radiation damage to the gastrointestinal tract.

First author (year)	Study location	Dates of enrolment	Number of patients included	No. of males	Mean age (years ± SD)	Co-morbidities[a]	Inclusion/exclusion criteria
Mayer (2001)	Austria	Jun 1995 to Mar 2000	18	18	71.2 Range: 64–77	Diabetes (6) Bladder cancer (1) Myelodysplasia (1) Amyloidosis (1) IgG-Kappa-plasmocytoma (1)	Inclusion: All patients suffering from radiation induced proctitis and/or cystitis able to undergo HBO treatment at the Division of Thoracic and Hyperbaric Surgery, Graz, Austria. Exclusion: Patients with severe emphysema and patients unable to achieve pressure adjustment in the middle ear.
Narozny (2005)	Poland	Jan 1998 to Dec 2002	7 of 8 (soft tissue radiation injury patients only)	5	52.6 ± 4.14 Range: 45–59	NR	Inclusion: Patients who failed conventional treatments for late post-radiation complications (more than 2 months from exposure) after receiving radiation therapy for head and neck cancer.
Neheman (2005)	Israel	Feb 1997 to Apr 2004	7	4	63 Range: 21–80	NR	Inclusion: Patients with radiation-induced haemorrhagic cystitis.
Rijkmans (1989)	Netherlands	Jan 1986 to Apr 1988	10	7	71 Range: 61–83	NR	Inclusion: Patients with severe haematuria induced by radiation cystitis.
Safra (2008)	Israel	Jan 2001 to Dec 2005	13	0	59.5 ± 17.23 Range: 32–88	NR	Inclusion: Patients who suffered chronic radiation-induced late side effects after pelvic surgery and adjuvant postoperative pelvic radiotherapy for pelvic malignancy at the Institute of Radiotherapy, Tel-Aviv Sourasky Medical Center.
Waring (2000)	Australia	Dec 1989 to Feb 1998	25	21	69 Range: 40–82	NR	Inclusion: Patients referred to the Fremantle Hospital Hyperbaric Unit for treatment of haemorrhagic radiation-induced cystitis. Exclusion: Patients unable to receive sufficient HBOT treatment.
Warren (1997)	USA	Sep 1992 to May 1995	14	12	68 ± 12.00 Range: 52–83	NR	Inclusion: Review of patients with chronic radiation proctitis treated with HBOT at Brookside Hospital, San Pablo, California, and Travis Air Force Base, California.
Williams (1992)	USA	1986 to 1991	14, with 15 soft tissue injuries	0	53 Range: 35–78	NR	Inclusion: Patients referred to the Department of Hyperbaric Medicine at Richland Memorial Hospital for treatment of radiation-induced soft tissue necrosis, which were free of active malignancy for at least 6 weeks before beginning treatment and had failure of healing after 3 months of conservative therapy. Exclusion: Therapy was discontinued in patients with histologic evidence of recurrent disease, and severe anxiety associated with confinement in the hyperbaric chamber.
Woo (1997)	Australia	NR	18	17	72	NR	Inclusion: All patients completing a course of HBO therapy at the Fremantle Hospital Medicine Unit, Western Australia for radiation proctitis as assessed by proctoscope, sigmoidoscope or colonoscope. Exclusion: Concomitant bleeding disorder such as haemophilia.

First author (year)	Study location	Dates of enrolment	Number of patients included	No. of males	Mean age (years ± SD)	Co-morbidities[a]	Inclusion/exclusion criteria
Yoshida (2008)	Japan	Jan 2001 to May 2007	8	5	64.3 ± 8.77 Range: 47–73	NR	Inclusion: Patients with radiation-induced haemorrhagic cystitis.
Yu (2002)	Republic of China (Taiwan)	Jun 1998 to May 1999	5 of 6 (soft tissue radiation injury patients only)	0	54 ± 6.57 Range: 49–67	NR	Inclusion: Patients with breast sequelae post-irradiation referred to the hyperbaric oxygen centre of the Changhua Christian Hospital, Changhua.

a Patients may have multiple co-morbidities.

COPD: chronic obstructive pulmonary disease; HBO: hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; NR: not reported; SD: standard deviation; USA: United States of America.

