RAPTOR: Randomised Controlled Trial of PENTOCLO* in Mandibular Osteoradionecrosis

*(Pentoxifylline, Tocopherol & Clodronate)

RAPTOR Protocol
V1.0 02/08/2022

Study Sponsor:
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Protocol Approval

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

Authorised by Chief Investigator:

Signature: _____ **Date:** _____

Professor Richard Shaw
Professor of Head & Neck Surgery, Honorary Consultant in Oral & Maxillofacial Surgery

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

Authorised on behalf of Sponsor:

Signature: _____ **Date:** _____

Karen Wilding
Senior Clinical Research Governance Manager
University of Liverpool

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

Authorised on behalf of the Lead Statistician:

Signature: _____ **Date:** _____

Dr Richard Jackson
Senior Trial Statistician
Liverpool Clinical Trials Centre

General Information

This document describes the RAPTOR trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Professor Richard Shaw via the clinical trials unit (CTU).

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 14.

The Liverpool Clinical Trials Centre (LCTC) brings together a wealth of expertise built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration CTU network since its establishment in 2007 (www.ukcrc.org). The LCTC has a diverse trial portfolio underpinned by methodological rigour, a Good Clinical Practice (GCP) compliant data management system, and core standard operating procedures.

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**
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Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**
Karen Wilding Senior Clinical Research Governance Manager The University of Liverpool Clinical Directorate Thompson Yates Building The Quadrangle, Brownlow Hill, Liverpool L3 5RB E-mail: sponsor@liverpool.ac.uk	Professor Richard Shaw Department of Molecular & Clinical Cancer Medicine University of Liverpool The University of Liverpool Cancer Research Centre, 200 London Road Liverpool L3 9TA Telephone Number: 0151 529 5290 E-mail: rjshaw@liv.ac.uk

In cases where the CI is unavailable to respond to urgent queries the following individuals will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:	**Medical Expert who will Evaluate SAE Reports:**
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Additional Contacts:
The contact details for the trial oversight committee members and participating sites are detailed in documents supplementary to the protocol and stored in the Trial Master File.

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2 GLOSSARY

AE	Adverse Event
APP	Application
APR	Annual Progress Report
AR	Adverse Reaction
BM	Blood Glucose
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DNA	Deoxyribonucleic Acid
DSUR	Developmental Safety Update Report
EME	Efficacy and Mechanism Evaluation
ePROM	Electronic Patient Reported Outcome Measure
EU	European Union
EUCTD	European Clinical Trials Directive
EUDRACT	European Clinical Trials Database
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GP	General Practitioner
HCP	Health Care Professional
HNSCC	Head and Neck Squamous Cell Carcinoma
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiotherapy
INR	International Normalised Ratio
IPD	Individual Participant Data
IS	Information Systems
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
LFT	Liver function tests
LWBC	Living With and Beyond Cancer
MA	Marketing Authorisation
MHRA	Medicines and Health care products Regulatory Agency
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health Care Excellence

NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
ORN	Osteoradionecrosis
PENTOCLO	Pentoxifylline, Tocopherol & Clodronate
PI	Principal Investigator
PISC	Participant Information Sheet and Consent
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
R&D	Research & Development
RAPTOR	Randomised Controlled Trial of PENTOCLO in Mandibular Osteoradionecrosis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
ROS	Reactive Oxygen Species
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOMA	Subjective, objective, management and analytic
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SSC	Standard Supportive Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UE	Urea & Electrolytes
USM	Urgent Safety Measure

