Clinical trial results:
Hyperbaric Oxygen for the Prevention of Osteoradionecrosis (HOPON): A Randomised Controlled Trial of Hyperbaric Oxygen to prevent Osteoradionecrosis of the Irradiated Mandible.

Summary

EudraCT number	2007-006225-27
Trial protocol	GB
Global end of trial date	24 January 2018

Results information

Result version number	v1 (current)
This version publication date	31 May 2019
First version publication date	31 May 2019

Trial information

Trial identification

Sponsor protocol code	SP000283141

Additional study identifiers

ISRCTN number	ISRCTN39634732
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	765 Brownlow Hill, Liverpool, United Kingdom, L69 7ZX
Public contact	Clinical Trials Information, Cancer Research UK Liverpool Cancer Trials Unit, 0044 01517948938, lctu@liverpool.ac.uk
Scientific contact	Clinical Trials Information, Cancer Research UK Liverpool Cancer Trials Unit, 0044 01517948938, lctu@liverpool.ac.uk
Sponsor organisation name	Aintree University Hospitals NHS Foundation Trust
Sponsor organisation address	Longmoor Lane, Liverpool, United Kingdom, L9 7AL
Public contact	Clinical Trials Information, Cancer Research UK Liverpool Cancer Trials Unit , 0044 0151 7948938, lctu@liverpool.ac.uk
Scientific contact	Clinical Trials Information, Cancer Research UK Liverpool Cancer Trials Unit , 0044 0151 7948938, lctu@liverpool.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2018
Global end of trial reached?	Yes
Global end of trial date	24 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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).

Protection of trial subjects:

Central and on-site monitoring was conducted to help protect patients and to monitor performance relating to trial procedures, trial intervention administration and laboratory/data collection processes. A risk assessment was carried out to determine the level of monitoring required, and subsequently a monitoring plan was developed to document how and when monitoring is conducted and to what extent. Patient safety was also monitored via LCTU pharmacovigilance procedures (reporting and review of adverse event data) and by an ISDMC.

A Trial Management Group regularly reviewed central monitoring reports and advised accordingly.

Serious adverse events were followed-up until resolution or death. Annual safety reports were submitted to the national regulatory authorities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 141
Country: Number of subjects enrolled	Denmark: 3
Worldwide total number of subjects	144
EEA total number of subjects	144

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	105
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The HOPON trial recruited 144 patients across 17 centres across England, Wales and Denmark between 24/09/2008 and 16/11/2016.

Pre-assignment

Screening details:

144 of the 256 patients screened were recruited to the study. Patients provided consent and then screening assessments were performed to determine eligibility prior to randomisation into standard or hyperbaric treatment arms.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial is open-label due to the different schedules of treatment administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care plus HBO

Arm description:

Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.

Arm type	Experimental
Investigational medicinal product name	Hyperbaric oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

20 pre-operation HBO dives and 10 Post operation HBO dives

Arm title	Standard preoperative care

Arm description:

Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.

Arm type	Standard management arm

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Standard care plus HBO	Standard preoperative care
Started	72	72
Completed	72	72

Period 2

Period 2 title	Therapy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial is open labelled

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care plus HBO

Arm description:

Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.

Arm type	Experimental
Investigational medicinal product name	Hyperbaric oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

20 pre-operation HBO dives and 10 Post operation HBO dives

Arm title	Standard preoperative care

Arm description:

Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.

Arm type	Standard management arm

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Standard care plus HBO	Standard preoperative care
Started	72	72
Completed	55	66
Not completed	17	6
Withdrew during/after HBO before surgery	3	-
Withdrew before HBO	14	-
Withdrew before surgery	-	6

Period 3

Period 3 title	Follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial is open label

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care plus HBO

Arm description:

Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.

Arm type	Experimental
Investigational medicinal product name	Hyperbaric oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

20 pre-operation HBO dives and 10 Post operation HBO dives

Arm title	Standard preoperative care

Arm description:

Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.

Arm type	Standard management arm

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Standard care plus HBO	Standard preoperative care
Started	55	66
Completed	44	51
Not completed	11	15
Withdrew after surgery	11	15

Baseline characteristics

Reporting groups	
Reporting group title	Standard care plus HBO
Reporting group description:	
Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.	
Reporting group title	Standard preoperative care
Reporting group description:	
Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.	