Table 63 Critical appraisal summary of case series: chronic non-diabetic wounds

First author (year)	Explicit inclusion /exclusion criteria[a]	Outcomes assessed in all patients	Uniform follow-up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/disease severity uniform across patients
Efrati (2007)	Yes	Yes	Yes	Ulcer healing defined as complete, partial	No	No	NR	University of Texas Wound Classification System: 1C (1) 1D (1) 2A (2) 2B (7) 2C (10) 2D (8) 3C (4) 3D (2)
Hawkins (n.d.)	Yes	No	Yes	Wounds described as fully or substantially healed	No	No	NR	NR
Hawkins (2006)	Yes	No	Yes	Wounds described as fully or substantially healed	No	No	NR	NR
Oubre (2007)	Yes	Yes	Yes	Reduction in wound area measured using digital wound images	Yes	Yes	NR	NR
Sidhom (n.d.)	Yes	No	Yes	Pain measured using visual analogue scale	Yes	No	NR	NR

a Despite explicit inclusion criteria being given, the decision to refer to HBO therapy may have been biased, dependent upon the referring physician.
NR: not reported.

Table 64 Critical appraisal summary of case series: non-neurological soft tissue radiation injuries

First author (year)	Explicit inclusion /exclusion criteria[a]	Outcomes assessed in all patients	Uniform follow-up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/disease severity uniform across patients
Abratt (1978)	No	No	No	Wound healing described as complete, partial or failed Subjective pain relief	No No	No No	NR	NR
Ashamalla (1996)	No	Yes	NR	Extraction wound healing	No	No	NR	No scoring system used. Number of extractions made reported for each patient.
Bevers (1995)	Yes	Yes	No	Effect of HBOT on haematuria described as good, moderate, or no effect	No	No	NR	No scoring system used. Description given of severity of haematuria.
Chavez (2001)	No	No	Yes	Extraction wound healing	No	No	NR	No scoring system used. Mean number of extractions per patient reported.
Clarke (2008)	Yes	No	No	Proctitis healing described as healed, improved or unchanged Late radiation-induced morbidity Quality of life	No	No	Yes	NR
Dall'Era (2006)	No	Yes	No	Overall proctitis response described as good, partial or no change Symptoms described as having resolved, improved or unchanged	No No	No No	NR	All patients had RTOG/EORTC acute Grade 3 or 4, or chronic Grade 2 to 4 toxicities.
David (2001)	Yes	Yes	No	Extraction wound healing	No	No	NR	No scoring system used. Number of extractions made reported for each patient.
Feldmeier (1993)	Yes	No	No	Laryngectomy required Preservation of voice	Yes No	Yes No	NR	Chandler Grade III (1) Chandler Grade IV (8)
Feldmeier (1995)	No	No	NR	Wound healing	No	No	NR	RTOG/EORTC Grade 3 radiation injury (2) RTOG/EORTC Grade 4 radiation injury (6)
Feldmeier (1996)	Yes	No	NR	Wound healing	No	No	NR	All patients had RTOG/EORTC Grade 4 radiation injury

First author (year)	Explicit inclusion /exclusion criteria[a]	Outcomes assessed in all patients	Uniform follow-up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/disease severity uniform across patients
Feldmeier (2000)	No	Yes	No	Wounds described as having healed or significantly improved Amputation required	No Yes	No Yes	NR	No scoring system used. Description given of the size but not severity of the wounds.
Ferguson (1987)	No	Yes	No	Symptom improvement Laryngectomy required	No Yes	No Yes	NR	Chandler Grade III (4) Chandler Grade IV (4)
Filntisis (2000)	Yes	No	No	Symptoms described as having major improvement or no response Laryngectomy required Preservation of voice	No Yes No	No Yes No	NR	Chandler Grade III (2) Chandler Grade IV (16)
Fink (2006)	Yes	Yes	No	Wounds or symptoms described as healed, >50% improved, <50% improved, or not improved	No	No	NR	NR
Girnius (2006)	Yes	Yes	No	Bleeding measured on 5-point scale	No	Yes	NR	Bleeding measured on 5-point scale: Grade 2 – persistent (≥2/week) bleeding(1) Grade 3 – daily bleeding or anaemia (3) Grade 4 – require transfusion (5)
Hampson (2007)	No	Yes	NR	Haematuria described as resolved, markedly improved, or unchanged/worsened	No	No	NR	NR
Hart (1976)	Yes	No	NR	Healing of soft tissue graft Wound healing described as healed without grafting, sufficient improvement to allow grafting, or did not heal	No No	No No	NR	NR
Jones (2006)	No	Yes	No	Symptoms described as resolved, improved, no response or worsening	No	No	NR	LENT-SOMA Grade 2 proctitis (7) LENT-SOMA Grade 3 proctitis (3)
Kaur (2009)	No	No	NR	Extraction wound healing	No	No	NR	No scoring system used. Number of extractions made reported for each patient.

