

## **Hyperbaric Oxygen Therapy Protocol**

### **1. Title of Research Question**

A systematic review of the clinical and cost effectiveness of Hyperbaric Oxygen Therapy (HBOT) use in adults.

### **2. Clarification of Research Question and Scope**

This review will examine the clinical and cost effectiveness of HBOT in the adult population to treat/manage a variety of health conditions (see Appendix 1 for list). For an assessment of clinical effectiveness, studies of any design such as randomised controlled trials (RCTs), cohort studies, case control studies, etc, will be included where HBOT is used as a mono or adjunct therapy to standard treatment(s) appropriate to the health condition(s) being treated or managed. Existing relevant systematic reviews will also be included. The evaluation of cost effectiveness will include all secondary and primary studies that compare HBOT to one or more standard treatments for the relevant health condition(s), which report both the costs and the outcomes of the alternatives. The studies could adopt cost minimisation, or cost effectiveness, or cost utility or cost benefit analysis.

#### **2.1 Objectives**

Outlined below are the key questions which this systematic review will address:

What are the health conditions for which HBOT is considered?

- a) of proven clinical effectiveness and cost effectiveness compared to standard treatment(s)
- b) of proven clinical effectiveness but not cost effective compared to standard treatment(s)

- c) of unproven clinical effectiveness but with sufficient suggestion of possible benefit
- d) of proven lack of clinical effectiveness.

### **3. Project Team**

#### **3.1 NHS QIS**

Dr Karen Ritchie (Senior Health Services Researcher/Project Lead)

Dr Susan Baxter (Health Services Researcher)

Ms Joyce Craig (Senior Health Economist)

Ms Jennifer Graham (Project Officer)

Dr Harpreet Kohli (Medical Advisor)

Ms Doreen Pedlar (Project Co-ordinator)

Ms Lisa Wilson (Health Economist)

Ms Suzanne Wilson (Information Scientist)

#### **3.2 Topic Proposers**

Professor Norman Waugh (Professor of Public Health, University of Aberdeen)

Dr John Ross (Senior Lecturer, University of Aberdeen)

Dr Ash Paul (Deputy Medical Director, Health Commission Wales)

Dr Helen Walters (Consultant in Public Health Medicine, Portsmouth PCT)

### **4. Plain Language Summary**

Individuals who undergo HBOT typically breathe 100% oxygen at a pressure higher than atmospheric pressure. HBOT may be delivered in a multiplace (multiple occupancy) or a monoplace chamber (single occupancy) where, through intermittent inhalation, high concentrations of oxygen is circulated around the body and delivered to the tissues.

Internationally there are a number of HBOT centres. In the UK, there are 17 HBOT centres, four of which are situated in Scotland and 13 in England, all providing 24 hour emergency cover and may also be used for elective HBOT therapy.

HBOT was initially used to treat decompression illness amongst divers but has subsequently been used to treat/manage an array of conditions, often in the absence of robust scientific evidence, and despite the risks associated with HBOT treatment (ie

barotraumas, fire, etc). Consequently, a degree of uncertainty has arisen regarding its usefulness to treat/manage certain conditions. However, it is believed that this may partly be due to the lack of good quality evidence available, making it difficult to assess the efficacy of HBOT in many conditions. As such, costs associated with HBOT from the perspective of the NHS, are likely to vary considerably owing to the individuality of the condition being treated or managed and patient compliance with HBOT treatment.

This systematic review will examine and synthesise the literature for which HBOT use is considered in adults in order to assess its clinical and cost effectiveness when compared to existing standard treatments for these conditions.

## **5. Existing Evidence**

This systematic review builds on the results of previous work, such as that undertaken by the Agency for Healthcare Research and Quality (AHRQ) Technology Assessment (2006) - A Horizon Scan: Uses of Hyperbaric Oxygen Therapy (<http://www.cms.hhs.gov/determinationprocess/downloads/id42TA.pdf>) and on the work presented at the European Consensus Conferences (<http://www.echm.org/ECHM-Conferences.htm>).

## **6. Search Strategy**

The search strategy will involve systematically searching electronic databases and relevant professional and manufacturers' websites. Electronic searches will be conducted to identify reports of published and ongoing studies. Such searches will be inclusive of a range of studies, including systematic reviews, where HBOT has been used either as mono or adjunct therapy in adults. The AHRQ report will be used as the source of literature published prior to 2006 but, in addition, searching will be carried out from January 2006 to the present for full text English papers. Studies published in other languages will not be included in the review. Electronic databases to be searched are detailed in Table 1. Appendix 2 provides details of the search strategy undertaken so far.