Reporting group values	Standard care plus HBO	Standard preoperative care	Total
Number of subjects	72	72	144
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	57.9	57.6	
standard deviation	± 11.3	± 11.1	-
Gender categorical Units: Subjects			
Female	53	53	106
Male	19	19	38
Smoking Units: Subjects			
Smoking - Never	23	23	46
Smoking - Past	31	33	64
Smoking-Current	14	15	29
Smoking - Not recorded	4	1	5
Alcohol Units: Subjects			
Alcohol - Never	5	4	9
Alcohol - Past	6	12	18
Alcohol - Current	33	34	67
Alcohol - Not recorded	28	22	50

R/Therapy dose (mean) Units: Gy			
arithmetic mean	63.5	62.3	
standard deviation	± 10.3	± 9.4	-
Radiotherapy duration Units: Weeks			
arithmetic mean	6.2	6	
standard deviation	± 1.6	± 1.7	-

End points

End points reporting groups

Reporting group title	Standard care plus HBO

Reporting group description:

Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.

Reporting group title	Standard preoperative care

Reporting group description:

Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.

Reporting group title	Standard care plus HBO

Reporting group description:

Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.

Reporting group title	Standard preoperative care

Reporting group description:

Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.

Reporting group title	Standard care plus HBO

Reporting group description:

Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.

Reporting group title	Standard preoperative care

Reporting group description:

Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Following discussion with the TSC Chair and DMC Statistician it was decided that the primary analyses will be performed on a “per protocol-like” basis, analysing only patients who received surgery according to the treatment group originally allocated. This will be supported by sensitivity analyses

Primary: Primary Endpoint

End point title	Primary Endpoint

End point description:

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

End point type	Primary

End point timeframe:

The presence of osteoradionecrosis at 6 months after surgery.

End point values	Standard care plus HBO	Standard preoperative care	Per Protocol	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	47	53	100	
Units: Patients	3	3	6	

Statistical analyses

Statistical analysis title	Mucosal Healing at 6 months
Comparison groups	Standard care plus HBO v Standard preoperative care
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	8.92
Variability estimate	Standard error of the mean
Dispersion value	1.06

Secondary: Mucosal Healing at 3 months

End point title	Mucosal Healing at 3 months

End point description:

End point type	Secondary

End point timeframe:

The presence of ORN at 3 months follow-up

End point values	Standard care plus HBO	Standard preoperative care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	55		
Units: Patients	9	12		

Statistical analyses

Statistical analysis title	Mucosal Healing at 3 months
Comparison groups	Standard care plus HBO v Standard preoperative care
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	0.56

Secondary: Mucosal Healing at 12 months	
End point title	Mucosal Healing at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
12 months follow-up	

End point values	Standard care plus HBO	Standard preoperative care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	50		
Units: Patients	5	6		

Statistical analyses

Statistical analysis title	Mucosal Healing at 12 months
Comparison groups	Standard care plus HBO v Standard preoperative care
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	3.81
Variability estimate	Standard error of the mean
Dispersion value	0.79

Secondary: Severity of Osteoradionecrosis

End point title	Severity of Osteoradionecrosis
End point description:	
End point type	Secondary
End point timeframe:	
6 months follow-up	

End point values	Standard care plus HBO	Standard preoperative care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	57		
Units: Patients				
Notani G1	7	7		
Notani G2	1	0		
Notani G3	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain

End point title	Pain
End point description:	
End point type	Secondary
End point timeframe:	
6 Months Follow-up	

End point values	Standard care plus HBO	Standard preoperative care	Standard care plus HBO	Standard preoperative care
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	69	51	54
Units: Patients				
median (inter-quartile range (Q1-Q3))	0.063 (0.011 to 0.234)	0.074 (0.02 to 0.389)	0.02 (0 to 0.106)	0.03 (0.011 to 0.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life

End point description:

End point type	Secondary

End point timeframe:

6 months follow-up

End point values	Standard care plus HBO	Standard preoperative care	Standard care plus HBO	Standard preoperative care
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	71	55	50
Units: Patients				
arithmetic mean (standard error)	60 (± 2.8)	58.8 (± 2.7)	54.2 (± 3.4)	59.6 (± 3.3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs that occur within 28 days following the last dose of trial treatment will be reported.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	3

Reporting groups	
Reporting group title	Standard care plus HBO
Reporting group description:	
Standard care plus 20 Hyperbaric Oxygen (HBO) treatments prior to surgery followed by a further 10 HBO treatments. HBO complies with dive table RN66.	
Reporting group title	Standard preoperative care
Reporting group description:	
Pre- and post- operative chlorohexidine mouthwash 0.2% – 10ml washed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively; antibiotic cover pre-and post-operatively.	