First author (year)	Explicit inclusion /exclusion criteria[a]	Outcomes assessed in all patients	Uniform follow-up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/disease severity uniform across patients
Lee (1994)	No	Yes	No	Haematuria described as completely resolved, markedly decreased, or no change	No	No	NR	NR
Marshall (2007)	No	Yes	No	Overall proctitis/enteritis response described as complete, partial, or failed	No	No	NR	NR
Mayer (2001)	No	No	No	Symptom resolution Late radiation-induced morbidity	No No	No No	NR	Modified RTOG/EORTC GI Grade 2 proctitis (4) Modified RTOG/EORTC GI Grade 3 proctitis (6) RTOG/EORTC GU Grade 2 cystitis (3) RTOG/EORTC GU Grade 3 cystitis (6) RTOG/EORTC GU Grade 4 cystitis (2)
Narozny (2005)	No	Yes	No	Symptom resolution	No	No	NR	Chandler Grade III (5) Chandler Grade IV (1) LENT-SOMA Grade 4 necrosis (1)
Neheman (2005)	No	Yes	No	Haematuria resolution	No	No	NR	NR
Rijkmans (1989)	No	Yes	No	Haematuria described as resolved or decreased	No	No	NR	NR
Safra (2008)	No	Yes	NR	Symptom resolution Late radiation-induced toxicity	No No	No No	NR	NR
Waring (2000)	No	No	Yes	Haematuria described as resolved, markedly reduced, decreased or unchanged Symptom resolution described as complete, partial, or poor/no response	No No	No No	NR	No scoring system used. Symptoms described as ‘moderate’ (16) or ‘severe’ (9)
Warren (1997)	No	Yes	No	Symptoms described as resolved, improved, improved with relapse, or not improved	No	No	NR	NR
Williams (1992)	Yes	Yes	NR	Wound healing	No	No	NR	NR

First author (year)	Explicit inclusion /exclusion criteria[a]	Outcomes assessed in all patients	Uniform follow-up	Measurement of outcomes	Outcomes quantified	Outcomes measured objectively	Blinded assessment of outcome	Indication/disease severity uniform across patients
Woo (1997)	Yes	Yes	No	Symptoms described as completely improved, partially improved or not improved	No	No	NR	NR
Yoshida (2008)	No	Yes	No	Haematuria resolution	No	No	NR	NR
Yu (2002)	No	Yes	Yes	Oedema resolution	No	No	NR	NR

[a] Despite explicit inclusion criteria being given, the decision to refer to HBO therapy may have been biased, dependent upon the referring physician. GI: gastrointestinal; GU: genitourinal; HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; NR: not reported; RTOG/EORTC: Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer.

Table 65 Results of case series of HBOT: chronic non-diabetic wounds

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Efrati (2007)	Vasculitis-induced non-healing skin ulcers	Wound healing Complete Partial No response	 28/35 (80.0%) 4/35 (11.4%) 3/35 (8.6%)	Immediately post-treatment
Hawkins (n.d.)	Peripheral vascular disease (88) Venous disease (55) Miscellaneous non-diabetic aetiologies (80)	Complete or substantial healing of wound: peripheral vascular disease Immediately post-treatment 1 month 6 months 12 months Complete or substantial healing of wound: venous disease Immediately post-treatment 1 month 6 months 12 months Complete or substantial healing of wound: miscellaneous aetiologies Immediately post-treatment 1 month 6 months 12 months	 35/87 (40.2%) 40/75 (53.3%) 33/54 (61.1%) 25/38 (65.8%) 30/55 (54.5%) 30/52 (57.7%) 28/41 (68.3%) 23/27 (85.2%) 33/80 (41.3%) 38/73 (52.1%) 41/66 (62.1%) 35/44 (79.5%)	12 months
Hawkins (2006)	Peripheral vascular disease (20) Venous disease (13) Miscellaneous non-diabetic aetiologies (15)	Complete or substantial healing of wound: peripheral vascular disease Immediately post-treatment 1 month 6 months 12 months Complete or substantial healing of wound: venous disease Immediately post-treatment 1 month 6 months 12 months	 4/17 (23.5%) 4/15 (26.7%) 10/12 (83.3%) 7/9 (77.8%) 5/11 (45.5%) 6/10 (60.0%) 8/8 (100.0%) 6/6 (100.0%)	12 months