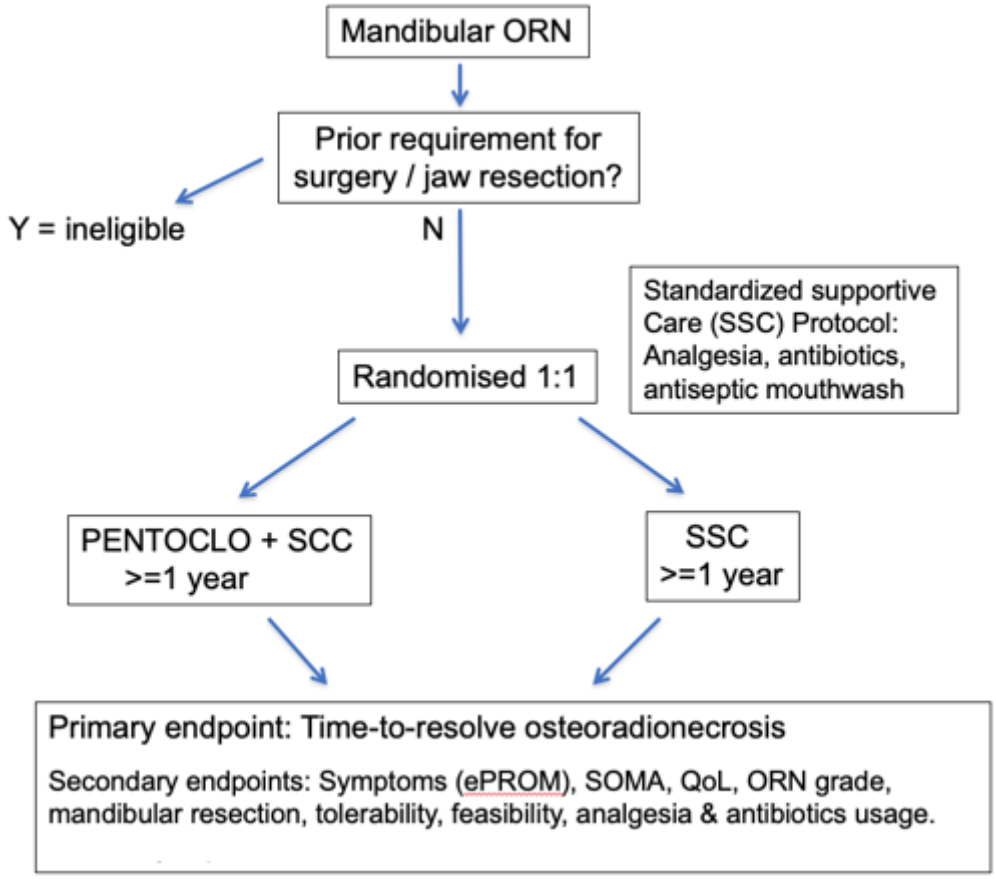
3 PROTOCOL OVERVIEW

Full Title:	Randomised Controlled Trial of PENTOCLO in Mandibular Osteoradionecrosis
Acronym:	RAPTOR
Phase:	II
Target Population:	RAPTOR aims to establish the value of the repurposed drug combination Pentoxifylline, Tocopherol & Clodronate (termed PENTOCLO) in treating osteoradionecrosis (ORN) of the mandible. The target population is patients who have previously been cured of head and neck cancer that have received radiotherapy, and who have ORN of the mandible.
Sample size:	120 patients
Inclusion Criteria:	1. Patients with ORN of the mandible 2. Patients considered suitable for medical management 3. Written and informed consent obtained from participant and agreement of participant to comply with the requirements of the study
Exclusion Criteria:	1. Cannot swallow tablets 2. Prior treatment with PENTOCLO or any element thereof within 12 months of the date of randomisation 3. Very early ORN (<20 mm^2 exposed bone) occurring within 12 months of a dental extraction or other dentoalveolar operation ('Minor Bone Spicules' see flowchart below) 4. Mandibular pathological fracture secondary to ORN 5. Extra-oral communicating fistula secondary to ORN 6. Prior surgery/jaw resection 7. Pregnancy 8. Lactation 9. Age <18 years 10. Acute infection at site of the necrotic bone. 11. Contraindications to PENTOCLO medications: a. Known hypersensitivity, allergy or anaphylaxis to pentoxifylline, tocopherol or sodium clodronate b. Treated hypotension c. Severe coronary artery disease, defined as grade IV of the Canadian Cardiology Society Angina Grading[(1)] d. Severe atrial fibrillation, defined as grade 4 on modified CCC-SAF[(2)] e. Myocardial infarction within 6 months f. Prior history of extensive retinal haemorrhage g. Prior history of intracranial bleeding h. Impaired renal function (Creatinine clearance <30 ml/minute, will be formally assessed only if U&E out of reference) i. Severe liver failure (class B or C Pugh-Child Score, will be formally assessed only if LFT values, out of reference)

	j. Concomitant prescription of anti-platelet agents: clopidogrel, eptifibatide, tirofiban, epoprostenol, iloprost, abciximab, anagrelide, NSAIDs, acetylsalicylates (ASA/LAS) including aspirin >75 mg*, ticlopidine, dipyridamole. (*low dose =<75 mg aspirin is permitted) k. Concomitant prescription of ketorolac, cimetidine, ciprofloxacin, theophylline, estramustine phosphate l. Hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency m. Concomitant prescription other bisphosphonates e.g. risedronate, alendronate, aIbandronate, zoledronic acid, pamidronate, etidronate or prescription of denosusamab n. Concomitant prescription of aminoglycoside antibiotics e.g. gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, paromomycin	
Study Sites and Distribution:	UK, Secondary and tertiary NHS hospitals	
Patient Study Duration:	Utilising a recruitment period of 2 years, the minimum follow-up period will be 1 year and maximum 3 years per patient. Duration of treatment: Minimum 1 year – maximum 3 years Duration of follow-up: maximum 3 years to a minimum 1 year from the last patient recruited	
Study Duration:	Start: September 2022 End: December 2025	
IMP/Intervention:	**Intervention:**	
	IMP: Form: Dose: Route:	Pentoxifylline 400 mg modified release tablet (TRENTAL 400) 800 mg per day, split as twice daily 400 mg tablets Oral
	IMP: Form: Dose: Route:	Tocopherol (Vitamin E) Suspension 1000 mg/day, single dose Oral
	IMP: Form: Dose: Route:	Sodium Clodronate 400 mg tablets 1600 mg/day as a single dose, only Mon-Fri Oral
	Control:	No medication received
Objectives:		
Objective:	RAPTOR aims to establish the value of the repurposed drug combination Pentoxifylline, Tocopherol & Clodronate (termed PENTOCLO) in treating ORN of the mandible.	