Serious adverse events	Standard care plus HBO	Standard preoperative care	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 58 (32.76%)	13 / 72 (18.06%)	
number of deaths (all causes)	7	5	
number of deaths resulting from adverse events	0	0	
Investigations			
Investigations - Other, specify			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other: Malignant Neoplasm			
subjects affected / exposed	8 / 58 (13.79%)	5 / 72 (6.94%)	
occurrences causally related to treatment / all	1 / 8	0 / 6	
deaths causally related to treatment / all	0 / 6	0 / 5	
Injury, poisoning and procedural complications			
Fracture			

subjects affected / exposed	2 / 58 (3.45%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders - Other, specify			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Other: ear barotrauma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hearing impaired			

subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Other: uterine Bleeding			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other: post-op hypoventilation & acidosis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	2 / 58 (3.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorder - Other, specify			

subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other: jaw ORN and associated infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Standard care plus HBO	Standard preoperative care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 58 (48.28%)	17 / 72 (23.61%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	4 / 58 (6.90%)	1 / 72 (1.39%)	
occurrences (all)	5	1	
Teratoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
death			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Lung cancer metastatic			

subjects affected / exposed	0 / 58 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
PATIENT ADMITTED TO HOSPICE FOR PALLIATIVE CARE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Bronchial carcinoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
endovascular repair for pre existing abdominal aortic aneurysm			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pain	Additional description: PAIN R MANDIBLE - UNDIAGNOSED CAUSE HOSPITALISATION FOR ACUTE FACIAL PAIN LEFT MANDIBLE		
subjects affected / exposed	2 / 58 (3.45%)	3 / 72 (4.17%)	
occurrences (all)	2	3	
Fatigue			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Uterine bleeding episode leading to hysteroscopy and biopsy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
PULMONARY OEDEMA:FAILED EXTUBATION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
POST OP HYPOVENTILATION/ACIDOSIS			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Fracture			
subjects affected / exposed	1 / 58 (1.72%)	2 / 72 (2.78%)	
occurrences (all)	1	2	
INPATIENT EPISODE TO REPAIR SUSTAINED FACIAL INJURIES			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
OXYGEN TOXICITY CONVULSION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
SEVERE PAIN FROM NERVE TO SCAPULA WITH PARESTHESIA OF HEMIPLEGIA ON THE RIGHT SIDE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
SLight CVA			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
OTIC BAROTRAUMA			
subjects affected / exposed	2 / 58 (3.45%)	0 / 72 (0.00%)	
occurrences (all)	3	0	
EPISTAXIS DURING DECOMPRESSION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
RESIDUAL DEFECT IN VISUAL FIELD OF RIGHT EYE			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
SUBCONJUCTIVAL HAEMORRHAGE			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Dysphagia	Additional description: DYSPHAGIA AND SUBSEQUENT ADMISSION FOR PEGTUBE PLACEMENT		
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
EXTRACTION LL5 (XLA WITH SEDATION)			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Endocrine disorders			
BLOCKED PAROTID DUCT L SIDE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
NECROTIC MANDIBULAR BONE EXPOSURE REQUIRING SURGICAL INTERVENTION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
INFECTED CHIN DRAINAGE			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
INFECTED SOCKET			
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Helicobacter infection	Additional description: PATIENT HOSPITALISED WITH VARIOUS SYMPTOMS AND DIAGNOSED WITH HELCOBACTER PYLORI - COLIFORM CHEST INFECTION AND VERTEBRAE WEDGE FRACTURES T12 TO L4		
subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
INTRA ORAL INFECTION			

subjects affected / exposed	0 / 58 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Chest infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 72 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2008	Protocol updated to version 2.0, 16 April 2008 after MREC and NCRN review, and included alterations to the Patient Information Sheet, GP letter and Consent form (which are included as appendices in the protocol and as separate documents and pdf files on the disk), typographical errors in the protocol, and amendments to the protocol. Also, Protocol version 1.0 detailed a gingival biopsy that was to be performed and tissue samples collected as part of a sub study. This is no longer the case and only blood will be collected from patients.
28 November 2008	Protocol updated to version 3.0, 04/11/2008 to include the following: Volume of blood collected changed from 5ml to 6ml as there are no 5ml blood collection vaccutainers on the market. General updates made to the protocol to make it easier to read, some addresses changes, site contact details added.
27 January 2010	Protocol updated to version 4.0, 09/12/2009 to cover the following: 1. Added list of abbreviations 2. Additional recruiting centres 3. Additional text added to the main inclusion criteria to clarify the evidence of cancer recurrence 4. Exclusion criteria clarified in the event of patient becoming pregnant 5. Primary and secondary outcome measures reworded for clarity 6. General updates made throughout the protocol to make it easier to read
02 July 2010	Protocol updated to version 5.0, 07/05/2010 to cover the following: 1. Details of recruitment of another 150 patients over the next three years followed by one year of follow up added. 2. References to phase II trial and potential phase III trial removed. 3. Trial end date changed. 4. Trial Steering Committee members updated. 5. Statistical and analytical details amended for phase III. 6. GP letter updated (removed reference to Feasibility study as is now phase III). 7. Additional trial sites added (University Hospital of Wales, Worcestershire Royal Hospital, University 8. Hospital Coventry and Warwickshire, Midlands Diving Chamber). 9. Principal Investigator in Leeds replaced. 10. Additional Secondary Endpoint 11. Other minor corrections.