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Oubre (2007)	NR	Overall percentage reduction in wound area	22.8% reduction in wound area	Immediately post-treatment
Sidhom (n.d.)	Peripheral vascular disease (36) Venous disease (32) Miscellaneous non-diabetic aetiologies (51)		Pre-HBOT median (IQR) Post-HBOT median (IQR)	6 months
		Pain score on visual analogue scale: peripheral vascular disease	6 (4–8) 0.5 (0–5) *p*<0.0001	
		Pain score on visual analogue scale: venous disease	5 (3–8) 0 (0–3) *p*<0.0001	
		Pain score on visual analogue scale: miscellaneous aetiologies	5 (4–8) 1 (0–4) *p*<0.0001	

HBOT: hyperbaric oxygen therapy; NR: not reported; IQR: interquartile range.

Table 66 Results of case series of HBOT: non-neurological soft tissue radiation injuries

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Radiation proctitis				
Clarke (2008)	Radiation proctitis	Overall proctitis healing Healed Improved Unchanged Cancer recurrence LENT-SOMA criteria score HBOT only HBOT following placebo EPIC Bowel Bother subscale score HBOT only HBOT following placebo EPIC Bowel Function subscale score HBOT only HBOT following placebo	3mons 6mons 1yr 2yrs 3yrs 4yrs 5yrs 7/103 7/103 7/105 7/61 5/38 4/29 1/13 57/103 54/103 62/105 33/61 27/38 22/29 10/13 36/103 36/103 33/105 19/61 6/38 3/29 1/13 3/103 6/103 3/105 2/61 0/38 0/29 1/13 3mons 6mons 1yr 2yrs 3yrs 4yrs 5yrs 5.96 6.85 5.29 3.61 3.55 4.21 3.71 7.17 7.31 6.72 6.20 3.89 4.00 4.29 3mons 6mons 1yr 2yrs 3yrs 4yrs 5yrs 58.16 64.49 69.12 73.16 83.33 79.63 85.71 74.14 73.76 74.70 71.20 71.42 76.78 69.38 3mons 6mons 1yr 2yrs 3yrs 4yrs 5yrs 69.72 75.34 77.48 82.01 81.34 82.01 88.69 80.33 77.50 75.35 73.36 77.29 78.38 76.53	Mean: 2.09 years Minimum: 1 year
Dall'Era (2006)	Radiation proctitis	Patient response Good Partial No change/failed Resolution of symptoms Bleeding Faecal urgency Pain Rectal ulcer	10/27 (37.0%) 8/27 (29.6%) 9/27 (33.3%) Resolved / Improved / No change/failed 12/25 (48.0%) / 7/25 (28.0%) / 5/25 (20.0%) 2/4 (50.0%) / 1/4 (25.0%) / 0/4 (0.0%) 0/8 (0.0%) / 6/8 (75.0%) / 1/8 (12.5%) 2/14 (14.3%) / 5/14 (35.7%) / 6/14 (42.9%)	Mean: 13 months Range: 1–60 months