**Table 1 Electronic Databases to be searched**

Electronic Databases
Medline & Medline in Process
Embase
Cochrane Database of Systematic Reviews
Cochrane Central Register of Controlled Trials
Science Citation Index (SCI)
Social Science Citation Index (SSCI)
HTA Database
Database of Abstracts of Reviews of Effects (DARE)
NHS Economic Evaluation Database (NHS EED)
Health Economics Evaluation Database (HEED)

**6.1. Inclusion and Exclusion Criteria****6.1.1 Clinical Effectiveness**

Two health service researchers will independently screen all titles and abstracts to ensure relevancy and consistency of paper selection. Full text English papers thought to be relevant based on title and abstract will be obtained where possible. The relevance of each study will be assessed according to the inclusion and exclusion criteria outline in Table 2. Studies which do not fulfil all of the criteria will be excluded with reasons for this documented, together with their biographic details. Any discrepancies in the relevancy of papers based on title and abstract will be resolved by consensus. If necessary, a third reviewer will be included.

**Table 2 Inclusion and Exclusion Criteria**

Inclusion Criteria	Exclusion Criteria
Any study design	Animal studies
Any size study	Paediatric studies
Systematic reviews	Studies published in languages other than English
Full English text	Narrative reviews, meeting abstracts, editorials, letters to the editor and opinion papers
HBOT as mono or adjunct therapy	

**6.1.2 Cost Effectiveness**

For the cost effectiveness analysis, the criteria in Table 2 will be augmented by the addition of further inclusion criteria requiring that the studies report both costs and

outcomes of the HBOT and one or more alternative treatments. Two health economists will independently screen all titles and abstracts to ensure relevancy and consistency of paper selection.

### **6.1.3 Interventions**

The intervention is HBOT, used either as mono or adjunct therapy for the treatment/management of health conditions. The comparator for both clinical and cost effectiveness should be the current standard treatment in the UK for the relevant health conditions.

### **6.1.4 Participants**

Individuals over the age of 16 years of age receiving HBOT as a mono or adjunct therapy.

### **6.1.5 Outcomes**

Data on the following clinical outcome measures will be included:

- Measurable response to HBOT
- Rate of HBOT use in relation to a specific condition
- Number of HBOT sessions
- Duration of HBOT sessions
- Time point in condition when HBOT is administered
- Adverse effects
- Length of follow up
- Quality of life
- Patient compliance/preference

The cost effectiveness analysis will include the following outcome measures:

- Direct costs disaggregated to resource quantities and unit process if reported
- Indirect costs
- Costing methods
- Discounting approach adopted and discount rates
- Results costs and outcomes and synthesis of costs and outcomes
- Sensitivity analysis
- Source of clinical effectiveness data

## **7. The Selection and Reviewing Process**

A review of the evidence for clinical and cost effectiveness of HBOT used in adults will be undertaken systematically according to the following data extraction and quality assessment strategy.

## **7.1 Data Extraction Strategy**

Studies which match the inclusion criteria will have the following clinical or cost effectiveness related information recorded:

- Study Details
  - Year of publication
  - Funding source
  - Country
  - Study objectives
  - Type of study
  - Setting
- Study population
  - Number and characteristics of participants
  - Inclusion and exclusion criteria
- Baseline Characteristics
  - Mean / SD age (years)
  - Gender (% male / % female)
  - Health condition(s) under investigation
  - Control
- Methodology
  - Methods : Pre-randomised and randomisation
  - Method of data collection
  - Concealment of allocation
  - Selection bias
  - Blinding procedures
  - Data / sensitivity analysis
  - Appropriateness of analysis method
  - Measure of health benefits
  - Valuation of health states
- Intervention details (i.e. HBOT and other)
  - Length, frequency, and dose of treatment
  - Length and frequency of follow up
  - No. of participants
  - Info on additional treatment (if any)
  - Comparator (details)
- Withdrawals
  - Number recruited / attrition
  - Reason for attrition

Any disagreement on an element of a study will be resolved through consensus or through consultation with a third reviewer. All reviewers will not be blinded to authors, institutes or publication details. Where there is insufficient information in the published text, contact will be made with the authors for clarification, if time constraints allow. Data from studies where there has been multiple publications will be reported as a single study.

## **7.2 Quality Assessment Strategy**

The quality of clinical papers will be assessed independently by two reviewers. Again, disagreement will be resolved through consensus, and if necessary, a third reviewer will be consulted. The quality of the different types of studies reviewed will be assessed using the appropriate checklist tool, such as the Critical Appraisal Skills Programme for assessing the quality of RCTs

([http://www.phru.nhs.uk/Doc\\_Links/rct%20appraisal%20tool.pdf](http://www.phru.nhs.uk/Doc_Links/rct%20appraisal%20tool.pdf)), Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist for systematic reviews and meta-analyses (<http://www.sign.ac.uk/guidelines/fulltext/50/checklist1.rtf>), SIGN checklist for cohort studies (<http://www.sign.ac.uk/guidelines/fulltext/50/checklist3.rtf>) etc.