04 October 2012	Protocol updated to version 6.0, 28/06/2012 to cover the following: 1. Typographical corrections 2. Additional expertise added in the form of a clinical oncologist, lecturer in medical oncology and an additional lay member. 3. Contact details for research team members updated 4. Protocol version 5 stated that for patients who had missed 3 or less HBO dives, they would have extra dives added on at the end to make sure that they had the full 30 HBO dives. The new version allows for any amount of HBO dives to have been missed (not just 3 or less) which will then be added on to the end of their treatment to ensure the full amount of dives have been given. This amendment has been advised by the HOPON TSC on 03/10/11. It also reaffirms that patients will be followed up as per protocol. 5. This text has been removed based on the advice of the HOPON TSC on 03/10/11. Patients who have missed 4 or more HBO sessions will continue to receive HBO treatment and follow up as per protocol. 6. Contact Numbers for the Centres and Investigators updated. Details for Leeds, Guy's, Plymouth, Cardiff and Aberdeen, corrected.
14 June 2013	Protocol updated to version 7.0, 25/04/2013 to cover the following: 1. Trial duration extended for patient recruitment. Previously it was May 2010 – May 2014. But it was updated to May 2014 – Feb 2018. 2. The total number of patients to be randomised will slightly increase from 200 to 221 to adjust for increased drop-out rate. 3. Reference Safety Information details added for information on relevant SmPC for trial IMP. 4. Annual recruitment, total recruitment and duration of recruitment amended to reflect the changes detailed above. 5. Site removed from list of participating sites as site is to be closed out (site closure already approved by MREC) 6. Site details added and name of Principal Investigators updated as were not present in previous version of protocol.
24 March 2016	Protocol updated to version 8.0, 26/11/2015 to cover the following: Change to the Primary Outcome measures. 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). Change in Title and address of the Chief Investigator and change of Trial Coordinator details throughout the protocol Change in email address of Mr Gerry Robertson (TSC Chair) Removal of a Trial Steering Committee member Change to the Secondary Outcome measures: 8.1.2. Secondary Outcomes: The diagnosis of osteoradionecrosis at 3 and 12 months (in the same way as the 6 month outcome) Severity of cases of diagnosed osteoradionecrosis, according to Notani grade Pain: patient questionnaire at baseline, 3, 6 and 12 months 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) 8.1.3. Safety Outcomes: Adverse events in HBO arm related to hyperbaric oxygen treatment 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. New Diagnosis of cancer, either recurrent or new site within 12 months following surgery Change to section 10.7 Randomisation Code List An update to Website for checking and downloading current versions of the SMPC: https://lakemedelsverket.se/LMF/?q=oxygen Update to section 13.1. Quality control Update to section 18. Statistical Considerations – this has been extensively revised and re-written so no concise summary is possible. Update to protocol for Change in the Principal Investigators at different sites Addition of New References to the protocol

08 February 2017	Protocol updated to version 9.0, 11/01/2017 to cover the following: 1. Minor Bone Spicules. Following clarification of the endpoints earlier in 2016, and changes to the protocol subsequently approved by HOPON trial governance committees, REC and MHRA, these changes were subject to external peer review and have recently been published: Refining the definition of mandibular osteoradionecrosis in clinical trials: The cancer research UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis). Shaw R, Tesfaye B, Bickerstaff M, Silcocks P, Butterworth C. Oral Oncol. 2017 Jan;64:73-77. doi: 10.1016/j.oraloncology.2016.12.002. At the most recent meeting of the HOPON Trial Steering Committee, it was decided that in order to properly implement the endpoints, the protocol required additional amendments with the aim of follow up of secondary endpoints for Minor Bone Spicules (MBS). (Only relevant for those patients who have MBS at the 12 month endpoint). This is in order to assess the risk of further deterioration for patients with MBS, and hence the validity of the current assumption that these patients do not in fact have osteoradionecrosis, instead having slightly delayed but otherwise normal and complete healing. 2. Implant retention. (Only relevant for those patients for whom eligibility was placement of dental implants) To analyse the effect of HBO on implant retention in the irradiated mandible. This outcome was in fact included within previous protocols, and the original approvals, but owing to an oversight on our behalf had been excluded from appropriate follow up arrangements. We now seek to properly address this secondary endpoint as originally intended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30851351