CONFIDENTIAL

HOPON
(Hyperbaric Oxygen for the Prevention of Osteoradionecrosis):

A Randomised Controlled Trial of Hyperbaric Oxygen to prevent Osteoradionecrosis of the Irradiated Mandible.

Study co-sponsors:
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EudraCT number: 2007-006225-27
Protocol version: 9
Date: 11th January 2017

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1. List of Abbreviations and Definition of Terms

Abbreviation	Abbreviated term
AE	Adverse Event
ATA	Atmosphere Absolute Pressure
AUC	Area Under Curve
CC	Clinical Coordinator
CI	Chief Investigator
CRF	Case Report Form
CR-UK	Cancer Research United Kingdom
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Curriculum Vitae
DNA	Deoxyribonucleic Acid
EDTA	Ethylene-diamineteraacetic acid
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FSC	Feasibility Study Committee
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Gy	Dose of radiotherapy in Grays
HBO	Hyperbaric Oxygen
HN CSG	Head & Neck Cancer Clinical Studies Group
ICH	International Conference on Harmonisation
IDSMC	Independent Data and Safety Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiotherapy
ITT	Intention to Treat
IV	Intravenous
LCTU	Liverpool Cancer Trials Unit
LECMC	Liverpool Experimental Cancer Medicine Centre
LREC	Local Ethical Research Committee
MBS	Minor Bone Spicules
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
min	Minimum
ml	Millilitre
MRC	Medical Research Council
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NHS	National Health Service
NNT	Number Needed to Treat
NRES	National Research Ethics Service
OPT	Orthopantomogram

ORN	Osteoradionecrosis
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Coordinator
TSC	Trial Steering Committee
UK	United Kingdom
UoW	University of Washington
VAS	Visual Analogue Scale
WHO	World Health Organisation

2. Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Signature: _____ **Date:** 22 MAR 17

Prof Richard Shaw, Chief Investigator

Signature: _____ **Date:** 24 JAN 17

Signed on behalf of the University of Liverpool

Signature: _____ **Date:** 24/Mar/17

Signed on behalf of the Aintree University Hospitals NHS Foundation Trust

Signature: _____ **Date:** 31/3/17.

Professor J. Neoptolemos, Director of the Cancer Research UK Liverpool Cancer Trials Unit

This protocol has been approved by:

- The Chief Investigator
- The University of Liverpool
- Aintree University Hospitals NHS Foundation Trust
- The Director of the Cancer Research UK Liverpool Cancer Trials Unit

3. Protocol Statements

3.1. Compliance with Good Clinical Practice

This Study Protocol is designed to comply with the Guideline established by the International Conference on Harmonisation (ICH) on the topic Good Clinical Practice (GCP) and published by the European Agency for the Evaluation of Medicinal Products as "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95) (Approval 17 July 1996) as well as other relevant guidelines issued by ICH, primarily the efficacy, safety and ethical guidelines.

3.2. Registration of Study

This study will have National Research Ethics Service (NRES) approval and hold a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA). Each centre must undergo Site Specific Assessment by the relevant Local Ethical Research Committee (LREC) and must be granted Research and Development Approval from each Trust where the trial will be carried out.

4. Protocol Synopsis

Investigational Medicinal Product (IMP):	Hyperbaric Oxygen (HBO) Treatment
Title of Study/ Protocol Number:	A phase III randomised controlled study investigating Hyperbaric Oxygen to Prevent Osteoradionecrosis (ORN) of the Irradiated Mandible.
Chief Investigator:	Professor Richard Shaw
Number of Study Centres and Distribution:	19 centres within the UK, four centres internationally.
Study Period:	May 2010 until February 2018.
Main Objective(s):	To determine the benefit of HBO in the prevention of osteoradionecrosis (ORN) subsequent to a surgical procedure in the "at risk" irradiated mandible. Questions in a number of key areas will be addressed by this trial: 1. **Incidence** of ORN in at risk procedures without HBO – published rates vary between 0 and 30%. 2. **Outcome** of ORN cases without HBO. 3. **Benefit of HBO**: **a.** What proportion of the risk of ORN might be prevented by HBO treatment? **b.** If not totally prevented, is the severity affected i.e. the distribution amongst grades I/II/III different between HBO and non-HBO arms? 4. **Morbidity of HBO**: measurement of adverse events in treatment arm related to hyperbaric oxygen treatment 5. **Acceptability of Randomisation:** to determine if clinicians / patients consent to recruitment for a HBO randomised control trial.
Methodology:	This study is designed as a phase III randomised control multi-centre study.
Translational study:	The translational element of the trial will involve the collection and storage of blood samples and will aim to identify biomarkers of risk of developing ORN or response to HBO treatment. The sample collection for each patient in each arm of the study is as follows: Blood sample x 1 – 6 ml venous blood 6ml standard EDTA tube All samples will be sent via pre-labelled 1st class postage to Liverpool Experimental Cancer Medicine Centre

	(LECMC) Good Clinical Laboratory Practice (GCLP) compliant labs at the University of Liverpool where they will be received and managed by an ECMC laboratory technician.
Number of Patients to be Enrolled:	221
Duration of Treatment:	This trial has a run-in-period (of up to four weeks) before randomisation, where all volunteers attend the assessment centres for trial eligibility assessment, consent procedure and advice regarding management of their condition. During this time volunteers will be assessed to confirm potential suitability for hyperbaric oxygen therapy. Then patients will be randomised to either:

5. Ethics

5.1. Independent Ethics Committees (IEC)

The protocol and relevant amendments must be approved by/receive favourable opinion from National Research Ethics Service (NRES) and Medicines and Healthcare Products Regulatory Agency (MHRA). Each UK NHS centre must receive approval to participate in the trial from MREC, MHRA and the relevant NHS R&D department before carrying out trial related activities. Non-NHS centres must receive approval from the MHRA and undergo Site Specific Assessment by the relevant Local Ethical Research Committee (LREC) and written evidence of approval must be made available to the Central Trials Office, CR-UK Liverpool Cancer Trials Unit (LCTU) prior to enrolment of subjects. The study may only commence when approval is granted.

5.2. Ethical Conduct of the Trial

The trial will be conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

The study will be conducted in accordance with the EU Directive 2001/20/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 and the principles of Good Clinical Practice.

Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries within and outside the EU, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

This study may be terminated at the request of the Chief Investigator, Independent Data and Safety Monitoring Committee, Independent Ethics Committee or the MHRA if, during the course of the study, concerns about the safety of further dosing emerge.

The Chief Investigator will update the ethics committee of any new information related to the study drug when appropriate.

5.3. Patient Information and Informed Consent

The consent process must be carried out by a medically or dentally qualified member of the research team. All patients will receive written and verbal information concerning the nature of the study, the known side effects that they might expect and the risks. This information will emphasise that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and for any reason. All patients will be given opportunity to ask questions and will be given sufficient time to consider before consenting.

Both the clinician taking consent and the patient must personally sign and date the form. The original copy of the signed Consent Form will be retained by the Investigator in the Study File. A copy will also be filed in the subject's notes and a further copy of the signed Consent Form will be given to the subject.

The patient's signed and dated informed consent to participate in the trial must be obtained **prior** to any trial related procedure and randomisation being carried out.

6. Study Administrative Structure

6.1. Investigators and Trial Centres

6.1.1. Chief Investigator

The Chief Investigator is responsible for approval of the protocol, CRF and the clinical report on behalf of all study investigators.

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Honorary Consultant in Oral & Maxillofacial Surgery,
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6.1.2. Working Group

The HOPON Working Group will be responsible for day-to-day management of the study.

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As above

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Clinical Trial Coordinator

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6.1.3. Independent Safety Data Monitoring Committee

The Independent Safety Data Monitoring Committee (ISDMC) will be responsible for reviewing and assessing recruitment, interim monitoring of safety, trial conduct and external data. Further to this, they will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

The ISDMC consists of an independent Clinical Oncologist, Head and Neck Surgeon and an independent Statistician, also expert in the field of oncology as below:

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6.1.4. Trial Steering Committee

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The Trial Steering Committee (TSC) will be responsible for monitoring and supervising the progress of the trial, reviewing data from other studies, resolving issues related to trial design, trial conduct and reporting and considering the recommendations of the ISDMC.

6.1.5. Principal Investigators

Each participating Principal Investigator (PI) will be responsible for all aspects of trial conduct at his/her site as agreed to in the Research Site Agreement, to be signed prior to trial initiation. Each PI will also be provided with details on how and when to report Serious Adverse Events in their Investigator Site File.

6.1.6. Sub-Investigators

Each participating sub-investigator will be responsible for aspects of trial conduct delegated to him/her by the PI at their site as described in the delegation log, to be signed prior to trial procedures performed by the sub-investigator.

6.1.7. Co-Investigators

Participating co-investigators are researchers who will provide significant intellectual input into the research and will be responsible for the day to day running of some aspects of the trial conduct.

6.1.8. Sponsor

The study is co-sponsored by:

Aintree University Hospitals NHS
Foundation Trust
Research & Development
Room 2.06 Clinical Science Centre
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Longmoor Lane
Liverpool
L9 7AL

The University of Liverpool,
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6.1.9. Trial Statistician

The trial statistician will input into the development of the protocol and provide advice on trial design, randomisation procedure, Case Report Form (CRF) and database design. The trial statistician will plan and undertake all interim and final analyses of the trial data reporting results to the ISDMC and will prepare results for presentation and publications.

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7. Introduction and Rationale

Background

The most feared complication of radiotherapy for head and neck cancer is osteoradionecrosis (ORN) of the jaws. ORN describes the process where irradiated bone undergoes necrosis and becomes exposed through the investing soft tissues for a period of at least 3 months. The most important risk factor for ORN is surgical trauma, commonly dental extractions in an irradiated jaw, but ORN can also occur spontaneously. ORN is painful and debilitating, sometimes requiring surgical resection of the jaw and/or hyperbaric oxygen (HBO) treatments. The morbidity and mortality of ORN is significant and treatment outcomes often unsatisfactory. As such, much attention has been given to methods of prevention. These include pre-radiotherapy extraction of teeth and the use of HBO treatments or prophylactic antibiotics for post-radiotherapy extractions.

The overall incidence of ORN among post-radiotherapy patients is not certain but may have declined[3] with improvement of radiotherapy techniques in recent decades. However the most recent changes in delivery of radiotherapy, in particular the rise in popularity of organ preservation, concomitant chemoradiotherapy and IMRT (intensity modulated radiotherapy) might reasonably be expected to increase the rate of ORN in the future.

The dose of radiotherapy is an important risk factor for the development of ORN. Most cases of ORN occur after doses >60 Gy and few cases occur after doses <50Gy. The risk of ORN is considered greater with post- than with pre- radiotherapy extractions. The incidence of ORN is higher in the posterior mandible compared with the maxilla or anterior mandible which is attributed to its relatively poor blood supply. Alcohol or tobacco use, although common in head and neck cancer patients, does not seem to be a direct cause of osteoradionecrosis. Poor dental health before radiotherapy may cause later ORN and clearly there is a case for thorough dental inspection and treatment prior to radiotherapy. This is not always achieved and also post-radiation oral changes often cause serious deterioration in dental health. Post radiation extractions should be performed atraumatically and antibiotics are commonly prescribed[4.]

There have only been limited studies of prophylactic HBO. In a randomised, prospective study[5], showed a significantly lower incidence of ORN after post radiotherapy dental extractions in the HBO group when compared with the control group. There were 2 cases of ORN in 37 patients (5.4%) receiving HBO undergoing 156 extractions, compared with 11 cases in 37 patients (29.9%) undergoing 135 extractions receiving prophylactic penicillin, resulting in a number needed to treat (NNT) of 4. This single trial was carried out within one US unit and was unblinded. Vudiniabola *et al*[6] showed that of 29 patients who received pre-extraction HBO, 1 (3.4%) developed ORN; and of 7 patients who did not receive HBO, 1 (14.3%) developed ORN. On the basis of these two small studies, many dentists and surgeons have prescribed prophylactic HBO to prevent ORN in post radiotherapy extraction patients. Prophylactic HBO therapy has become the "treatment of choice"[7]; the "optimum management"[8] for the prevention of ORN.

Hyperbaric oxygen therapy is a time-consuming and relatively costly process (approx £3000 per course in Merseyside for NHS patients, this excluding patient costs such as transport & loss of income). The typical protocol calls for 30 hours of preoperative treatment in 20 90-minute sessions in a hyperbaric chamber, followed by 15 hours of postoperative treatment in 10 90-minute sessions. A doctor, medical assistant and technical staff, are required for each session. There are risks associated with HBO therapy. One study of 90 HBO patients recorded serious adverse events, including seizure (3.4%), stroke (1.1%), and myocardial infarction (1.1%)[9]. There were also cases of eustachian tube dysfunction requiring

myringotomy (2.2%). The overall incidence of complications of HBO was 7.8%. Subsequent series have, however, reported much lower complication rates and this impression has been confirmed by more reassuring safety data from the British Hyperbaric Association. The most comprehensive recent review[10] cites 33 research papers. This review estimates the risks as temporary visual problems "common", Eustachian tube problems 2%, claustrophobia 2%, seizure <0.01%, and MI and stroke are not considered to be risks as such. There is a theoretical risk of decompression sickness if decompression occurs uncontrollably and a risk of explosion both from the oxygen-rich environment of the hyperbaric chamber and the pressure of the chamber itself.