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Girnius (2006)	Radiation proctitis	Bleeding resolution Complete Partial No response Rectal bleeding scale for radiation-induced haemorrhagic proctitis	7/9 (77.8%) 2/9 (22.2%) 0/9 (0.0%) Pre-HBOT / Post-HBOT Transfusion required 5 / 0 Daily bleeding or anaemia 3 / 0 Persistent bleeding (≥2/wk) 1 / 0 Intermittent bleeding (≤1/wk) 0 / 2 No bleeding 0 / 7	Median: 17 months Range: 1–77 months
Jones (2006)	Radiation proctitis	Resolution of symptoms Bleeding Rectal pain Diarrhoea	Resolved / Improved / No response / Worsening 4/9 (44.4%) / 3/9 (33.3%) / 1/9 (11.1%) / 1/9 (11.1%) 3/5 (60.0%) / 1/5 (20.0%) / 1/5 (20.0%) / 0/5 (0.0%) 1/5 (20.0%) / 3/5 (60.0%) / 1/5 (20.0%) / 0/5 (0.0%)	Median: 25 months Range: 6–43 months
Warren (1997)	Radiation proctitis	Overall symptom response Rectal bleeding Diarrhoea Proctalgia (pain) Colic Mucus Tenesmus	Resolved / Improved / Failed 9/14 (64.3%) / 3/14 (21.4%) / 2/14 (14.3%) 6/11 (54.5%) / 1/11 (9.1%) / 4/11 (36.4%) 4/5 (80.0%) / 0/5 (0.0%) / 1/5 (20.0%) 0/3 (0.0%) / 1/3 (33.3%) / 2/3 (66.7%) 2/3 (66.7%) / 0/3 (0.0%) / 1/3 (33.3%) 1/2 (50.0%) / 0/2 (0.0%) / 1/2 (50.0%) 2/2 (100.0%) / 0/2 (0.0%) / 0/2 (0.0%)	Mean: 14.6 months Range: 2–35 months
Woo (1997)	Radiation proctitis	Resolution of all symptoms Bleeding Mild, no transfusions Moderate Severe Diarrhoea Pain Incontinence	Complete / Partial / Not improved 2/18 (11.1%) / 8/18 (44.4%) / 8/18 (44.4%) 4/17 (23.5%) / 3/17 (17.6%) / 10/17 (58.8%) 4/11 (36.4%) / 1/11 (9.1%) / 6/11 (54.5%) 0/4 (0.0%) / 1/4 (25.0%) / 3/4 (75.0%) 0/2 (0.0%) / 1/2 (50.0%) / 1/2 (50.0%) 2/8 (25.0%) / 2/8 (25.0%) / 4/8 (50.0%) 2/4 (50.0%) / 1/4 (25.0%) / 1/4 (25.0%) 1/4 (25.0%) / 1/4 (25.0%) / 2/4 (50.0%)	NR
Wounds in irradiated soft tissue of the head and neck region				
Ashamalla (1996)	Dental extraction wounds in irradiated tissue	Complete healing of all extraction sites (patients)	4/4 (100.0%)	Minimum: 2 months

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Chavez (2001)	Dental extraction wounds in irradiated tissue	Wound healing immediately post-treatment (patients) Excellent Good Fair Poor Indeterminate Wound healing 1 month after treatment (patients) Healed Not healed Wound healing 12 months after treatment (patients) Healed Not healed Unhealed extraction sites 12 months after treatment	 27/40 (67.5%) 10/40 (25.0%) 1/40 (2.5%) 0/40 (0.0%) 2/40 (5.0%) 31/37 (83.8%) 6/37 (16.2%) 31/35 (88.6%) 4/35 (11.4%) 6/371 (1.6%)	12 months
David (2001)	Dental extraction wounds in irradiated tissue	All extraction sites free of osteoradionecrosis (patients) Extraction sites free of osteoradionecrosis	 24/24 (100.0%) 54/54 (100.0%)	Mean: 10.3 months Range: 6–27.6 months
Feldmeier (1993)	Laryngeal radionecrosis	Laryngectomy not required Decannulation of tracheostomy Functional voice quality Good quality voice Slight hoarseness Fistulae closure Without surgery Surgery required	9/9 (100.0%) 3/3 (100.0%) 7/9 (77.8%) 2/9 (22.2%) 2/4 (50.0%) 2/4 (50.0%)	Mean: 6 years Median: 6 years Range 2–10 years
Ferguson (1987)	Laryngeal radionecrosis	Laryngectomy not required Symptom improvement Recurrence of symptoms after improvement Decannulation of tracheostomy	7/8 (87.5%) 7/8 (87.5%) 1/7 (14.3%) 2/3 (66.7%)	Minimum: 14 months
Filntisis (2000)	Laryngeal radionecrosis	Laryngectomy not required Major improvement Decannulation of tracheostomy	13/18 (72.2%) 13/18 (72.2%) 4/13 (30.8%)	Mean: 23 months Range: 5 months – 4 years
Kaur (2009)	Dental extraction wounds in irradiated tissue	Wound healing, without symptoms or post-treatment complications (patients)	25/26 (96.2%)	NR