Primary:	The primary aim is to determine if PENTOCLO triple therapy is effective in healing of mandibular ORN.
Secondary:	To evaluate the impact on PENTOCOLO on: • Patients pain and mouth function • Patients ability to receive treatment and control the disease • Patients analgesia and antibiotic use • Patients anthropological measurements • Severity of disease • Overall Quality of Life • Mandibular preservation • Associated toxicity
Translational:	To provide genomic DNA from a cohort of patients with ORN for future studies on the genomic determinants of late radiation toxicity.

3.1 Schematic of Study Design



4 ROLES AND RESPONSIBILITIES

Chief Investigator (CI): Professor Richard Shaw is the CI for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators (PI): In each participating site a PI will be identified to be responsible for identification, recruitment, data collection and completion of case report forms (CRFs), along with follow-up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: Liverpool Clinical Trial Centre (LCTC) at the University of Liverpool in collaboration with the CI, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File (TMF) management (limited to duties delegated to LCTC), safety reporting, data management, ePROM development, randomisation, statistical analysis and participating site coordination.

4.1 Sponsor

The University of Liverpool is the Sponsoring organisation and is legally responsible for the study. They will formally delegate specific Sponsoring roles to the CI and CTU.

4.2 Funder

This project (NIHR131050) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

Funder(s)	**Financial and Non-financial Support Given**
NIHR Efficacy and Mechanism Evaluation Programme	Financial support given

4.3 Oversight Committees

The RAPTOR trial is subject to oversight from the following committees:

Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the CI, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, 2 independent experts in the field of oral surgery, oral & maxillofacial surgery, head and neck surgery or clinical oncology, biostatistician, including the CI and observers. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The decision for the continuation of the trial lies with the TSC and as such they will meet throughout the trial (at least annually).

Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) will consist of an independent chairperson, in a related area of expertise, plus 2 independent members; one of whom is also an expert in a related area of expertise, and an independent biostatistician.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in Section 12.4 and 13.3 respectively.

The IDSMC will provide a recommendation to the TSC concerning the continuation of the study.

4.4 Protocol Contributors

Name	Affiliations	Contribution to protocol
Professor Richard Shaw	University of Liverpool, Liverpool University Foundation Trust	Inception of study, led the writing of this protocol, clinical and scientific arrangements, trial design and conduct
Dr Richard Jackson	LCTC, University of Liverpool	Statistical Design
Ms Rebecca Tangney	Liverpool University Foundation Trust Pharmacy	Pharmacy and PV
Professor Stefano Fedele	University College London, Eastman Dental institute and University College London Hospital, Royal National ENT & Eastman Dental Hospitals	Co-applicant and contributor to specialty-specific aspects of protocol
Professor Anastasios Kanatas	St James Institute of Oncology, Leeds Dental Institute, Leeds General Infirmary and University of Leeds	Co-applicant and contributor to specialty-specific aspects of protocol
Dr Vinod Patel	Kings College London & Guys Dental Hospital	Co-applicant and contributor to specialty-specific aspects of protocol
Mr Mandeep Bajwa	University of Liverpool, Liverpool University Foundation Trust	Co-applicant and contributor to specialty-specific aspects of protocol, ePROM
Ms Tracy Moitt	LCTC, University of Liverpool	Protocol development, governance arrangements and trial conduct
Ms Ayten Basoglu	LCTC, University of Liverpool	Protocol development, governance arrangements and trial conduct

5 INTRODUCTION

5.1 Background

Osteoradionecrosis (ORN) is defined as exposed irradiated bone that fails to heal over a period of 3 months in the absence of recurrent malignancy[3]. It is the most feared complication of radiotherapy often causing repeated infection, jaw fracture, fistula, malnutrition, opiate dependency and sometimes death. Current practice includes symptomatic/conservative care which is reported to resolve between 25-44% of cases[4]. Conservative management includes: analgesia, control of infection with chlorohexidine mouthwash, antibiotics, alleviation of any trauma caused by sharp or mobile bone sequestra using minor outpatient interventions using, at most, local anaesthetic. Other accepted treatment includes surgical intervention, involving complete resection of all involved bone and reconstruction as necessary[5, 6]. This is a very major and invasive intervention requiring 8-10 hours of twin team surgery, requiring microvascular reconstruction and has a high cost and complication rate. Understandably it is reserved as a 'last resort' for patients with worsening and otherwise unmanageable symptoms or increasing extent of ORN.