In addition to the potential for adverse events associated with HBO, retrospective evidence offers contradictory data regarding any protective benefits. Sulaiman et al[11] review a series of 180 consecutive dental extractions in a 3 year period amongst the irradiated population of Memorial Sloan-Kettering without the use of HBO. They report only 4 cases of ORN (2.2%), although it is important to note that the favourable socioeconomic profile and oral hygiene / compliance of that particular population is likely to be atypical of the general head and neck squamous cell carcinoma population. A simple pooling performed by Wahl[12] of 8 published retrospective studies of dental extractions without HBO from 1986-2005 (including Sulaiman) finds 16 cases of ORN from 461 extractions (3.5%), advising that prophylactic HBO should be reconsidered.

A postal questionnaire[13] of UK practice reveals that, in the management of "at risk" extraction of a lower molar in an irradiated mandible, 33% "never", 41% "sometimes" and 26% "usually" / "always" prescribe prophylactic HBO. This highlights the current state of equipoise in the UK. A questionnaires of attitude to RCTs for HBO[14] revealed that 93% of responders would wish to recruit such patients into a NCRI/Cancer Research UK backed trial.

With regard to implant placement, the case for HBO is made both on the basis of ORN and a potential beneficial effect on implant survival. A retrospective series[15] of 172 osseointegrated implants placed in 38 irradiated patients was performed. Implant loss was not influenced by HBO (HBO:19% vs No HBO:18%). Potential confounding variables were explored but were not biased between the groups. ORN was seen at a frequency of 6% but only occurred in patients treated with HBO. Schoen (*Oral Oncol.* 2006 Sep 21) reported on 26 similar patients, 13 of whom received HBO. Implant loss was actually higher in the HBO group (14.8% vs 6.1%) with one case of ORN occurring in the HBO group. In contrast, Granstrom[16] reported HBO significantly improved implant survival in a case-control study of irradiated bone from 34 of 43 implants lost to 5 of 42 lost (P =0.008). Further work by Granstrom[17] reinforced these earlier data finding that treatment with HBO reduced the implant failure rate.

There has also been considerable previous interest in a RCT for the treatment of established ORN using HBO within the National Cancer Research Institute (NCRI) Head & Neck Clinical Study Group (NCRI HN CSG). The considerable difficulties in trial design have been emphasised by the RCT published by Annane et al[18]. This study is notable for its double blind design, controversially using "sham" hyperbaric oxygen as placebo. The data appear to show that at least 75% of the treatment group failed to receive the protocol minimum 30 treatments. At one year, the recovery in the HBO arm was 19.3% and 32.4% in the placebo arm. The fact that the trial ended early under the protocol stopping rules must question the value of therapeutic HBO for established ORN. Many have questioned the relevance of this study in attempting to use HBO alone: Marx had suggested HBO as an adjunct to appropriate surgery. In closing the trial, one might assume that the issue of HBO in ORN had been settled. In the UK, however, considerable debate ensued, both published[19] and within the NCRI HN CSG. It was felt that this study highlighted the need for adequately funded, robust, randomised trials of HBO in the UK backed by the NCRI.

Rationale for the study

Following discussion within the NCRI HN CSG, it was apparent that the area of greatest polarisation regarding treatment protocols, but also agreement as to a satisfactory trial design, was in the area of prophylactic HBO. A randomised trial in the prophylactic use for all indications was conceived i.e. dental extractions, implant placement & other forms of surgery in the at risk jaw. Unfortunately, hyperbaric oxygen protocols have evolved with some differences around the UK. An early assurance has been gained from all HBO chambers that a protocol consistent with Marx's original protocol based around a version of Royal Navy Therapeutic table no. 66 which will be uniformly applied in the trial. A Cancer Research UK Feasibility Study Committee (FSC) application was thus developed. The original FSC study has now been extended into a full phase III Clinical Trials Awards and Advisory Committee (CTAAC) application. This phase III trial has been designed to incorporate the data generated by the pilot. An appropriate statistical adjustment (such as Fisher's combination test) would be used to preserve the overall type I error rate when combining the data across the two phases.

The clinical review period is one year in order to detect any differences in the severity and course of osteoradionecrosis encountered in each arm. This allows the rate of implant retention to be more realistically measured where appropriate.

The health economics of HBO are also pertinent. HBO costs around £3000-£6000 per treatment course in the UK and currently this expense is being actively questioned by NHS funding bodies in the absence of adequate data. A detailed cost analysis will be generated by this phase III trial. This will weigh the extra expense of treating excess ORN cases with that of extending HBO more widely in the preventative setting.

8. Study Objectives

Questions in a number of key areas are addressed by this trial:

1. **Incidence of ORN:** what is the incidence of ORN following 'at risk' procedures, and how is this affected by the use of prophylactic HBO?
2. **Outcome of ORN**: what proportion of ORN cases progress to the most serious outcomes, and how is this influenced by the use of prophylactic HBO?
3. **Morbidity of HBO**: measurement of adverse events in treatment arm related to HBO therapy.
4. **Cost effectiveness**: what is the financial justification for prophylactic HBO in this setting?
5. **Oral rehabilitation:** how is osseointegrated implant retention affected by HBO independent of any effect on the incidence if ORN?
6. **Late follow up of MBS (Minor Bone Spicules)** to assess risk of further deterioration for patients with MBS (see Appendix 11)
7. **Late follow up of implant survival:** How many implants were lost since completing the HOPON assessments? (See Appendix 12).

8.1. Outcome Measures

8.1.1. Primary Outcome:

The presence of osteoradionecrosis at 6 months after surgery defined according to the Chief Investigator's revised criteria (see appendix 9), as determined by blinded central review of Clinical photograph, Radiography and PI assessment (see algorithm, appendix 10).

8.1.2. Secondary Outcomes:

1. The diagnosis of osteoradionecrosis at 3 and 12 months (in the same way as the 6 month outcome)
2. Severity of cases of diagnosed osteoradionecrosis, according to Notani grade
3. Pain: patient questionnaire at baseline, 3, 6 and 12 months
4. Quality of life (QoL): following randomisation, and at 3, 6 and 12 months following surgery (as determined by a modified University of Washington Head and Neck QoL questionnaire - Appendix 6)
5. Implant survival and outcome of MBS

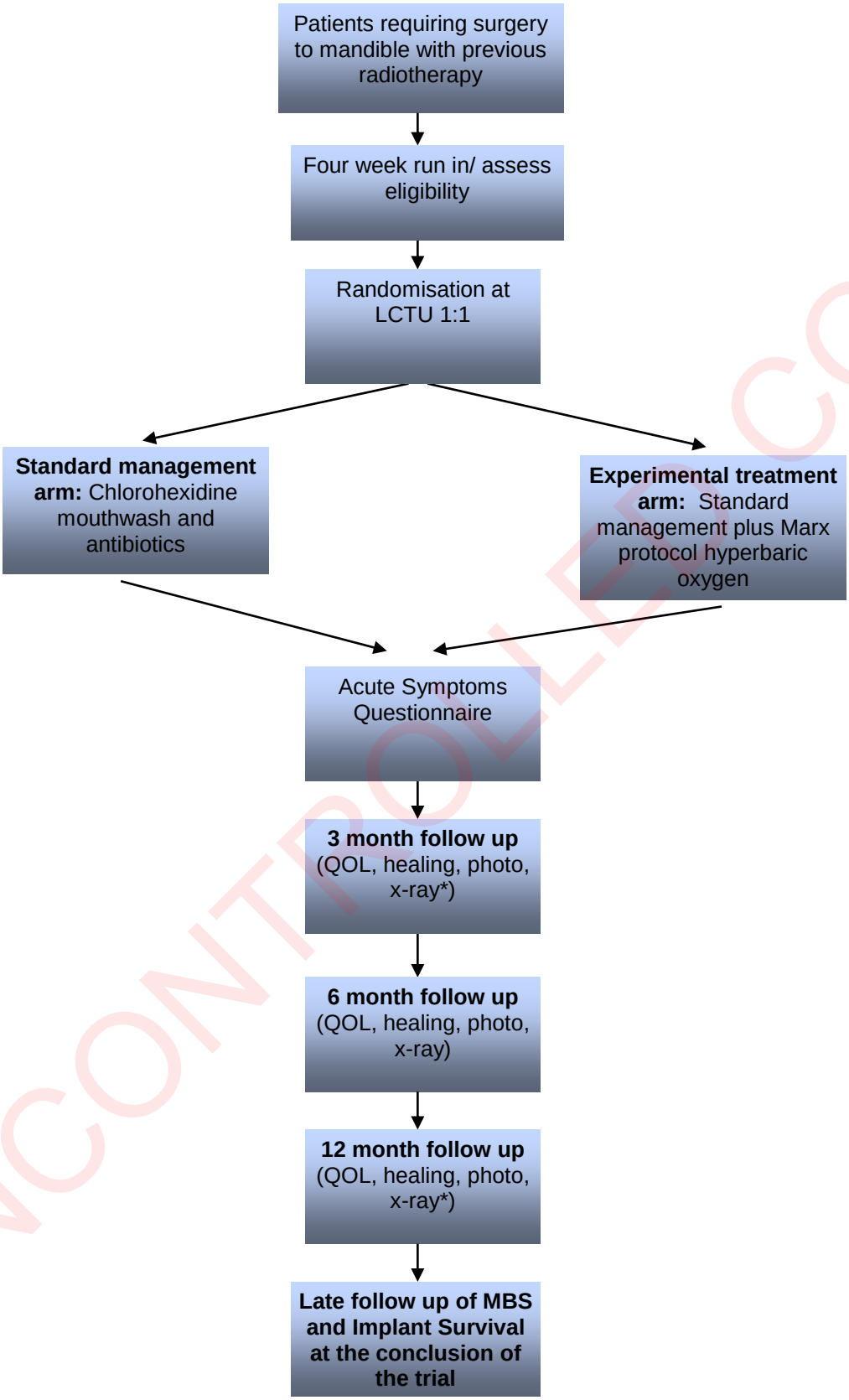
8.1.3. Safety Outcomes:

1. Adverse events in HBO arm related to hyperbaric oxygen treatment
2. The number and proportion of patients with hospital admissions, operations and complications (e.g. major bleeding, sepsis or mortality) occurring within 12 months post-surgery.
3. New Diagnosis of cancer, either recurrent or new site within 12 months following surgery

9. Investigational Plan

9.1. Study Design

9.1.1. Overall Design



* OPT at 3 and 12 months if no mucosal healing

9.1.2. Arm 1: Standard management[19]:

1. Pre- and post- operative chlorohexidine[1] mouthwash 0.2% – use 10ml (i.e. one capful) washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively.
   [1a]In case of chlorohexidine allergy use warm salt mouthwash at 1 teaspoon per cup of warm water.

2. Oral antibiotics (amoxicillin[2] 3g oral 1 hour pre-operatively (or 1g intravenously) and 250mg tds x 5 days post-operatively
   [2a]in penicillin allergy: 600mg oral clindamycin (orally either 600mg tablet (or same dose of 75mg/5ml suspension if tablets not tolerated) 1 hour pre-operatively or intravenously 600mg at time of surgery) 1 hour pre-operatively and 200mg metronidazole (patients should be warned of interaction between alcohol and metronidazole) tds x 5 days post-operatively.

3. Minimally traumatic surgical technique

9.1.3. Arm 2: Standard management plus HBO[1]

Patients will undergo 20 HBO treatments prior to surgery followed by a further 10 HBO treatments. See section 10.4. Administration of Investigational Products.

9.2. Time Schedule

Planned start date of phase III May 2010.
Planned end date of phase III: February 2018.

9.3. Criteria for Patient Selection

9.3.1. Inclusion Criteria

1. Age > 18 years
2. Prior history of external beam radiotherapy (dose > 50Gy) to mandible or prior history of brachytherapy with equivalent radiation dose as above.
3. No evidence of cancer recurrence
   Patients with previous head and neck cancer are at risk of further malignancy. Care should be taken to exclude this possibility with particular regard to:

i. Local, regional or distant recurrence of originally treated tumour
ii. Second primary tumour in head and neck region
iii. Second primary tumour outside the head and neck (e.g. lung)

Careful clinical examination by a head and neck oncology specialist to exclude malignancy, blood biochemistry, head &neck / thoracic imaging and flexible nasendoscopy should be completed in keeping with local protocols and appropriate to the site and stage of the original tumour and disease free interval

4. Condition requiring surgery to mandible (commonest examples but not limited to: dental extraction, implant placement, surgical tooth, cyst or osteosynthesis plate removal)
5. Patient has read and understood information leaflet and is willing to be randomised.
6. Patient competent to consent and psychologically / physically fit for HBO.