First author (year)	Type/location of wound(s)	Outcomes reported	Results			Follow-up
Narozny (2005)	Laryngeal radionecrosis	Symptoms resolved Decannulation of tracheostomy Fistulae closure Surgery required	6/6 (100.0%) 3/3 (100.0%) 1/1 (100.0%)			Mean: 40.4 months Median: 42 months Range: 18–60 months
Radiation-induced soft tissue oedema						
Yu (2002)	Axilla, breast and chest wall	Resolution of axillary oedema Resolution of movement limitation Resolution of breast/chest wall oedema Resolution of non-healing ulcer	5/5 (100.0%) 4/5 (80.0%) 4/4 (100.0%) 3/3 (100.0%)			Minimum: 24 months
Radiation cystitis						
Bevers (1995)	Radiation cystitis Slight (10) Moderate (12) Severe (18)	Haematuria resolution Overall Slight Moderate Severe Recurrence of severe macroscopic haematuria	Good 30/40 (75.0%) 9/10 (90.0%) 9/12 (75.0%) 12/18 (66.7%) 9/37 (24.3%)	Moderate 7/40 (17.5%) 1/10 (10.0%) 3/12 (25.0%) 3/18 (16.7%)	No effect 3/40 (7.5%) 0/10 (0.0%) 0/12 (0.0%) 3/18 (16.7%)	Mean: 23.1 months Median: 13 months Range: 1–74 months
Hampson (2007)	Radiation cystitis	Haematuria resolution Complete Marked improvement Unchanged/worsened	 38/94 (40.4%) 40/94 (42.6%) 16/94 (17.0%)			NR
Lee (1994)	Radiation cystitis	Haematuria resolution Complete Marked improvement No response	 16/19 (84.2%) 2/19 (10.5%) 1/19 (5.3%)			Mean: 14 months Range: 5–41 months
Neheman (2005)	Radiation cystitis	Initial complete resolution or marked improvement of haematuria Recurrence of haematuria Improved cystoscopic bladder mucosa appearance	7/7 (100.0%) 2/7 (28.6%) 6/6 (100.0%)			Mean: 24 months Range: 3–53 months
Rijkmans (1989)	Radiation cystitis	Complete resolution of haematuria Improvement in haematuria	6/10 (60.0%) 4/10 (40.0%)			Range: 2–24 months

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Waring (2000)	Radiation cystitis	Haematuria resolution Complete Marked reduction Decreased but intermittent No change Information not reported Recurrence of haematuria Symptom improvement immediately after treatment Resolution of symptoms 1 month after treatment Complete resolution Partial resolution Poor/no response Cystoscopic evaluation of bladder appearance Normal Improved Recurrent tumour Ongoing radiation cystitis Various (including infection, erythema, old clots)	 6/25 (24.0%) 11/25 (44.0%) 1/25 (4.0%) 4/25 (16.0%) 2/25 (8.0%) 5/25 (20.0%) 24/25 (96.0%) 10/25 (40.0%) 12/25 (48.0%) 3/25 (12.0%) 2/17 (11.8%) 2/17 (11.8%) 2/17 (11.8%) 5/17 (29.4%) 6/17 (35.3%)	Mean: 5 months Range: 1–18 months
Yoshida (2008)	Radiation cystitis	Haematuria resolution Complete No resolution or improvement Recurrence of haematuria	 6/8 (75.0%) 2/8 (25.0%) 1/8 (12.5%)	Mean: 15.5 months Range: 2–31 months
Soft tissue radiation injury to the pelvis, abdomen, chest wall and extremities				
Feldmeier (1995)	Chest wall	Wound healed HBOT discontinued due to recurrent cancer	7/9 (77.8%) 2/9 (22.2%)	NR
Feldmeier (2000)	Extremities	Wound healing Healed Significant improvement Amputation Patient discharged to hospice (lung metastases)	 10/16 (62.5%) 1/16 (6.3%) 4/16 (25.0%) 1/16 (6.3%)	NR