Cost effectiveness will be assessed using CRD Guidance for NHS economic evaluations (<http://www.york.ac.uk/inst/crd/pdf/6guidance.pdf>). The quality of the evidence base for economic evaluations will be summarised for each condition using a completed considered judgement form

(<http://www.sign.ac.uk/guidelines/fulltext/50/compjudgement.html>). This captures information on the volume of evidence, consistency of results, applicability to the NHS and generalisability.

## **8. Multiple Publications of the Same Data**

For studies with multiple publications, only the most up-to-date or complete data will be included in this review.

## **9. Data Synthesis**

Data synthesis will initially involve a tabular summary of study characteristics giving a descriptive overview of the findings. If two or more primary studies are considered comparable, data will then be pooled in a meta-analysis to determine the clinical effectiveness of HBOT. Studies will be considered comparable if they have drawn participants from comparable populations, used similar interventions and have comparable outcome measures. Heterogeneity between comparable studies will be assessed where appropriate.

## 10. Review Timetable

The key milestones for this project are noted in Table 3 below:

**Table 3 Review Timetable**

Data collection	July 2007-October 2007
Draft report production	October 2007-December 2007
Final report production	December 2007-February 2008
Distribution/publication	February 2008

## 11. Dissemination

The results of this review will be disseminated to the following groups:

- HBOT Project Team
- UK based NHS funded HBOT centres
- Chairs and Chief Executives of NHS boards in Scotland
- Directors of Planning
- Scottish Government Health Directorates
- Directors of Nursing
- Directors of Public Health
- Medical Directors
- Health and Community Care Committee
- Minister for Health and Social Services, National Assembly for Wales
- Minister for Health, Social Services and Public Safety, Northern Ireland Assembly

## Appendix 1

### Conditions by type (HBOT)

<b>Infection</b> Actinomycosis (Anaerobic bacterium) Aerobic septicemia/ (other than) clostricial Fungal infection HIV infection Lyme disease Meningitis Systemic aerobic infection Tetanus
<b>Respiratory</b> Acute thermal/chemical pulmonary damage Carbon monoxide poisoning / smoke inhalation Chemical poisoning Cyanide poisoning Decompression illness Pulmonary emphysema Lung transplantation
<b>Cardiology</b> Acute coronary syndrome Cardiogenic shock Coronary stenting Myocardial perfusion
<b>Neurology</b> Acute/chronic cerebrovascular insufficiency Acute cerebral odema (TBI – traumatic brain injury) Autism Cerebral palsy Closed head/spinal cord injury Facial palsy (Bell's) Intracranial abscess Migraine (other headaches) MS Nerve Block Non vascular causes of chronic brain syndrome Prophylaxis against neuropsychological impairment after CABG Reflex sympathetic dystrophy Senility - Dementia Stroke (hemorrhagic/ischemic)
<b>Pain</b> Fibromyalgia Post traumatic regional pain syndrome
<b>Dermatology</b> Actinic skin damage Chronic wounds – various etiology Cystic acne

<p>Lepromatous leprosy  Melasma  Necrotising arachnidism  Non diabetic ulcers (pressure ulcers/venous stasis ulcers)  Ophthalmologic diseases  Pyoderma gangrenosum  Skin burns  Skin flaps/grafts</p>
<p><b>Orthopaedic</b>  Arthritic disease  Bone grafts/fracture healing  Chronic refractory osteomyelitis  Osteoporosis</p>
<p><b>Haematology</b>  Acute air/gas embolism  Avascular necrosis  Blood loss/anemia</p>
<p><b>Oncology</b>  Bladder/neck, head, cervix neoplasms  Cancer  Carcinoma, cervix  Hemorrhagic cystitis after radiotherapy  Osteoradionecrosis (following maxillo facial surgery)  Post radiotherapy optic neuropathy  Radiation injuries</p>
<p><b>Gastric</b>  Crohn's disease  Opium poisoning  Pneumatosis cystoides intestinalis</p>
<p><b>Dental</b>  Dental implants (following irradiation)  Periodontitis</p>
<p><b>Surgery</b>  Liver (Post operative)  Organ transplantation  Reconstructive surgery</p>
<p><b>Wounds</b>  Acute peripheral arterial insufficiency  Acute traumatic peripheral  Chronic refractory osteomyelitis  Compromised skin grafts  Crush injuries/suturing of severed limbs  Gas gangrene  Lower wound extremities  Non healing diabetic ulcer  Osteoradionecrosis  Progressive necrotizing infections</p>