9.3.2. Exclusion Criteria

1. Known contraindications to HBO

   a. Lung disease: Severe chronic obstructive airways disease; bullous lung disease, acute or chronic pulmonary infection; uncontrolled asthma, untreated pneumothorax
   b. Middle ear disease (such as previous middle ear operations, eustachian tube dysfunction or recurrent attacks of vertigo) that proves refractory to simple interventions such as grommet insertion
2. Prior hyperbaric oxygen therapy
3. Prior diagnosis of osteoradionecrosis of the mandible
4. Previous surgery for osteoradionecrosis
5. Any history of systemic bisphosphonate therapy, pentoxyphylline or tocopherol.
6. Pregnancy

   The use of hyperbaric oxygen during pregnancy is controversial and has been carried out infrequently - in the case where pregnancy occurs, urgent advice should be sought from the trials unit.

9.3.3. Patient Screening Log

Screening will be performed upon a patient's possible eligibility for the study and must be documented on the "Patient Screening/Randomisation Log". Screening is defined as beginning with the issuing of the patient information and consent forms to the patient.

9.3.4. Patient monitoring and criteria for withdrawal from treatment

1. Patients will be assessed for physical and psychological fitness prior to treatment by experienced and appropriate hyperbaric medical staff.
2. All patients will be assessed daily for intercurrent illness prior to commencing the HBO therapy by an appropriate medical professional. Qualified appropriate attendants will be present during each HBO session.
3. Patients who develop intercurrent upper respiratory infections during the treatment course who are unable to equalise the pressure in the middle ear will be offered:
   a. Decongestant therapy (pseudoephedrine hydrochloride, 60 mg, 8 hourly)
   b. If, despite this equalisation, the patient is sufficiently impaired to preclude HBO treatment for 3 consecutive days, he/she will be offered elective myringotomy / grommet insertion or withdrawal from the study.
4. Where HBO sessions have been missed (from either 20 pre-op HBO sessions or 10 post-op HBO sessions), additional treatments will be added to the end of the course to compensate and patients will continue to be followed up as per protocol.
5. If the patient withdraws from the trial prior to treatment commencing, the patient will not be followed-up for measurement of all endpoints.

Therefore, patients may withdraw from randomised treatment for any of the following reasons:

1. Patient decision to discontinue treatment.
2. Intolerable adverse effects as judged by the investigator or the patient as described above.

If a patient is withdrawn from randomised treatment the End of Study CRF will be completed to capture date and reason(s) for treatment withdrawal. Following withdrawal from randomised treatment, patients will be treated according to local practice and will continue to be followed up as per the trial protocol unless the patient withdraws consent.

10. Investigational Products

10.1. Investigational Medicinal Product Description

10.1.1. Hyperbaric oxygen

The manufacturer and/ or supplier of the oxygen to be used will be dependent on standard practise within each Hyperbaric Unit.

10.2. Packaging and Labelling of Investigational Products

The investigational products will not be subject to any special packaging or labelling.

10.3. Preparation of Investigational Products

This will be in accordance with the standard practise at each Hyperbaric Unit.

10.4. Administration of Investigational Products

Treatment will be administered based around a version of the Royal Navy Therapeutic Table 66 - Repeat Hyperbaric Oxygen Therapy.

The patient is pressurised to 2.4 ATA at a tolerable rate. The patient is decompressed after 100% oxygen has been breathed at 2.4 ATA for a total of between 80 and 90 minutes. Air breaks while at 2.4 ATA may be introduced routinely or as required. The decompression is scheduled to control satisfactorily any risk to the patient and, if present, to the in-chamber attendant. Patients should breathe oxygen at an inspired partial pressure greater than 2.0 ATA for no more than 110 minutes during each individual treatment.

10.5 Non Investigational Medicinal Product Descriptions

Chlorohexidine Mouthwash:

An antibacterial solution inhibiting dental plaque formation and an aid in the treatment and prevention of gingivitis, maintaining oral hygiene, particularly in situations where toothbrushing is difficult to carry out. It is valuable in the management of aphtous ulceration and oral candidal infections and can be used as an adjuvant treatment for minor infections of the throat.

Is prescribed from hospital stock and will not be subject to any HOPON trial labelling.

Formulation: Clear colourless Oromucosal solution.

Packaging, storage and stability: Please refer to the SmPC.

Supplier's name: Local hospital pharmacy

Active ingredient name/dose: Chlorohexidine - Pre and post-operative chlorohexidine mouthwash 0.2% - use 10ml (i.e. one capful) washed around the mouth for around one minute and then spat out, three times daily for 5 days post-operatively.

Amoxicillin:

Amoxicillin is a moderate-spectrum, bacteriolytic, β-lactam antibiotic used to treat bacterial infections caused by susceptible microorganisms.

Is prescribed from hospital stock and will not be subject to any HOPON trial labelling.

Formulation: White to off-white granular powder filled in hard gelatine capsule shells size '2'. Scarlet colour cap, buff colour body printed with 'AMOXY' on cap and '250' on body.

Packaging, storage and stability: Please refer to the SmPC

Supplier's name: Local hospital pharmacy

Active ingredient name/dose: Amoxicillin - 3g oral one hour pre-operatively (or 1g intravenously) and 250mg tds x five days post-operatively.

10.6 Treatment Assignment (Randomisation)

Patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be randomised by the randomisation centre at the Cancer Research UK Liverpool Cancer Trials Unit (LCTU).

To ensure essential entry criteria are fulfilled, randomisation can only occur following the completion and forwarding of the trial registration documents by the investigators:

- Inclusion and Exclusion Criteria
- Randomisation Form
- Consent form

The registration documents should be faxed to the LCTU. Details of the relevant fax number for randomisation are shown on the registration CRF.

Personnel from the LCTU will review the randomisation documents, confirm eligibility and record essential demographic data before allocating a unique "trial number" for each patient. The patient will then be randomised and the LCTU will contact the site by fax to confirm the treatment allocation.

Once the fax confirming randomised treatment allocation has been received by the investigator, the Investigator should add the patient's trial number and treatment allocation details to the Screening/Randomisation Log.

The subject number is to be filled in on each copy of each page on the CRF used for that patient.

10.7 Randomisation Code List

The randomisation code list will be generated by the LCTU trial statistician by means of the Stata user-written package ralloc using block randomisation with randomly varying block length. Randomisation will be stratified by centre with allocation to treatment arms in the ratio 1:1.

Central allocation, by fax, will be undertaken by the LCTU. This will allow the patient eligibility criteria to be scrutinised and will minimise the potential for selection bias by concealing the randomisation code list from all recruiting clinicians and trial participants.

10.8 Accountability for hyperbaric oxygen treatment

The Investigator is fully responsible for the delivery of hyperbaric oxygen at each site.

10.9 Treatment Compliance

Hyperbaric oxygen will be given within the limitations previously specified in 9.3.4. The maximum treatment break between the initial 20 dives and post-operative 10 dives is 3 weeks. Patients not recommencing their HBO in the specified period will continue with their normal follow-up measurements but this protocol violation will also be recorded on the CRF.

11. Study Procedures and Assessments

Table 4. Schematic Diagram

Procedure	Following randomisation	At time of Surgery	3 months following surgery	6 months following surgery	12 months following surgery	End of trial (casenote review of MBS and implant survival)
Orthopantomogram	X		Only in cases where ORN present	X	Only in cases where ORN present	
Clinical Photograph	X		X	X	X	
Clinical Assessment	X		X	X	X	
Pain Assessment Chart (Appendix 7)	X		X	X	X	
UoW QOL v4 Questionnaire (modified) (Appendix 6)	X		X	X	X	
Assessment of suitability for HBO	X					
Acute symptoms questionnaire (Appendix 8)		X				
Blood Sample		X (or at any time after randomisation if not at the time of surgery)				
Assessment of severity of diagnosed osteoradionecrosis (where appropriate)			X	X	X	Only in cases where patients have received ongoing clinical review since completing HOPON assessments

Assessment of implants (where appropriate)			X	X	X	Only in cases where patients have received ongoing clinical review since completing HOPON assessments

12. Safety Reporting

12.1. Definitions:

12.1.1. Adverse Event:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs include the following:

- All suspected adverse medication reactions,
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents. *Note that if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate AEs.*

Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).

12.1.2. Serious Adverse Event (SAE)

Severity of any AE will be graded according to the World Health Organisation (WHO) toxicity criteria/National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3, where applicable.

For each episode, the highest severity grade attained should be reported.

If an AE occurs that is not listed in the WHO/CTCAE, the Investigator will evaluate its severity using the definitions in Table 5.

Table 5. Definition of Severity of Adverse Events

Mild	Grade 1 - Does not interfere with subject's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with subject's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with subject's usual function (incapacity to work or to do usual activities [unacceptable])
Life Threatening	Grade 4 - Results in risk of death, organ damage, or permanent disability (unacceptable)
Death	Grade 5 – Results in death (unacceptable)

Note the distinction between the seriousness and the intensity of an AE. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed below:

- results in death or is life-threatening*
- requires hospitalisation or prolongation of hospitalisation
- results in persistent or significant disability or incapacity
- results in congenital anomaly

* The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Serious adverse events will be followed-up until progressive disease or death.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

12.1.3. Serious Adverse Reaction (SAR)

SAE suspected to have been caused by a trial drug

12.1.4. Suspected Unexpected SAR (SUSAR)

Any suspected adverse reactions related to an IMP that are both unexpected and serious.

12.2. Assessment of Adverse Events

Seriousness

This assessment is to be undertaken by the clinician responsible for the patient.

Causality (relationship to study drug)

This assessment is to be undertaken by the clinician responsible for the patient.

Definitely, probably or possibly related = adverse reaction.

Unlikely or not related = other adverse event.

Clinical assessment: Chief Investigator and the LCTU may give their own assessment but cannot over-ride that of the clinician.

The Chief Investigator will be responsible for reviewing all SAEs.

Expectedness

Not included (or more severe than) reactions listed in the applicable product information in the Summary of Product Characteristics (SMPC, data sheet) for an authorised product.

12.3. Reporting

12.3.1. Adverse Events

AEs that occur within 28 days following the last dose of trial treatment will be recorded in the CRF and are not part of the expedited reporting procedure.

All completed AE forms must be signed off by a medically or dentally qualified member of the research team as listed on the delegation log.

12.3.2. Serious Adverse Event Reporting

Investigators **MUST REPORT ALL SERIOUS ADVERSE EVENTS (SAEs),** including disease related as well as treatment related events that occur within 28 days following the last dose of trial treatment. New diagnosis of cancer or recurrence of cancer will be reported as an SAE for the duration of the patient's involvement in the study up to 12 months follow up after surgery.

All completed SAE forms must be signed off by a medically or dentally qualified member of the research team as listed on the delegation log.

SAEs must be reported within **24 hours** of sites becoming aware of them by faxing a completed **SERIOUS ADVERSE EVENT FORM** (Appendix 4) to the LCTU, Fax: 00 44 151 794 8930/8931. Sites will receive an acknowledgement fax within two hours to confirm the SAE has been received at the LCTU. If this acknowledgement is not received, please contact the LCTU.

The Investigator must institute appropriate therapeutic action and follow-up measures in accordance with Good Medical Practice but should notify the study co-ordinator of such actions.

The minimum dataset required for a preliminary report should include the following.

Page 1

- Research subject trial number and initials.
- Date of onset of event
- Brief description of event and CTC or severity grade
- Causality relationship
- Dated signature of investigator/co-investigator and clearly printed name

Page 2

- Date of last administration of study drug.
- Causality relationship
- Dated signature of investigator/co-investigator and clearly printed name

The Chief Investigator and the LCTU will provide an annual **a Development Safety Update Report** to the UK Competent Authority and Ethical Committee.

12.3.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

The minimum data required for initial reporting is:

- The suspected Investigational Medicinal Product (IMP)
- An identifiable subject
- An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
- An identifiable reporting source

The Chief Investigator and the LCTU will ensure that all SUSARs are reported to Competent Authorities and Ethical Committees.

- Fatal or life threatening SUSARs < 7 days after receiving the information
- All other SUSARs <15 days after receiving the information

The Chief Investigator and the LCTU will **inform all investigators of SUSARs** as they occur.

Expedited Reporting

- MHRA Clinical Trials Unit
- Relevant Ethics Committee.

12.3.4. Annual Reporting to MHRA and MREC

The required details will include:

- Line listing of all SARs, including SUSARs
- Aggregate table of all SARs, including SUSARs
- Summary of safety of the subjects in the trial
- Summary of published literature relevant to safety

Reference Safety Information

The reference safety information (RSI) for the IMP used in this trial is as follows:

- Medicinsk Oxygen AGA 100%, Medicinal Gas, Compressed: Section 4 of the Summary of Product Characteristics

The current version of the SmPC can be downloaded from the following website address:
https://lakemedelsverket.se/LMF/?q=oxygen

RSI documents applicable to the trial and current reporting period are available from the HOPON Trial Coordinator.

13. Quality Assurance/Audit

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Standard Operating Procedures (SOPs) are implemented to ensure that clinical trials are conducted in compliance with regulatory requirements and Good Clinical Practice (GCP). Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The HOPON trial Investigational sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities or IEC. Such audits/inspections may take place at any site where trial related activity is taking place (the Sponsor's site(s), LCTU or at any investigator's site including laboratories, pharmacies etc.)

The site staff should assist in all aspects of audit/inspection and be fully cognisant of the LCTU communication strategy for multicentre trials.