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Mixed soft tissue radiation injuries				
Abratt (1978)	Mouth and mandible (3) Skin of buttock (2) Tonsil (1) Pharynx (1) Tongue (1)	Wound healing Completely healed Partially healed Failed to heal Subjective pain relief Complete Partial Failed Not reported	 3/8 (37.5%) 3/8 (37.5%) 2/8 (25.0%) 2/8 (25.0%) 3/8 (37.5%) 2/8 (25.0%) 1/8 (12.5%)	Mean: 17.6 months Median: 15.5 months Range: 6–30 months
Feldmeier (1996)	Abdominal wall (15) Groin (13) Perineum (7) Vagina (5) Small bowel (1) Skin of buttocks (1)	Wound healing Healed Did not heal Inadequate course of HBOT Lost to follow-up	 25/42 (59.5%) 6/42 (14.3%) 8/42 (19.0%) 3/42 (7.1%)	NR
Fink (2006)	Vaginal ulceration (5) Proctitis (2) Proctitis and cystitis (2) Cystitis (1) Cystitis exacerbation (1) Enteritis (1) Enteritis and vaginitis (1) Vaginal induration (1) Dermatitis and stenosis of vaginal region (1)	Symptom/ulcer healing Healed >50% improvement <50% improvement No improvement Symptom/ulcer healing (patients with cystitis): Healed >50% improvement <50% improvement No improvement Recurrence of bleeding Symptom/ulcer healing (patients with proctitis): Healed >50% improvement <50% improvement No improvement Recurrence of bleeding	 5/15 (33.3%) 6/15 (40.0%) 4/15 (26.7%) 0/15 (0.0%) 2/4 (50.0%) 0/4 (0.0%) 2/4 (50.0%) 0/4 (0.0%) 1/4 (25.0%) 1/4 (25.0%) 1/4 (25.0%) 2/4 (50.0%) 0/4 (0.0%) 1/4 (25.0%)	Mean: 32.5 months Range: 6–70 months

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Hart (1976)	Soft-tissue flaps in irradiated tissue (6) Pelvic/lumbar region (6) Laryngeal (5)	Patients with chest wall necrosis: Healing of tissue graft Patients with pelvic/lumbar necrosis: Healed without grafting Wound became receptive enough for grafting Did not heal Patients with laryngeal fistula: Healed without grafting Wound became receptive enough for grafting Died of aspiration unrelated to HBOT	 6/6 (100.0%) 4/6 (66.7%) 1/6 (16.7%) 1/6 (16.7%) 3/5 (60.0%) 1/5 (20.0%) 1/5 (20.0%)	NR
Marshall (2007)	Rectum (proctitis) (54) Proximal (enteritis) (15) Small bowel (7) Colon (6) Duodenum (6) Stomach (4) (4 patients had injuries of both rectum and proximal sites)	Overall response (symptom frequency, subjective complaints, documented healing) Complete response Partial response Failure In patients with proctitis: Complete response Partial response Failure	 28/65 (43.1%) 16/65 (24.6%) 21/65 (32.3%) 21/54 (38.9%) 14/54 (25.9%) 19/54 (35.2%)	Mean: 23 months Median: 20 months Range: 1–70 months

First author (year)	Type/location of wound(s)	Outcomes reported	Results			Follow-up
Mayer (2001)	Cystitis (8) Proctitis (7) Cystitis and proctitis (3)			Pre-HBOT	Post-HBOT	Mean: 15.0 months Median: 11.4 months Range: 2.2–51.6 months
		RTOG/EORTC GU late morbidity criteria	Grade 0	0	2	
			Grade 1	0	4	
			Grade 2	3	2	
			Grade 3	6	1	
			Grade 4	2	1	
			Inadeq. HBOT	NA	1	
		Modified RTOG/EORTC GI late morbidity criteria	Grade 0	0	3	
			Grade 1	0	5	
			Grade 2	4	1	
			Grade 3	6	0	
			Grade 4	0	0	
			Inadeq. HBOT	NA	1	
		Patients with cystitis: Haematuria stopped	6/8 (75.0%)			
		Patients with proctitis: Bleeding stopped	5/5 (100.0%)			
Safra (2008)	Cystitis and proctitis (6) Vaginal ulceration and fistulas (5) Wound healing complications (2)			Pre-HBOT	Post-HBOT	NR
		Common Toxicity Criteria	Grade 0	0	10	
			Grade 1	0	2	
			Grade 2	2	1	
			Grade 3	5	0	
			Grade 4	6	0	
		Patients with proctitis: Rectal bleeding stopped	5/6 (83.3%)			
		Patients with cystitis: Dysuria stopped Macroscopic haematuria stopped	6/7 (85.7%) 7/7 (100.0%)			
		Patients with wound healing/scar complications: Complications resolved	2/2 (100.0%)			