**Other**

Acute hydrogen sulfide poisoning

Arterial CO<sub>2</sub> embolism after laparoscopic surgery

Calciophylaxis

Felon (abscess on finger)

Frostbite

Hearing disorders (Sudden hearing loss/ Tinnitus/Trauma acoustic)

Hepatic necrosis

Infertility treatment

Interstitial cystitis

Intra abdominal abscess

Liquid nitrogen freeze injury

Livedoid vasculopathy

Malabsorption in a radiation damaged short bowel

Multiple branch retinal arteriolar occlusions (associated with smallpox vaccination)

Purtscher's retinopathy (induced by chest injury)

Severe blunt chest injuries

Sickle cell anemia

Sickle cell crisis/hematuria

Sports injuries (bony/soft tissue?)

Viral hepatitis

Spider bites

## Appendix 2

### Hyperbaric Oxygen Therapy Search Narrative

#### June 2007

Web search for [organisations](#) offering or researching HBOT (UK and international); [patient groups](#); [manufacturers](#).

#### 4 - 9 July 2007

##### Websites

Agency for Health Care Research and Quality (AHRQ) <http://www.ahrq.gov>  
Alberta Heritage Foundation for Medical Research <http://www.ahfmr.ab.ca/>  
Agence d'Évaluation des Technologies et de Modes d'intervention en Santé (AETMIS)  
<http://www.aetmis.gouv.qc.ca/site/home.phtml>  
Canadian Agency for Drugs and Technologies in Health <http://www.cadth.ca/>  
Canadian Medical Association <http://mdm.ca/cpgsnew/cpgs/index.asp>  
Centre for Clinical Effectiveness (Australia) <http://www.monash.edu.au/>  
Centers for Medicare and Medicaid Services <http://www.cms.hhs.gov/>  
CIGNA <http://www.cigna.com/index.html>  
Clinical Evidence <http://www.clinicalevidence.com/ceweb/index.jsp>  
ECRI <http://www.ecri.org/Pages/default.aspx>  
Health Technology Assessment <http://www.hta.nhsweb.nhs.uk/>  
Medical Service Advisory Committee – Australia <http://www.msac.gov.au/>  
NHS Centre for Reviews and Dissemination <http://www.york.ac.uk/inst/crd/index.htm>  
National Institute for Clinical Excellence (NICE) <http://www.nice.org.uk/>  
National Electronic Library for Health <http://www.york.ac.uk/inst/crd/index.htm>  
National Guideline Clearinghouse <http://www.guidelines.gov/index.asp>  
National Health and Medical Research Council (NHMRC)  
<http://www.nhmrc.gov.au/publications/index.htm>  
New Zealand Guidelines Group <http://www.nzgg.org.nz/>  
Swedish Council on Technology Assessment in Health Care (SBU)  
<http://www.sbu.se/www/index.asp>  
TRiP <http://www.tripdatabase.com/index.html>  
UpToDate <http://www.uptodate.com/>  
US National Institutes of Health <http://www.nih.gov/>

##### Scotland:

Chief Scientists Office (CSO) <http://www.sehd.scot.nhs.uk/cso/>  
Health Services Research Unit (HSRU) <http://www.abdn.ac.uk/hsru/>  
NHS Quality Improvement Scotland <http://www.nhshealthquality.org>  
Scottish Health on the Web (SHOW) <http://www.sehd.scot.nhs.uk/>  
Scottish Intercollegiate Guidelines Network (SIGN) <http://www.sign.ac.uk/>

##### Economics:

NHS EED (via CD)  
HEED <http://clarinet-nt.clarinet.co.uk/OHE/CnIsapi.dll?nuni=62450&usr=0&alias=OHE&uni=1&fld=X&Jump=password>

##### Ongoing research:

National Research Register <http://www.nrr.nhs.uk/>

Results saved at: [HBOT web results.doc](#)

#### 10 July 2007

**Database: Ovid MEDLINE(R) (mesz), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (prem)**

Search Strategy:

- 
- 1 Hyperbaric Oxygenation/
  - 2 hyperbar\$.tw.
  - 3 (chamber\$ adj2 (oxygen\$ or monoplace or multiplace or "atmosphere exposure")).tw.
  - 4 (HBO or HBOT or HDO or HDOT).tw.
  - 5 or/1-4
  - 6 limit 5 to yr="2006 - 2007"
  - 7 limit 6 to english language
  - 8 from 7 keep 1-551