13.1. Quality control

Signed CVs and GCP certificates of all clinicians and research staff will be submitted to the LCTU prior to the site opening to recruitment for the HOPON trial. This is in line with established LCTU systems and processes for ensuring the highest standard of governance for clinical trials. The Green Light Checklist in place at the LCTU means that no patients can be recruited at a particular trial site without the green light being given. It ensures that all relevant approvals, contracts/agreements and essential documents are in place before any patients are recruited to the trial.

The Trial Co-ordinator maintains a communication strategy with all centres and will signpost any centre requiring clarification in the procedure. As part of the HOPON working group, investigators attend regular Steering Committee meetings which include continuous review and discussion. Advice is available to all investigators from experts in the field at any point during the trial. All new centres recruiting patients will have the first sets of images audited, and then 10% thereafter. These will be scored as adequate / inadequate to assess the presence of ORN by an appropriate panel assembled, viewed independently by three qualified clinicians, on reviewing anonymised images. Any centres submitting photographs of inadequate standard will be offered advice and training.

13.2. Risk assessment

In accordance with the LCTU Standard Operating Procedure, a risk assessment has been completed in partnership with:

- Representatives
- Trial Sponsors
- Trial Co-ordinator
- Trial Statistician
- LCTU Operational Director

In conducting this risk assessment, the contributors consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.
The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:
Score ≤ 33% = Low risk
Score ≥ 34 to ≤67% = Moderate risk
Score ≥ 68 to ≤ 100% = High Risk

The LCTU will review recruitment rates, withdrawals and losses to follow-up, and identified problems will be reviewed by the trial working party and remedial action taken as necessary. Data submitted to the database will be centrally monitored by the LCTU to ensure that data collected are consistent with adherence to the trial protocol. Data will be checked for unusual values (range checks) and checked for consistency with participants over time. Discrepancies that have been raised can be queried, and resolved at the LCTU, or by contact with the individual site. A complete log of discrepancies and data amendments, including the date of each change and the person who changed it will be kept.

14. Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Paper CRFs will be labelled with patient initials and unique trial registration number. Consent forms sent to the LCTU as part of the randomisation process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Such information will be stored within the patient folders in secure, locked cabinets.

15. Case Report Forms and Data Handling

15.1. Case Report Forms

LCTU will provide the investigator with duplicate NCR Case Report Forms (CRF). A separate CRF will be used for each patient enrolled and will include a carbon copy of each CRF page for the investigator to

keep. The original copy will be sent to the LCTU. The CRFs have been written following the LCTU Standard Operating Procedures.

The CRFs must be kept on file by the investigator and maintained in an up-to-date condition at all times. The investigator, or a delegated member of the research team authorised by the investigator, must sign and date all sections of CRFs used, and also any specific forms used, as indicated on the form.

Any correction(s) will be made by the investigator or designated staff on the forms before the originals are removed from the CRF, so that the corrections will appear on the investigator's copy. All such corrections must be initialled and dated by the investigator or designated staff and the reason for the correction stated unless obvious. Any corrections needed after collection of the original Forms will be by use of Data Queries. Trial sites must make a copy of any completed data query form they complete and keep these copies with the CRFs for the relevant trial patient.

Only medically qualified (sub-) investigators or delegated staff (who have been approved and signed off by the investigator on the delegation log) can sign off data on clinical assessments/safety.

15.2. Data Handling

Data recorded on the CRFs will be entered into the LCTU MACRO database.

Systematic data validation is performed by the LCTU Trial Coordinator and the Trial Statistician to obtain a clean data base prior to the statistical analysis. The HOPON Data Validation Plan will be executed following the LCTU SOPs for data management. A full data Validation Report will be produced by the Trial Coordinator and any issued resolved.

Data will be processed in accordance with the general terms and conditions of the authorisation from the 'Information Commissioner's Office' to LCTU, as required, according to national legislation implementing the Data Protection Directive; 95/46/EC.

16. Protocol Amendments

Deviations from the protocol should not occur and protocol exceptions will not be granted.

Neither the investigator(s) nor LCTU will change the Study Protocol without the written agreement between LCTU and the Chief Investigator. Any significant modification would require approval/favourable opinion by the appropriate Regulatory Authority and IEC.

Protocol Amendments become effective when written approval has been provided by the Chief Investigator, the Director of LCTU, and approval/favourable opinion from Regulatory Authorities and/or IEC has been obtained as required.

17. Agreements

17.1. Research Site Agreement

Before the initiation of the clinical trial at a site, the arrangements between LCTU and investigator/institution as laid down in the Research Site Agreement must be confirmed in writing.

Completion of Trial

17.2. Trial Completion Procedures

Investigators will be informed when patient recruitment is to cease.

Trial enrolment may be stopped at a site when the total requested number of subjects for the trial has been obtained.

The ISDMC may recommend to the TSC that the trial be stopped prematurely. Such premature termination/suspension of trial will be notified to Regulatory Authorities and IECs as required.

17.3. Archiving of Trial Documents

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File, until the LCTU informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTU undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

At present according to ICH Guideline:
Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. (ICH E6, 4.9.5)

18. Statistical Considerations

18.1. Introduction

This is a multicentre, parallel group, individually randomised superiority trial in a secondary/ tertiary referral care setting.

18.2. Blinding

The trial is open-labelled due to the different schedules of treatment administration. However, the primary outcome, the diagnosis of osteoradionecrosis at 6 months i.e. incomplete mucosal healing and presence of necrotic bone, will be assessed, via clinical photographs and radiographs by a blinded observer panel to reduce bias being introduced by knowledge of treatment allocation.

18.3. Missing Data

Missing data will be closely monitored during the trial and its occurrence will be minimised by adopting the following strategy:

(i) A general CRF completion guideline document will be provided to each site and staff will be instructed to complete the CRF in accordance with this document.

(ii) A separate data management plan that will include instructions for checking missing data will be developed to give a detailed account of the procedures for data management.

(iii) Data from the CRF will be entered onto a MACRO database with extensive data validation checks alerting all missing data to be queried.

(iv) Central statistical data monitoring will summarise missing or inconsistent data periodically.

(v) If missing data occurs consistently for particular clinicians or sites, this will be raised as a training issue.

Where missing data remain, as much information as possible will be collected about the reasons for missing data.

18.4. Sample Size

Assuming an ORN rate of 5% in the HBO arm at 6m following surgery, 103 patients per group will provide 80% power to detect a hazard ratio of 0.25 or odds ratio of 0.23 (equivalent to detecting an absolute difference of 13.5% between treatment arms) at the 5% two-sided significance level. After allowance for 6.8% drop out, 221 need to be recruited.

18.5. Patient Accrual

Recruitment is planned at 30 patients per annum until the end of the study, which in addition to 50 patients recruited from the FSC constitutes 221 in total. The total duration of the study is therefore expected to be approximately 9 years (including the feasibility study) in order to recruit the target number of patients and for all endpoints to be assessed. The trial will close after the last study follow up visit or end of study form has been completed by all patients.

18.6. Statistical Analysis Plan

The trigger for the final analysis will be when all participating patients who have received surgery have completed 12 months of post-surgery follow-up, unless the trial is terminated earlier for reasons of safety, efficacy or futility.

The trial will be analysed using Stata v13 or higher, and reported following the 'CONSORT' guidelines.

Categorical variables will be summarised as frequencies and percentages (with 95% confidence intervals) , continuous variables by mean, Standard Deviation, median and interquartile range. All hypothesis tests will be undertaken using a 5% two-sided significance level.

Because the primary analysis is based on patients who actually received surgery, demographic and clinical factors for the HBO and control groups will be presented both "as randomised" and also "as receiving surgery". A multiple logistic regression analysis will be performed to confirm that these factors remain jointly uninformative for receiving surgery.

18.7.1. Patient Groups for Analysis

For this trial it will not be possible to follow the Intention to Treat (ITT) principle of "analysing as randomised" because patients do not have the intervention (HBO or standard care) until they have been randomised *and* had surgery. Some patients drop out before surgery, and this occurs more frequently in

the HBO arm. Furthermore the clinical question to be answered is the effect of HBO among those given surgery, and not the effect of HBO in itself.

Full Analysis set: This will consist of all randomised patients who have received surgery excepting for a) patients withdrawing consent between randomisation and receiving surgery b) patients withdrawn from the study after randomisation because of irregularities with the consent process and c) patients whose information determining ineligibility existed before randomisation but was not read until after randomisation. In effect this is a "per protocol" set that may include some patients with major deviations.

Safety set: All patients who received any trial treatment.

Efficacy analyses will be performed on the full analysis set and Safety analyses will be performed on the safety set.

18.7.2. Handling of mis-randomised patients and dropouts

For efficacy analyses mis-randomised patients will be analysed as randomised, in order to follow the ITT principle. For safety analyses patients will be analysed as treated.

18.7.3. Identification and Handling of outliers

Potential outliers for continuous variables will be defined as follows:
Mild outliers:
UQ+1.5×IQ to UQ+3×IQR
LQ - 1.5×IQ to LQ-3×IQR
Severe outliers: values more extreme than the above
(Note: UQ=Upper Quartile, LQ=Lower Quartile, IQR=Inter Quartile Range)

If after transformation (chosen using a "ladder of powers" approach using the Stata command *ladder*) no outliers are apparent then no action will be taken even if values appear as outliers on the original scale, apart from use of the transformation if normality is required for a particular statistical procedure, or to remove the leverage effect of the outlying values.

Outliers that are still present on the transformed scale will be winsorised before analysis – such values will be queried but no other action taken if the result is not amended.

18.7.4. Study centre effects

Consistency of effect for the primary outcome will be assessed across the centres by a model that incorporates Centre and Treatment by Centre random effects. There will be limited capacity to investigate these formally and such centre effects are to be expected by chance.

18.7.5. Adjustment for covariates

See sensitivity analyses (below).

18.7.6. Multiplicity adjustments

No formal adjustment for multiple significance testing is to be applied.

18.7.7. Missing data

If feasible, missing baseline covariate, ORN response data and Part One (the visual analogue scale) of the pain scores will be handled by multiple imputation, performing separate multiple imputations by

treatment arm using chained equations, as implemented in the Stata command mi impute. Plausible sets of explanatory variables will be identified in discussion with the CI. Missing Quality of life and Acute symptoms scores will not be imputed.

Once the sets of explanatory variables have been identified, separate data sets will be created for each treatment arm and 5 multiple imputations will be created for each arm, after ensuring that the primary response is included in each of the sets of explanatory variables. The multiply-imputed data sets will then be recombined for formal analysis, either using the *mim* command prefix, or if necessary a bespoke routine to estimate parameter values and combine them using Rubin's rules.

18.7.8. Sensitivity analyses

These will consist of:

1. Assessing effects of assuming:
A all presurgery dropouts would have developed ORN
B no presurgery dropouts would have developed ORN
C all presurgery dropouts would have developed ORN with risk for their arm
D all presurgery dropouts would have developed ORN with mean risk across both arms

2. Assessing the effect of adjustment in analysis of the primary outcome for radiotherapy dose, age, sex, cigarettes & alcohol use.

3. Inclusion of Multiply-imputed primary endpoint responses for all randomised patients.

4. Comparison of results using the PI's original assessment of ORN (as with the primary analysis, this will include assessment of centre effects)

5. Analysis of "blind review" ORN after including Minor Bone Spicules vs excluding cases with only Minor Bone Spicules

18.7.9. Prespecified subgroup analyses

Separate analyses will be presented for patients undergoing dental extraction, and a summary and comparison of minor bone spicule dimensions will be performed.

18.7.10. Assessment of study quality & compliance

This will be based on:

- observed and expected numbers of CRF pages separately by treatment arm and by site
- proportion of patients with major deviations by treatment arm
- proportion of patients with missing values for primary outcome, treatment arm, & covariates (as defined above)
- proportions of patients withdrawing from treatment/lost to follow-up, overall and by treatment arm

18.7.11. Definitions & Derived variables

See appendices for details of derivation of independently reviewed ORN, and details of University of Washington Quality of life (UW-QoL) presentation and analysis.

18.7.12. Description of baseline subject characteristics

Because the primary analysis is based on patients who actually received surgery, demographic and clinical factors at baseline (Age, Sex, Smoking category, Alcohol category, Radiotherapy dose and Radiotherapy duration, University of Washington Quality of life, pain scores) will be presented for the HBO and control groups both "as randomised" and also "as receiving surgery". Categorical variables will be summarised as frequencies and percentages (with 95% confidence intervals), continuous variables by mean, Standard Deviation, median and interquartile range.

A multiple logistic regression analysis will be performed to confirm that these factors remain jointly uninformative for receiving surgery (ie all p-values high).