First author (year)	Type/location of wound(s)	Outcomes reported	Results	Follow-up
Williams (1992)	Vaginal vault (11) Vaginal vault with rectovaginal fistula (2) Abdominal wall (panniculus) (1) Abdominal wall, sacrum and vagina, with vesicovaginal and rectovaginal fistulas (1)	Necrosis healing Healed Necrosis progressed	 13/14 (92.9%) 1/14 (7.1%)	NR

EPIC: Expanded Prostate cancer Index Composite; GI: gastrointestinal; GU: genitourinal; HBOT: hyperbaric oxygen therapy; LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic; NA: not applicable; NR: not reported; RTOG/EORTC: Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer.

Appendix J Studies reporting on adverse events

Ear barotrauma

Chavez, J. A. and Adkinson, C. D. 2001. 'Adjunctive hyperbaric oxygen in irradiated patients requiring dental extractions: outcomes and complications', *Journal of Oral and Maxillofacial Surgery*, 59 (5), 518–522.

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Marshall, G. T., Thirlby, R. C., et al, 2007. 'Treatment of gastrointestinal radiation injury with hyperbaric oxygen', *Undersea & Hyperbaric Medicine*, 34 (1), 35–42.

Mayer, R., Klemen, H., et al, 2001. 'Hyperbaric oxygen--an effective tool to treat radiation morbidity in prostate cancer', *Radiotherapy and Oncology*, 61 (2), 151–156.

Neovius, E. B., Lind, M. G., et al, 1997. 'Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck: a review of the literature and a report of 15 consecutive patients', *Head & Neck*, 19 (4), 315–322.

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Woo, T. C., Joseph, D., et al, 1997. 'Hyperbaric oxygen treatment for radiation proctitis', *International Journal of Radiation Oncology, Biology and Physics*, 38 (3), 619–622.

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Transient vision change

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Oxygen toxicity of the central nervous system

Dall'Era, M. A., Hampson, N. B., et al, 2006. 'Hyperbaric oxygen therapy for radiation induced proctopathy in men treated for prostate cancer', *Journal of Urology*, 176 (1), 87–90.

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Hypertension

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Shortened forms

AHHA	Australian Healthcare and Hospitals Association
AHRQ	Agency for Healthcare Research and Quality
ANZHMG	Australian and New Zealand Hyperbaric Medicine Group
APC	argon plasma coagulation
AR-DRG	Australian Refined Diagnostic Related Group
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Society of Anaesthetists
ASERNIP—S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical
ATA	atmosphere absolute
CHERE	Centre for Health Economics Research and Evaluation
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
DORCTIHM	Database of Randomized Trials in Hyperbaric Medicine
DRG	Diagnosis Related Group
EMSN	Extended Medicare Safety Net
EPIC	Expanded Prostate cancer Index Composite
GI	gastrointestinal
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GU	genitourinal
HBOT	hyperbaric oxygen therapy
HTA	health technology assessment
HTNA	Hyperbaric Technicians and Nurses Association

ICER	incremental cost-effectiveness ratio
IQR	interquartile range
kPa	kilopascals
LENT-SOMA	Late Effects of Normal Tissues – Subjective Objective Management Analysis
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
PASC	Protocol Advisory Sub-Committee
PICO	population, intervention, comparator, outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
psi	pounds per square inch
PUPPS	pressure ulcer point prevalence survey
QALY	quality-adjusted life year
RCT	randomised controlled trial
RR	relative risk
RTOG/EORTC	Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer
SA	sensitivity analysis
SD	standard deviation
SF-12	Short Form 12
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SPUMS	South Pacific Underwater Medicine Society
UHMS	Undersea and Hyperbaric Medicine Society
UK	United Kingdom
USA	United States of America
VAS	visual analogue scale