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18.7.13. Specification and estimation of efficacy parameters

Table 1: Summary of Outcome variables and corresponding efficacy parameters

Outcome variable	***Efficacy parameter***	***Comment***	***Method***
Occurrence of ORN at 6 months post-surgery	*Odds ratio (relative to Standard Care)*	*A clinically significant response to treatment is defined as an odds ratio <= 0.23 relative to Standard Care*	*Exact logistic regression*
Occurrence of ORN at 6 & 12 months post-surgery	*Odds ratio (relative to Standard Care)*	-	*Exact logistic regression*
Severity of ORN	*Odds ratio*	-	*Ordinal logistic model (if feasible)*
Quality of life	*Difference in "% best score", and difference in % of patients choosing the domain by time point and domain*	-	*Exact logistic regression*
Pain score VAS	*Difference in mean score, by time point*	-	*Linear regression with separate variances*
Acute symptoms	*Difference in AUC over 7 days (by item) and difference in proportions comfortable*	-	*Multivariate regression for item-specific AUC and binary "comfortable"*

			variable

18.8. Analysis of primary outcome

18.8.1. Test of efficacy

The primary test of efficacy in terms of risk of ORN at 6 months will be carried out on the Full Analysis Set using an exact logistic regression including a fixed term for treatment arm.

The null hypothesis is that inclusion of HBO treatment pre-surgery is not more effective than Standard Care alone, that is, the odds ratio is not statistically different from 1, while the alternate hypothesis is that HBO treatment is superior to Standard Care with an odds ratio of 0.23 or less. The test will be two-sided and a P-value of less than 0.05 will be declared statistically significant. Two-sided 95% confidence limits for the odds ratio will be presented for consistency with the significance test.

Significance tests for secondary endpoints will also be two-sided at 5% accompanied by 95% two-sided confidence intervals.

18.8.2. Tests of assumptions

No specific tests of assumptions for the primary endpoint are planned.

18.8.3. Analysis of secondary outcomes

The presence of ORN at 3 and 12 months will be analysed as detailed above for the primary outcome.

Severity of ORN cases (classified as either Notani grade I, II, III) will be tabulated using counts and percentages for each treatment group separately and treatment effect assessed using an ordinal logistic model with covariates as identified for the primary outcome, and a random effect for centre. This analysis will include patients without ORN as a notional grade 0 but exclude patients whose severity is unevaluable.

University of Washington Quality of life (UW-QoL) forms completed at baseline, 3, 6 and 12 months following surgery will be summarised by timepoint according to their Guidance for scoring and presentation (Derek Lowe & Simon N Rogers 2012). Scoring is scaled so that a score of 0 represents the worst possible response, and a score of 100 represents the best possible response.
A) frequency of each score by treatment arm and domain (pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety) with means and standard errors. Formal comparison of treatment arms at each time point after baseline for each domain will be based on the "% best score" defined as a score of 100%
B) frequency of Health-related and Overall QoL scores over preceding 7 days (the cancer-related score will be omitted because this is compared to the month before cancer was diagnosed, and these patients are cancer-free) with means and standard errors. Formal comparison of treatment arms at each time point after baseline for each domain will again be based on the "% best score" defined as a score of at least 60.
C) frequency and percentage of patients choosing each domain as "important" by treatment arm. Formal comparison of treatment arms at each time point after baseline for each domain will use the % of patients choosing the domain.

Pain Assessment Charts completed at baseline, 3, 6 and 12 months following surgery, will be summarised by timepoint using only Part One (the visual analogue scale) in terms of mean and standard deviation by treatment arm. Formal comparison of treatment arms at each time point will compare the mean pain score between treatment arms by a linear model that allows for differences in variance, as implemented using *xtmixed* command with the option *residuals(independent,by(trt))* where trt denotes the dummy variable for treatment arm.

Acute symptoms questionnaire (completed for days 1-7 post-surgery). Mean scores will be tabulated by treatment arm and day for each item of Pain, Swelling, Bleeding, Difficulty in opening mouth, Difficulty in eating normal diet. For Day 8 the number (%) comfortable and able to eat normally will also be displayed. Formal comparison of treatment arms will compare the mean AUC over the 7 days for each arm and the numbers comfortable at 8 days, using a multivariate regression model that permits both binary and continuous outcomes as specified in the Stata user-written package *gllamm* (26).

Outcome of MBS and Implant survival. Descriptive analyses only of, respectively proportion progressing to Notani 1 or more or proportion of implants retained. If possible, actuarial methods will be used to estimate progression and survival.

18.8.4. Analysis of safety

Surgery: the number and proportion of patients with death, hospital admission, operations and complications (e.g. major bleeding, sepsis) occurring within 12 months post-surgery will be reported for each treatment group separately.
HBO treatment: adverse events related to hyperbaric insult (ege otic trauma, epistaxis) will be reported in terms of incidence and severity. This will also include events occurring within 6 months of most recent HBO treatment for patients in that arm who did not receive surgery.
New Diagnosis of cancer, either recurrent or new site within 12 months following surgery will be tabulated as number (%) with formal comparison between arms based on the difference in proportions.

18.9. Interim analysis and data monitoring committee

Analyses of trial data for the Independent Safety Data Monitoring Committee (ISDMC) review are initially planned at 12-monthly intervals, to assess recruitment rates and toxicity.

A single formal interim analysis will be carried out when 100 dental extraction patients have been followed up for 6 months. The Peto stopping rule will be implemented for the primary efficacy outcome (ORN rate at 6 months following surgery), and a futility analysis will also be carried out.

The Peto stopping rule (for efficacy) uses a fixed critical z value of 3 for the interim analysis, with no adjustment to the fixed sample size z value at the final analysis (Haybittle, 1971; Peto, 1976). The futility analysis will be in the form of an estimate of conditional power comparing the two treatment arms with respect to the primary endpoint.

No formal stopping rule has been adopted for futility, and the result will act purely as a guideline, to be interpreted in the light of recruitment, toxicity and results from other trials with the default intention of proceeding to the planned sample size (unless stopping early for efficacy). The target of 100 dental extraction patients corresponds to a total of approximately118 patients. All interim analyses will be

unblinded and performed by the trial statistician. Access to the results of these analyses will be restricted to the trial statistician unless otherwise authorised by the DMC.

The formula that will be used to estimate conditional power is (Piantadosi, 2005):

$$Conditional\ power = Pr\left[z > \frac{z_{1-\alpha} - \{\sqrt{f}Z_f + \delta(1-f)\}}{\sqrt{1-f}}\right]$$
$$= 1 - \Phi\left[\frac{z_{1-\alpha} - \{\sqrt{f}Z_f + \delta(1-f)\}}{\sqrt{1-f}}\right]$$

Where:

- f = the fraction of the target sample size at the interim analysis. The target sample size (for which the study is powered) is 200 patients. However a check on the sample size estimate indicates that this should be 206, so we expect f will be ≈ 0.57
- $z_{1-\alpha}$ = 1.96 (the standard Normal deviate corresponding to the alpha error in the sample size estimate)
- Z_f = value of the test statistic observed at the interim
- δ= drift parameter.

There are three scenarios of interest:

a) Conditional power assuming the original δ |H1 when we use the formula with $\delta=(z_{1-\alpha}+ z_{1-\beta})$

b) Conditional power assuming the current estimate of δ given by: $\delta = Z_f/\sqrt{f}$

c) Conditional power assuming the original δ |H0 for which δ=0

All three estimates will be presented. However, in monitoring with the aim of possible stopping for futility, note that true futility occurs when despite possible late evidence of efficacy, the probability of a statistically significant result remains low (Moye´, 2006). Hence the most "optimistic" estimate of conditional power is under scenario a) with typical thresholds for conditional power in the range 0.10 to 0.15 (Proschan et al, 2006)

Other information that may affect the decision of the DMC are:

- whether the confidence limits exclude the designed-for treatment effect
- whether the treatment effect is in the "wrong" direction: ie causing harm
- whether the above effects are robust to the planned sensitivity analyses

The trial may be terminated early by the ISDMC if there are serious concerns for patient safety. In such a case, ISDMC members will make formal recommendations to the trial working group and TSC regarding the continuation of recruitment of patients into the study and will comply with a trial-specific ISDMC charter according to ICH GCP guidelines.

Further details will be included in a separate DMC Report Plan to be signed-off before the formal interim analysis.

19. Use of information

All unpublished information relating to this study and/or to the Investigational Product(s) is considered confidential by the LCTU.

The investigator should understand and agree that LCTU may use the information from this clinical trial in connection with the development of the product, and therefore, may disclose it as required to other investigators, to government licensing authorities, to regulatory agencies of other governments and commercial partners.

20. Publications

A draft manuscript for joint publication will be prepared and submitted in collaboration between the LCTU and the investigators, whatever the outcome of the study.

Investigators must undertake not to submit any part of their individual data for publication without the prior consent of the LCTU.

21. Contact numbers for the randomisation centre and Investigators

Surgical Units: These Units will provide screening / randomisation and surgical treatment within the HOPON trial – data recording and sample collections.

ST LUKE'S HOSPITAL:

Mr Michael Ho
Consultant Maxillofacial/Head and Neck Surgeon BIHR Head and Neck Cancer Research Lead
Maxillofacial Unit | Maxillofacial Unit, Horton Wing,
St. Luke's Hospital, BD5 ORN
Bradford Teaching Hospitals NHS Foundation Trust

LEEDS:
Mr Peter Nixon, Locum Consultant in Restorative Dentistry
Leeds Dental Institute & Leeds Institute of Oncology
Leeds Teaching Hospitals NHS trust
Level 6
Clarendon Way
Leeds
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MUSGROVE PARK HOSPITAL:
Mr Manuel Blanco-Guzman
Consultant Oral & Maxillofacial Surgeons
Maxillofacial Unit
Musgrove Park Hospital
Taunton and Somerset NHS Trust
Taunton TA1 5DA

ABERDEEN ROYAL INFIRMARY:
Dr Ruth Stephenson
Consultant in Anaesthesia and Hyperbaric Medicine
Hyperbaric Unit
Aberdeen Royal Infirmary

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Aberdeen
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QUEEN ALEXANDRA HOSPITAL:
Professor Peter Brennan
Consultant Oral & Maxillofacial Surgeon & Professor of Surgery
Department of Oral & Maxillofacial Surgery
Portsmouth Hospitals NHS Trust
Queen Alexandra Hospital
Cosham
Portsmouth
PO6 3LY

ST RICHARD'S HOSPITAL:
Peyman Alam
Consultant Oral & Maxillofacial Surgeon
Clinical Lead for Head & Neck Surgical Oncology
Clinical Lead for Thyroid/
Parathyroid Surgery
St Richard's Hospital
Chicheser
West Sussex
PO19 4SE

WORTHING GENERAL HOSPITAL:
Peyman Alam
Consultant Oral & Maxillofacial Surgeon
Clinical Lead for Head & Neck Surgical Oncology
Clinical Lead for Thyroid/
Parathyroid Surgery
St Richard's Hospital
Chicheser
West Sussex
PO19 4SE

UNIVERSITY HOSPITAL AINTREE:
Professor Richard Shaw
Professor of Head & Neck Surgery
Honorary Consultant in Oral & Maxillofacial Surgery
&Mr Christopher Butterworth
Consultant in Restorative Dentistry
University Hospital Aintree NHS Foundation Trust
Lower Lane
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LIVERPOOL UNIVERSITY DENTAL HOSPITAL
Mr Christopher Butterworth
Consultant in Restorative Dentistry
The School of Dental Sciences
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UNIVERSITY HOSPITAL BIRMINGHAM Mr Prav Praveen
Consultant Maxillofacial Surgeon
University Hospital Birmingham NHS Foundation Trust
Dept Maxillofacial Surgery
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ST BARTHOLOMEW'S HOPSITAL
Professor Iain Hutchison
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ROYAL DEVON AND EXTER HOSPITAL
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Consultant Oral and Maxillofacial Surgeon
Department of Oral and Maxillofacial Surgery
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EX2 5DW

NORTH DEVON DISTRICT HOSPITAL
Mr John Bowden
Consultant Oral and Maxillofacial Surgeon
Exeter and North Devon Combined Maxillofacial Unit
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EX31 4JB

YEOVIL DISTRICT HOSPITAL
Mr Manuel Blanco-Guzman
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GUY'S HOSPITAL
Mr Andrew Lyons
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Dr Matt Beasley
Consultant Clinical Oncologist
Bristol Haematology and Oncology Centre
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NORTHWICK PARK HOSPITAL
Mr Bhavin Visavadia
Consultant Oral & Maxillofacial Surgeon
Maxillofacial Unit
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UNIVERSITY COLLEGE HOSPITAL
Mr Colin Liew
Consultant Head and Neck/Maxillofacial Surgery
Head & Neck Centre
1st Floor East Wing
250 Euston Road
London
NW1 2PG

Hyperbaric Units: These Units will provide hyperbaric oxygen therapy to participants referred by recruiting centres / assess each participant referred to this unit for fitness for pressure exposures prior to hyperbaric oxygen therapy.

WIRRAL
Dr Tristan Cope MBChB FRCA FFICM
Medical Director
North West Emergency Recompression Unit
Spire Murrayfield Hospital
Holmwood Drive
Thingwall
Wirral
CH61 1AU

ABERDEEN
As Above

HULL
Dr G Purdy, North of England Medical Hyperbaric Unit, BUPA Hospital Lowfield Road, Anlaby, Hull HU10 7AZ

PLYMOUTH

Dr Christine Cridge, Medical Director,The Hyperbaric Medical Centre, Tamar Science Park, Research Way, Derriford, Plymouth, Devon. PL6 8BU

LONDON
Dr Pieter Bothma, Medical Director
London Hyperbaric Medicine and Wound healing Centre, Leytonstone, London, E11 1RG

PORTSMOUTH
Dr Mark Glover, Medical Director, Hyperbaric Medicine Unit, St Richard's Hospital, Spitalfield Lane, Chichester, West Sussex, PO19 6SE

CARDIFF
Dr Christine Cridge, Medical Director,South Wales Hyperbaric Centre (DDRC), Spire Cardiff Hospital, Croescadarn Road, Pentwyn, Cardiff, CF23 8XL.

22. REFERENCES

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APPENDIX 1. Patient Consent Form

<To be printed on Trust headed paper>

PATIENT CONSENT FORM (please read carefully)

HOPON: Hyperbaric Oxygen to Prevent Osteoradionecrosis

Name of Researcher:_____

Please initial

1. I confirm that I have read and understand the information sheet dated …… (version .....) describing the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. a) I give permission for a sample of my blood to be taken and stored for research into the effects of radiotherapy. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐
4. b) I give permission for DNA to be extracted from the blood for current and future genetic research into the effects of radiotherapy. ☐
5. I give permission for a copy of my consent form to be sent to the Liverpool Clinical Trials Unit (where it will be kept in a secure location), to allow confirmation that my consent was given. ☐
6. I agree to allow my General Practitioner and any other relevant medical practitioner to be informed of my involvement in the study. ☐
7. I agree to take part in the above study. ☐
8. I agree that data from the study can be sent outside the EU. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Three copies required: one for patient, one for researcher and one for hospital case notes.

APPENDIX 2. Patient Information Sheet.

<To be printed on Trust headed paper>

PATIENT INFORMATION SHEET

HOPON: Hyperbaric Oxygen to Prevent Osteoradionecrosis

You have been invited to take part in a research study. Before you decide it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others if you wish.

- Part One tells you the purpose of the study and what will happen to you if you take part.
- Part Two gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1

What is the purpose of the trial?

This study has been designed to find out whether the use of oxygen treatment may help your jaw heal after minor surgery. Healing problems can occur more often after radiotherapy.

We will take precautions to reduce the effects of surgery, but even so there is a small risk of healing difficulties. Having the extra oxygen treatment might prevent this although at the moment nobody knows this for certain.

This trial is to find whether there is any difference between two different types of treatment. If you agree to take part, you will be randomly allocated to one of two groups:

1) Surgery with antiseptic mouthwash and antibiotics.
2) Surgery with antiseptic mouthwash and antibiotics, also with oxygen treatment.

This means that half of all patients will be given oxygen treatment. Therefore whether you are allocated to be treated with oxygen will be decided by chance. Whichever group you are allocated you will be monitored closely.

Why have I been chosen?

You have previously received radiotherapy and now require minor jaw surgery. This may be to treat a dental problem, to place implants or simply the removal of teeth. After this surgery, difficulties with healing can occur and doctors use the term “osteoradionecrosis” of the jaw in these cases.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do you will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not take part, will not affect the standard of care you receive.

Attendances, travelling additional costs

Involvement in the HOPON trial will require appointments at three and six months after jaw surgery. For those patients receiving oxygen treatment, daily visits to the oxygen treatment centre will be arranged. It may be possible for the health service to help with transport if needed, but these arrangements will vary in different trial centres. Please discuss transport arrangements if you feel this may be a problem.

What will happen to me during the trial?

For the patients receiving the oxygen treatment, they will receive it at a dedicated clinic. The oxygen treatment lasts about one and a half hours per day and is given as an outpatient, or in other words, you will be free to go home after this. The oxygen treatment consists of 20 treatments prior to surgery and 10 afterwards.

For the patients treated without oxygen, the surgery is carried out after giving antibiotics in the usual way.

For either group, whether surgery is done under local or general anaesthetic will be decided on by your surgeon or dentist in the usual way.

After you have been treated you will be required to attend hospital for a follow-up visit at 3,6 and 12 months. During these visits you will have an examination. Jaw x-rays and clinical photographs will also be taken.

One aspect of this study involves assessing how any treatment you receive affects the quality of your life and post-operative recovery. Our research nurses will ask you to fill in a questionnaire that asks these questions. The questionnaire will be completed when you consent to enter the study and attend for your treatment or follow-up appointments. It is very important for you to answer all the questions in the questionnaires for us to accurately assess the impact of the disease and treatment upon you.

Blood samples

Radiotherapy may lead to damage to tissues in and around the jaws. In order to further understand these changes we wish to collect and store a blood sample at the time of your minor surgery. These would be stored and used for scientific research but would not help with your care.

What are the alternatives for treatment?

If you decide not to participate in the study, then your doctor will discuss other options with you.

Are there any side-effects associated with these treatments?

Hyperbaric Oxygen Treatment:

Oxygen treatment in a high-pressure chamber has a proven safety record and many patients are routinely treated in this way. There are some medical conditions that prevent us recommending oxygen treatment therefore we will ask you particularly about some lung and ear disorders which may be relevant.

People having repeated treatments with high-pressure oxygen therapy sometimes notice a feeling of tiredness. This effect is apparent later in the day after a treatment in the morning and disappears by the following day. It is rarely, if ever, enough to interfere with normal daily activities. Some people notice temporary changes in their vision over the course of many treatments. This may cause a mild degree of short-sightedness, which may improve or worsen vision, depending on any pre-existing short- or long-sightedness. If this does occur, you can expect it to have returned fully to normal within twelve weeks of

finishing treatment. Tiredness and temporary mild visual changes are common but will always resolve after these oxygen treatments.

The changes in pressure can cause damage to the middle ear or sinus if the pressures in them are not equalised. This may cause problems such as pain and/or a ruptured eardrum but is not common, occurring around one in fifty patients (2%). This can be prevented easily by notifying the attendant that you have a problem and the compression or decompression can be stopped immediately. These problems can often be anticipated and simple procedures may be used, such as drainage tubes in the ears, to prevent them if necessary.

The high-pressure chamber is a relatively confined space and it occasionally induces feelings of claustrophobia. About one person in fifty may be affected (2%). If you are, please remember that you are in control at all times and that you can leave the chamber at any time.

A very rare side effect of breathing oxygen at the pressure used is having a fit (seizure) and this occurs less than one in ten thousand patients (0.01%). This is short-lived and easily dealt with and there are no lasting effects. You may not be eligible to take part if you have had any seizures in the past, as this may predispose you to having an oxygen seizure. If there are abnormalities in the lung, or the person holds her breath, it is possible for gas bubbles to enter the blood and to cause problems. These complications are extremely unlikely with the slow pressure changes used in this study and can be totally avoided by carefully screening patients for lung problems, and by breathing normally at all times.

Antibiotic Treatment:

Antibiotics of all types occasionally cause allergy or upset stomach. The antibiotics used in this study are in routine use.

What are the possible benefits of taking part?

We hope that the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of patients who have had radiotherapy to their jaws.

What are the possible disadvantages and risks of taking part?

As part of the study you will undergo at least two jaw x-rays. The dose of radiation you will receive could be equivalent to around one week of natural background radiation. The National Radiological Protection Board described this natural background radiation as ‘Low Risk’. However, you would receive the same dose from the x-rays in this trial as those required by routine care in the NHS (UK) so you are not exposed to very much additional radiation by taking part in this trial.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in this study be kept confidential?

Yes. All information which is collected about you during the course of this research will be kept strictly confidential. With your permission we will inform your GP of your participation in the study. Other than this, any information about you that leaves the hospital will have your name and address removed so you cannot be identified from it. A copy of your signed consent form will be sent to the Liverpool Cancer Trials Unit (where it will be kept in a secure location), to allow confirmation that your consent was given.

Contact for Further Information

Should you have any further queries regarding this study or about any of the treatments described above:

Please feel free to ask your doctors any questions about the study or about any of the treatments described above.

Please contact_____
Name and Title

On_____

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?

If you do not wish to continue attending hospital, we would be grateful if you would allow us keep in touch with your General Practitioner and Dentist to let us know your progress. If you withdraw, information collected may still be used if you allow. Any stored blood samples that can still be identified as yours will be destroyed if you wish.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this trough the NHS Complaints Procedure. Details can be obtained from the hospital.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints mechanisms should be available to you (if appropriate).

In the event of defective product then you may have grounds for a legal action for compensation against the manufacturer, but you may have to pay for your legal costs.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from Cancer Research UK or their collaborators who also involved in organising this research project. They may also be looked at by representatives of regulatory authorities and by authorised people from the Trust or other NHS bodies to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

Data collected during the study may be transferred for the purpose of analysis/registration within or outside the European Union. Some countries outside Europe may not have laws which protect your privacy to the same extent as the Data Protection Act in the UK or European Law. We will take all reasonable steps to protect your privacy.

Involvement of the general practitioner/ family doctor (GP)

With your consent, your GP will be informed of your involvement in the trial. Any other medical practitioners who treat you, e.g. should you be admitted to hospital for any reason, will also be informed.

What will happen to any samples I give?

With your permission, we would like to transfer a blood sample we take from you to the University of Liverpool and store it there. The researchers at the University of Liverpool work closely with other scientists and, with your permission, your samples may be transferred to these research collaborators for use in future scientific studies. These samples will be used only for investigating the effect of your genetic (DNA) information on the severity of radiation damage and will not be used for any commercial purposes.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, address and GP details) will be kept locally and not made available to collaborators.

Your sample will be coded and the researchers carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not plan to do this unless there is a good research reason to do so. We will maintain this information so that we can properly manage the samples donated. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of tests.

Will any genetic tests be done?

There are some known genes that alter the body's response to radiotherapy and we may try to carry out research into these genes on your samples.

What will happen to the results of the research study?

It is intended that once the study is complete a report will be written and the results will be published to make them available to the public and medical community. You will not be named or identified in any publication.

Who is organising and funding this research?

This research project is funded by Cancer Research UK; they are supporting this study by providing funding for staff to co-ordinate this trial. It is being sponsored by the University Hospital Aintree NHS Foundation Trust and the University of Liverpool.

Your doctor will not receive any payment for including you in this study.

Who has reviewed the study?

The study has been reviewed for scientific content by members of the Cancer Research UK peer review committee and a Multi-Centre Research Ethics Committee has reviewed the study for ethical considerations. The trial has the support of the National Cancer Research Institute.

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

APPENDIX 3 – Serious Adverse Event Form

Version 3—17/06/10

Serious Adverse Event Form (Page 1)

H	O	P	O	N

Project | Trial Number | Patient Initials

All follow up information MUST be added to THIS form __/__/____ dd/mm/yyyy

Date initial report sent to Liverpool Cancer Trials Unit

Please complete an adverse event form for each SERIOUS Adverse Event (SAE) the subject experiences.

Patient's Treatment Arm

☐ Standard Management

☐ Standard Management plus HBO

If HBO, date of last HBO treatment: __/__/____ (dd/mm/yyyy)

Date and time of onset __/__/____ dd/mm/yyyy ☐☐ 24 hr Clock

Date and time of offset (if resolved) __/__/____ dd/mm/yyyy ☐☐ 24 hr Clock

Outcome

☐ Resolved ☐ Worse

☐ Improved ☐ Death

☐ Unchanged ☐ Unknown

Date/time of death (if applicable) __/__/____ dd/mm/yyyy ☐☐ 24 hr Clock

Adverse Event: Description (signs and symptoms) and diagnosis (if applicable)	**Severity*** 1 = Mild 2 = Moderate 3 = Severe
Overall Diagnosis:	

Relevant test results/lab data

CHANGE IN HBO

HBO Withdrawn	Yes ☐	No ☐
HBO reduced	Yes ☐	No ☐
If withdrawn/reduced, did symptoms resolve?	Yes ☐	No ☐
Did event reappear if HBO reintroduced?	Yes ☐	No ☐

CAUSALITY:

In your opinion was the adverse event related to:	Definitely Related	Probably Related	Possibly Related	Probably Unrelated	Unrelated
HBO Treatment	☐	☐	☐	☐	☐
Subject's original condition/ other illness	☐	☐	☐	☐	☐

DEFINITION OF "SERIOUS"

CHECK ALL APPROPRIATE

- Subject died ☐
- Hospitalisation ☐
- Involved permanent or significant disability or incapacity ☐
- Life threatening ☐
- Congenital anomaly ☐

Investigator Signature _____

Investigator Name _____ Date ☐☐☐ dd mm yyyy

Only medically qualified delegated clinicians (who have been approved and signed off by the Principal Investigator on the delegation log) can sign off data on the SAE form.

Version 3—17/06/10

Serious Adverse Event Form (Page 2)

H	O	P	O	N

Project

Trial Number

Patient Initials

All follow up information MUST be added to THIS form

Trial medication and concurrent drug information

	Drug	Route	Daily Dose/ Units (of infusion rate if IV)	Date/time started dd/mm/yyyy hh:mm	Date/time stopped dd/mm/yyyy hh:mm	Disease indication	Is drug suspected of causing SAE? Y	N
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								

Investigator signature _____ Date dd mm yyyy

Please fax completed form to the Liverpool Cancer Trials Unit 0151 794 8930

SIGNED: _____ PRINT NAME: _____ DATE: __/__/____

Only medically qualified delegated clinicians (who have been approved and signed off by the Principal Investigator on the delegation log) can sign off data on the SAE form.

APPENDIX 4. GP Letter

INSERT SITE HEADER

GP Name
GP Address 1
GP Address 2
GP Address 3
GP Post Code

Dear Dr.

RE: HOPON - A Randomised Control Trial of Hyperbaric Oxygen (HBO) to prevent Osteoradionecrosis of the Irradiated Mandible.

Patient Name:……

Date of Birth: ……

NHS Number:……

After giving written informed consent, the above patient has been entered into a clinical trial which aims to investigate the benefit of HBO in the prevention of osteoradionecrosis (ORN) at the time of a surgical procedure to the "at risk" irradiated mandible.

Your patient has been randomised to receive:

1) **Arm 1*:** Standard management : i.e.: pre- and post- operative chlorohexidine mouthwash, antibiotics, minimally traumatic surgical technique
2) **Arm 2*:** Standard management plus HBO: Patients will undergo 20 HBO treatments prior to surgery followed by a further 10 daily HBO treatments.

*** Delete as appropriate.**

Hyperbaric Oxygen treatment is occasionally associated with side effects such as decompression illness, oxygen toxicity, barotraumas and claustrophobia.

If your patient has been randomised to receive HBO (arm 2), they will be required to attend the specified Hyperbaric Unit in your area for a total of 30 treatments as part of the trial.

If you require further details please contact…….

Yours sincerely,

APPENDIX 5. HOPON Registration/ Randomisation form

Version 5, 29/04/2010

HOPON
(Hyperbaric Oxygen for the Prevention of Osteoradionecrosis):
A Randomised Controlled Trial of Hyperbaric Oxygen to prevent Osteoradionecrosis of the

Date: _ _ / _ _ / _ _ _ _ (dd mm yyyy) Hospital:.....

Consultant:.....

Unit telephone no: ..... Unit fax no: .....

Randomising Clinician (if different from consultant):.....

Patient Initials: | | | | Date of Birth: _ _ / _ _ / _ _ _ _ (dd mm yyyy)

Screening Number: | | | | | | | (Taken from Screening Log)

Eligibility Criteria

1. Age > 18 years ☐
2. Prior history of external beam radiotherapy (dose > 50Gy) to mandible or prior history of brachytherapy with equivalent radiation dose as above. ☐
3. No evidence of cancer recurrence ☐
   Patients with previous head and neck cancer are at risk of further malignancy. Care should be taken to exclude this possibility with particular regard to:
   i) Local, regional or distant recurrence of originally treated tumour
   II) Second primary tumour in head and neck region
   III) Second primary tumour outside the head and neck (e.g. lung).
   Careful clinical examination by a head and neck oncology specialist to exclude malignancy, blood biochemistry, head &neck / thoracic imaging and flexible nasendoscopy should be completed in keeping with local protocols and appropriate to the site and stage of the original tumour and disease free interval.
4. New diagnosis of condition requiring surgery to mandible (commonest examples but not limited to: dental extraction, implant placement, surgical tooth, cyst or osteosynthesis plate removal) ☐
5. Patient has read and understood information leaflet and is willing to be randomised. ☐
6. Patient competent to consent and psychologically / physically fit for HBO. ☐
7. No known contraindications to HBO (see inside front cover of CRF booklet) ☐
8. No prior hyperbaric oxygen therapy ☐
9. No prior diagnosis of osteoradionecrosis of the mandible ☐
10. No history of systemic bisphosphonate therapy, pentoxyphylline or tocopherol. ☐
11. Not pregnant ☐

Which hyperbaric chamber unit will the patient be referred to if they are randomised to the HBO arm?

.....

To randomise, please telephone the CR-UK Liverpool Cancer Trials Unit (0151 794 8934) to give notice, then fax this form along with a copy of the patient's signed Written Informed Consent form to Fax: 0151 794 8930.

INVESTIGATOR'S NAME: _____ **SIGNATURE:** _____ **DATE:** _ _ / _ _ / _ _ _ _

The patient will not be randomised unless a medically qualified delegated clinician (as indicated on the delegation log) has signed this section to declare the above information is correct and that the patient is eligible to be randomised into the HOPON trial.

TRIALS OFFICE USE ONLY

Patient Randomised to: Standard Treatment ☐ Standard Treatment + HBO ☐ **Date:** _ _ / _ _ / _ _ _ _ (dd mm yyyy)

Randomised by: _____ **Trial Number:** | | | | | | |

APPENDIX 6. Quality of Life Questionnaire

Version 3—09/12/2009 **Patient Questionnaire - Baseline** *Page 1 of 3*

H	O	P	O	N										
Project					Trial Number							Patient Initials		

This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by ticking one box for each question.

Date of assessment __/__/____ *dd/mm/yyyy*

1. **Pain**. (Tick one box)

☐ I have no pain.
☐ There is mild pain not needing medication.
☐ I have moderate pain - requires regular medication (e.g. paracetamol).
☐ I have severe pain controlled only by prescription medicine (e.g. morphine).
☐ I have severe pain, not controlled by medication.

2. **Appearance**. (Tick one box)

☐ There is no change in my appearance.
☐ The change in my appearance is minor.
☐ My appearance bothers me but I remain active.
☐ I feel significantly disfigured and limit my activities due to my appearance.
☐ I cannot be with people due to my appearance.

3. **Activity**. (Tick one box)

☐ I am as active as I have ever been.
☐ There are times when I can't keep up my old pace, but not often.
☐ I am often tired and have slowed down my activities although I still get out.
☐ I don't go out because I don't have the strength.
☐ I am usually in bed or chair and don't leave home.

4. **Recreation**. (Tick one box)

☐ There are no limitations to recreation at home or away from home.
☐ There are a few things I can't do but I still get out and enjoy life.
☐ There are many times when I wish I could get out more, but I'm not up to it.
☐ There are severe limitations to what I can do, mostly I stay at home and watch TV.
☐ I can't do anything enjoyable.

5. **Swallowing**. (Tick one box)

☐ I can swallow as well as ever.
☐ I cannot swallow certain solid foods.
☐ I can only swallow liquid food.
☐ I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing**. (Tick one box)

☐ I can chew as well as ever.
☐ I can eat soft solids but cannot chew some foods.
☐ I cannot even chew soft solids.

7. **Speech**. (Tick one box)

☐ My speech is the same as always.
☐ I have difficulty saying some words but I can be understood over the phone.
☐ Only my family and friends can understand me.
☐ I cannot be understood.

FOR SITE STAFF ONLY: SIGNED: _____ **PRINT NAME:** _____ **DATE:** __/__/____

H	O	P	O	N

Project

Trial Number

Patient Initials

8. **Shoulder**. (Tick one box)

- ☐ I have no problem with my shoulder.
- ☐ My shoulder is stiff but it has not affected my activity or strength.
- ☐ Pain or weakness in my shoulder has caused me to change my work / hobbies.
- ☐ I cannot work or do my hobbies due to problems with my shoulder.

9. **Taste**. (Tick one box)

- ☐ I can taste food normally.
- ☐ I can taste most foods normally.
- ☐ I can taste some foods.
- ☐ I cannot taste any foods.

10. **Saliva**. (Tick one box)

- ☐ My saliva is of normal consistency.
- ☐ I have less saliva than normal, but it is enough.
- ☐ I have too little saliva.
- ☐ I have no saliva.

11. **Mood**. (Tick one box)

- ☐ My mood is excellent.
- ☐ My mood is generally good.
- ☐ I am neither in a good mood nor depressed.
- ☐ I am somewhat depressed.
- ☐ I am extremely depressed.

12. **Anxiety**. (Tick one box)

- ☐ I am not anxious.
- ☐ I am a little anxious.
- ☐ I am anxious.
- ☐ I am very anxious.

---

13. Which issues have been the most important to you during the past 7 days?
Tick up to 3 boxes.

- ☐ Pain
- ☐ Swallowing
- ☐ Taste
- ☐ Appearance
- ☐ Chewing
- ☐ Saliva
- ☐ Activity
- ☐ Speech
- ☐ Mood
- ☐ Recreation
- ☐ Shoulder
- ☐ Anxiety

FOR SITE STAFF ONLY: SIGNED: _____ **PRINT NAME:** _____ **DATE:** __ / __ / ____

H	O	P	O	N

Project

Trial Number

Patient Initials

14. In general, would you say your **health-related quality of life** during the past 7 days has been: (Tick one box)

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

15. Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (Tick one box)

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

16. **Mobility**. (Tick one box)

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

17. **Self Care**. (Tick one box)

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

18. Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

……
……
……
……
……
……
……
……
……

FOR SITE STAFF ONLY: SIGNED: _____ **PRINT NAME:** _____ **DATE:** __/__/____

APPENDIX 7. Pain Assessment Questionnaire

Version 4—20/07/2010 **Pain Assessment Questionnaire - Baseline** *Page 1 of 1*

H	O	P	O	N									
Project					Trial Number						Patient Initials		

Part One

Please describe the pain you have experienced in your jaw or mouth over the last 24 hours – please cross the part of the chart that best matches your pain.

Least Possible Pain ——————————— **Worst Possible Pain**

Part Two

Use of painkillers

Which painkillers have you used over the last 24 hours?

None ☐ Listed as follows ☐

Painkiller 1

Name ----------

Dose ---------- *Please state units*

How often used?

Occasionally ☐ Once daily ☐ Twice daily ☐

Three times daily ☐ Four times daily ☐ Other ☐

If Other, specify.....

Painkiller 2

Name ----------

Dose ---------- *Please state units*

How often used?

Occasionally ☐ Once daily ☐ Twice daily ☐

Three times daily ☐ Four times daily ☐ Other ☐

If Other, specify.....

Painkiller 3

Name ----------

Dose ---------- *Please state units*

How often used?

Occasionally ☐ Once daily ☐ Twice daily ☐

Three times daily ☐ Four times daily ☐ Other ☐

If Other, specify.....

FOR SITE STAFF ONLY: SIGNED: _____ **PRINT NAME:** _____ **DATE:** __/__/____

APPENDIX 8. Acute Symptoms Chart

Acute Symptoms Questionnaire

H	O	P	O	N

Project

Trial Number

Patient Initials

Please indicate your experience of the following side-effects in the first week after your surgery by circling the appropriate answer. If you seek professional advice please fill in the extra form

EXAMPLE (if you are experiencing quite a lot of pain then you would circle number 4 - "quite a lot")	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	(4)	5

Day 1 (day after surgery)	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	4	5
Swelling	1	2	3	4	5
Bleeding	1	2	3	4	5
Difficulty in opening mouth	1	2	3	4	5
Difficulty in eating normal diet	1	2	3	4	5

Day 2	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	4	5
Swelling	1	2	3	4	5
Bleeding	1	2	3	4	5
Difficulty in opening mouth	1	2	3	4	5
Difficulty in eating normal diet	1	2	3	4	5

Day 3	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	4	5
Swelling	1	2	3	4	5
Bleeding	1	2	3	4	5
Difficulty in opening mouth	1	2	3	4	5
Difficulty in eating normal diet	1	2	3	4	5

Day 4	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	4	5
Swelling	1	2	3	4	5
Bleeding	1	2	3	4	5
Difficulty in opening mouth	1	2	3	4	5
Difficulty in eating normal diet	1	2	3	4	5

Page 1 of 2

Acute Symptoms Questionnaire

H	O	P	O	N

Project

Trial Number

Patient Initials

Day 5	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	4	5
Swelling	1	2	3	4	5
Bleeding	1	2	3	4	5
Difficulty in opening mouth	1	2	3	4	5
Difficulty in eating normal diet	1	2	3	4	5

Day 6	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	4	5
Swelling	1	2	3	4	5
Bleeding	1	2	3	4	5
Difficulty in opening mouth	1	2	3	4	5
Difficulty in eating normal diet	1	2	3	4	5

Day 7	None	A little	Some	Quite a lot	A lot
Pain	1	2	3	4	5
Swelling	1	2	3	4	5
Bleeding	1	2	3	4	5
Difficulty in opening mouth	1	2	3	4	5
Difficulty in eating normal diet	1	2	3	4	5

At day 8, one week after your surgery, are you comfortable and able to eat normally?

Yes ☐ No ☐

Page 2 of 2

APPENDIX 9. Case for change to definition of the primary endpoint: HOPON trial.

Case for change to definition of the primary endpoint: HOPON trial.

In the current protocol, the primary endpoint of the trial simply relates to the presence / absence of osteoradionecrosis. This is described in textbooks and research articles over the previous 3 decades as:

"Exposed and necrotic bone associated with ulcerated or necrotic surrounding soft tissue which persists for greater than three months in an area that had been previously irradiated (not caused by tumour recurrence)."[1,2]

This description has been adopted as closely as possible for a definition of the primary endpoint: that if at 6 months, there is incomplete mucosal healing with exposed bone the case is described as ORN, if there is complete bony healing without exposed bone it is not ORN.

Upon seeing patients at their 6/12 primary endpoint, and further on review of blinded images of cases, the HOPON team noted a small but significant number of cases where there was near total or total mucosal healing associated with minor bone spicules. In clinical practice the investigators would not regard them as ORN, they are not symptomatic, and they probably reflect delayed healing rather than progressive necrosis, although the latter is conjecture.

The HOPON team were concerned that classifying these cases as either "healed" or "ORN" was unsatisfactory. They felt that an additional class "minor bone spicules" should be used to enhance clarity, where the total area of exposed bone <4 x5mm, or 10x 2mm ie. <20mm^2. For the purpose of the HOPON trial, minor bone spicules will be analysed as if healed (grouped with "not ORN"), as the clinical significance is equivalent to this. There was a concern that if the PI were reporting as ORN, and by chance they were skewed to one or other arm of the trial, this would unfavourably distort the results, possibly undermining the whole trial. If minor bone spicules were seen equally distributed in both arms of the trial, then this would likely not affect the result, but would lead to a misleading, high, incidence of ORN for this cohort of patients. As the incidence of ORN after surgery is unknown, the overall level of risk of developing ORN should be accurately reported as an important outcome of HOPON.

Because the trial is powered on clinically significant ORN (as has, we presume, been reported in previous audits, cohorts and trials), this has no impact on the differences between the arms necessary to change practice, the power calculation, or the sample size.

The classification for the purposes of the HOPON trial will therefore be: Not ORN: mucosa healed or minor bone spicules (<20mm^2); ORN present & further subdivided to Notani[3] 1 (& >20mm^2) Notani 2 or Notani 3. Having encountered this problem, we feel it would be worth publishing this modified scoring system for use in classifying ORN in clinical trials. The problem arises in taking a reasonable working textbook definition of a condition and too literally applying it as a primary endpoint on a clinical trial.

1. M. Harris. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. Br J Oral Maxillofac Surg, 30 (1992), pp. 313–318
2. Shaw RJ, Dhanda J. Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part I: treatment. Br J Oral Maxillofac Surg. 2011 Jan;49(1):2-8.
3. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, Nakamura M. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy.. Head Neck. 2003 Mar;25(3):181

APPENDIX 10: Procedure for reviewing HOPON Photographs and OPT images at 6 month following surgery

Introduction

This document describes the procedure for reviewing the primary endpoint for HOPON and deriving a "definitive" outcome to be used for the DMC and Final analyses.

Procedure

Upon receipt of the 6 month HOPON photographs and OPT images at LCTU, the HOPON Trial Coordinator will send the photographs and OPT images to the CI (Prof. Richard Shaw) and CC (Mr. Chris Butterworth) simultaneously but separately for a review. If 6 month images are not received, please see below.

The CI and CC will then review the images and reach an agreement on the assessment of ORN. If they cannot reach an agreement, please see below. If the 6 month images are inadequate (in that they alone are of insufficient quality to assess ORN), then the result of the 3 and 12 month images will be used to base their decision (eg if ORN is present at 3 months and 12 months it will be assumed present at 6 months). If both of their reviews are the same as the site Principal Investigator (PI), then the final ORN assessment will be that of the PI.

If the CI and CC's consensus assessment differs from the site PI, or if the CI & CC cannot agree a consensus diagnosis then the TC will liaise with the relevant site PI/co-investigator and make arrangements to discuss the relevant patient with the CI and CC. If the CI, CC and site local investigator reach an agreement on the assessment of ORN taking into account the 3 and 12 month results (if available), then the final ORN diagnosis will be determined. If agreement is not reached, a majority vote will be taken.

If the blinded review is not possible for example due to lack of/poor quality patient images, then the local Investigator's assessment will be used to determine the final outcome and the observation will be down weighted in the statistical analysis. Instances of exposed bone which are less than 20mm squared will not be considered as ORN, but classed as "minor bone spicules".

The table below will be distributed separately to CI and CC and their separate diagnoses entered before merging with each other and the 3 month, 6 month and 12 month PI diagnoses.

The CC and CI will complete the following columns (listed by A-I):

1) E and F
2) They will return their assessments to the TC
3) The TC will merge the results into a single table
4) The TC will complete column G
5) The TC will complete columns A to D
6) If there is no consensus between the CI and CC, the CI and CC will be informed and asked to discuss the individual cases taking into account the local investigator's data in columns B and D
7) If there is a consensus between the CI and CC, but not the local investigator, or if the image quality is insufficient to allow an assessment to be made, this will be shown in column G and the TC will then contact the local investigator to arrange discussions between the local investigator, CI and CC
8) Once a consensus is reached by all parties, this will be reflected in column I
9) Column H will be completed in cases were the local investigator revises their original 6 month decision to match that of the CI and CC, using the classifications shown in Table B below
10) If a consensus is not reached, a majority decision will be taken and column I will be update
11) If the blinded review is not possible for example due to lack of/poor quality patient images, then the local Investigator's assessment will be used to determine the final outcome and the observation. This will be indicated in column I and J
12) The data shown on columns A, I and J will be used to update MACRO

TABLE A:

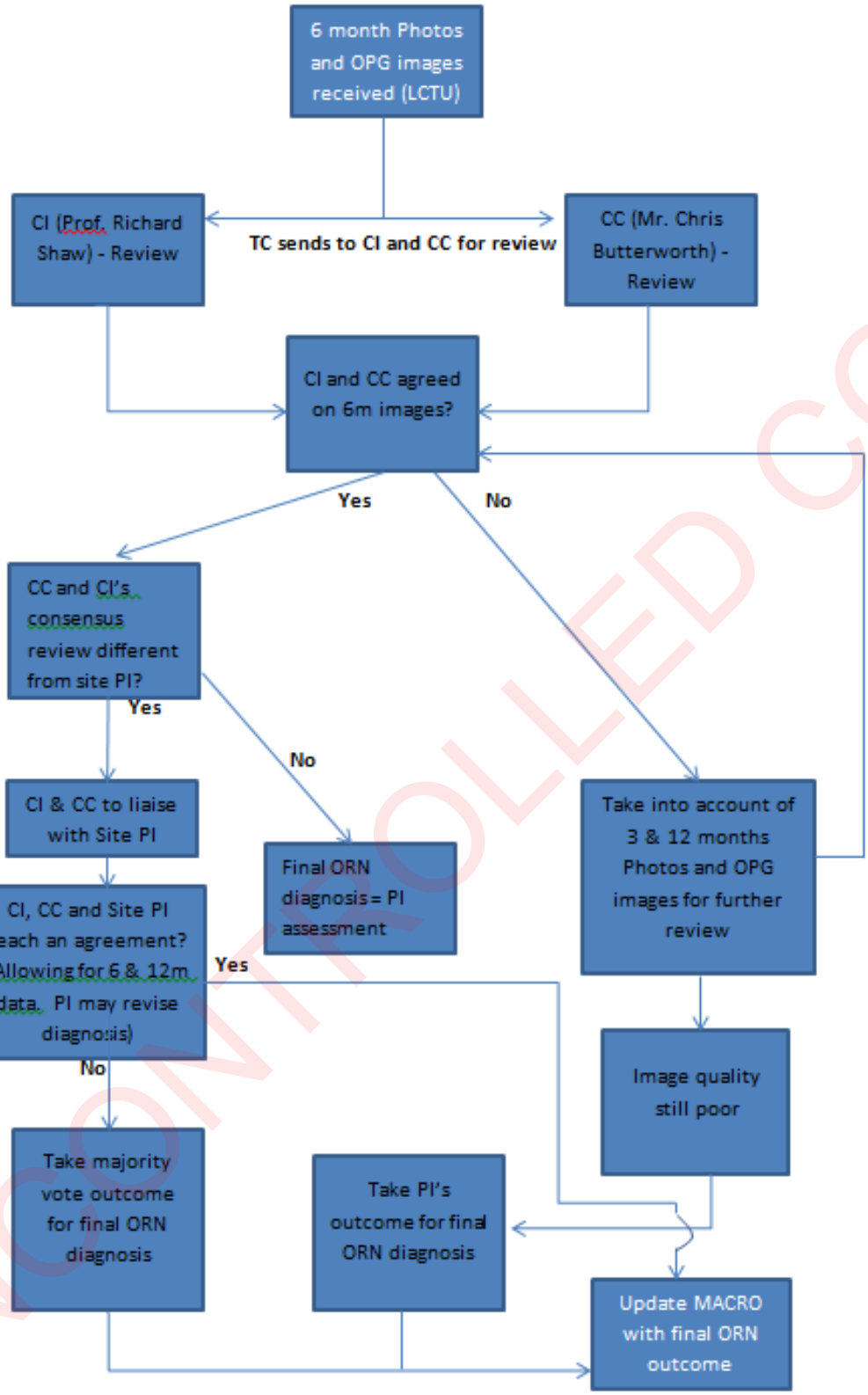
A Patient no	B PI 3mth	C PI 6mth (Primary EP)	D PI 12mth	E CI review 6m	F CC review 6m	G 3 Way Discussion (y/n)	H Revised PI diagnosis (if applies)	I Final diagnosis	J Final diagnosis based on original PI assessment only (y/n)
		Mucosal healing		1	2	yes		1	
		Notani 1							
		Notani 2							
		Notani 3							

TABLE B

Diagnoses will be coded as follows:

Mucosal healing	1
Minor bone spicules	2
Notani 1	3
Notani 2	4
Notani 3	5

Flowchart of process



APPENDIX 11: Late follow up of MBS (Minor Bone Spicules)

Version 1—09/01/2017 **HOPON Late Follow Up CRF** *Page 1 of 1*

H	O	P	O	N									

Project — Trial Number — Patient Initials

Late follow up of MBS (Minor Bone Spicules)

Selection - diagnosis of MBS at 12 month HOPON trial visit (or last recorded trial visit in the event that the 12 month visit was omitted)

1. Has the patient received ongoing clinical review since completing HOPON assessments?

   No ☐ Yes ☐

   If "No" please go to the final step of posting off the form.

2. Can it be determined from patient records if areas of surgery in HOPON trial were fully healed or had exposed bone?

   No ☐ Yes ☐

   If "No" please go to the final step of posting off the form.

Please complete one row of this table for each appointment since the HOPON 12 month trial visit.

If there were more than one area of exposed bone, please state the worst severity as per the grading: Healed / Minor Bone Spicule (MBS) / Notani 1 / Notani 2 / Notani 3

Date of assessment	Result* Please tick ONLY one box for each date
__/__/____ dd/mm/yyyy	☐ Healed ☐ MBS ☐ Notani 1 ☐ Notani 2 ☐ Notani 3
__/__/____ dd/mm/yyyy	☐ Healed ☐ MBS ☐ Notani 1 ☐ Notani 2 ☐ Notani 3
__/__/____ dd/mm/yyyy	☐ Healed ☐ MBS ☐ Notani 1 ☐ Notani 2 ☐ Notani 3
__/__/____ dd/mm/yyyy	☐ Healed ☐ MBS ☐ Notani 1 ☐ Notani 2 ☐ Notani 3
__/__/____ dd/mm/yyyy	☐ Healed ☐ MBS ☐ Notani 1 ☐ Notani 2 ☐ Notani 3

***Definition:**
'Healed' – full mucosal / skin healing in area of previous surgery
'MBS' – Minor Bone Spicules - <=20mm2 exposed bone (i.e. 4 x 5mm, or 2 x 10mm)
'Notani 1' - Exposed bone, extent limited to dentoalveolar bone
'Notani 2' – Exposed bone, limited to area above ID canal
'Notani 3' – Exposed bone, full thickness of mandible, or pathological fracture, or extra-oral fistula.

Please post the completed form to the HOPON Trial Coordinator:
CRUK LCTU, University of Liverpool, 1st floor Block C, Waterhouse Building,
3 Brownlow Street, Liverpool L69 3GL

FOR SITE STAFF ONLY: SIGNED: ____________ PRINT NAME: ____________ DATE: __/__/___

APPENDIX 12: Late follow up of implant survival

Version 1—09/01/2017 **HOPON Late Follow Up CRF** *Page 1 of 1*

H	O	P	O	N

Project | Trial Number | Patient Initials

Late follow up of implant survival

Selection – patients in HOPON trial – eligibility was placement of implants

1. How many implants were placed in the mandible? ☐

2. Were any implants recorded as lost during HOPON follow-up?

No ☐ *If "No" then please go to step 3*

Yes ☐ *If "Yes" then please specify dates implants lost and return form*

__/__/____ *dd/mm/yyyy*
__/__/____ *dd/mm/yyyy*
__/__/____ *dd/mm/yyyy*
__/__/____ *dd/mm/yyyy*

3. Has the patient received ongoing clinical review since completing HOPON assessments?

No ☐ *If "No" please go to the final step of posting off the form.*

Yes ☐

4. Please give date of most recent review since completing HOPON assessments

__/__/____ *dd/mm/yyyy*

5. Do patient records show if any implants have been lost?

No ☐ *If "No" please go to the final step of posting off the form.*

Yes ☐

6. Please give dates on which implants were lost since completing HOPON assessments

__/__/____ *dd/mm/yyyy*
__/__/____ *dd/mm/yyyy*
__/__/____ *dd/mm/yyyy*
__/__/____ *dd/mm/yyyy*

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FOR SITE STAFF ONLY: SIGNED: _____ **PRINT NAME:** _____ **DATE:** __/__/____