Recent clinical trials indicate that the main historical alternative to surgery, hyperbaric oxygen, is ineffective in preventing[7] or treating[8] ORN. Some clinicians have started using PENTOCLO 'ad hoc', and with some variations in protocol, prior to planned surgery[6], further compounding costs to the NHS. There is an urgent need for rigorous trials of PENTOCLO therapy in the management of ORN of the mandible. This phase II proposal will establish the first robust signal of efficacy, an estimate of effect size, and the safety/tolerability of PENTOCLO in mandibular ORN. Additionally, it will inform the need for and help with design of any subsequent phase III trial.

Knowledge gap that this research addresses:
The pentoxifylline-tocopherol combination is thought to reverse soft tissue fibrosis induced by radiotherapy[9]. Potentiation of this combination by clodronate is indicated for osseous lesions, such as ORN of the mandible[10], without resorting to surgical resection and reconstruction. The current trial proposal is intended to establish if this drug combination (PENTOCLO) is clinically active in the first line management of mandibular ORN. Currently, there is no phase II or III, controlled or randomised data available. Additionally, a repository of blood samples from the trial will allow future studies to explore the genomic determinants of susceptibility to ORN[11, 12].

Existing relevant literature:
Very few clinical trials have been identified addressing the prevention or management of mandibular ORN from the appropriate trial registries (Clinicaltrials.gov and clincialtrialsregsiter.eu) searching by ORN, pentoxifylline and PENTOCLO. Additionally, the uncontrolled and observational studies of PENTOCLO are summarised in two recent comprehensive systematic reviews[13, 14].

Clinical Trials:
In the setting of mandibular ORN, the International DAHANCA21 trial compared HBO with surgery versus surgery alone. The results, currently submitted for publication (and posted in clinicaltrials.gov NCT00760682, additionally RJS is a co-author of the DAHANCA21 primary outcome submission), showed that one year after surgery, healing was observed in similar proportion of cases (p=0.19) with an odds ratio for being healed of 2.0 (96% CI: 0.6-6.3). Taken with the previous Annane trial[8], the three randomised controlled trials (RCT) carried out in HBO show little convincing evidence to support its further use. The DAHANCA21 trial demonstrated feasibility of an RCT and clinician support for trials in mandibular ORN. Additionally, we have recently reported that there is significant interest in PENTOCLO, and 96% of UK head & neck surgeons stated they would be willing to recruit to a multicentre trial[6]. A small study of 24 patients randomised between standard care and the twin combination of pentoxifylline and tocopherol (Dr Martos-Fernandez, NCT02368457) has been recorded on clinicaltrials.gov. This trial does not include clodronate which current theory has suggested is essential in osseous lesions, as below. It is not possible from the limited data posted to determine activity or efficacy. There have been as yet no randomised controlled trials of PENTOCLO versus standard of care in mandibular ORN.

Uncontrolled studies/case series:
There is some evidence defining some therapeutic effect from retrospective case series and meta-analyses. In a single-site, one arm design, Delanian et al.[10] showed 54 patients with ORN experienced complete resolution of early ORN after a median of 9 months with the PENTOCLO protocol. Subsequently a number of centres have documented their retrospective case experience. This evidence has been subject to systematic review by two groups, with broadly similar conclusions[13, 14]. Martos-Fernandez et.al.[14] analysed 10 published series with a total of 334 patients included, finding all studies of a low or moderate methodological quality. Little numerical analysis was attempted with a largely descriptive methodology, but it was found that resolution occurred between 3 to 13 months with 60% of patients showing clinical improvement or total healing. Healing in more advanced cases (Notani III) is less predictable, took longer, approx. 18-24 months. Heterogeneity in methodology and endpoints were a barrier to further quantitative analyses. Kolokythas et.al.[13] studied 7 papers reporting 186 patients using tighter inclusion criteria. 126 of patients fully recovered or improved significantly, ORN was stable in 60 patients and progressed such that patients needed jaw resections in 15 patients. The estimated proportions of full resolution were 62.7% ((SD) 3.4%, 95% (CI) 55.8-69.1%); of reduction in SOMA score were 86.5% (SD 4.0%, 95% CI 76.7-92.6%); and of reduction of area exposed bone were 62.0% (SD 4.1%, 95% CI 76.7-92.6%). Challenges in analysis were created by a lack of standardisation of treatment and outcome reporting. Both reviews concluded that patients tolerated PENTOCLO well, the commonest side effect being mild gastrointestinal (GI) disturbance.

The existing literature on PENTOCLO, therefore, constitutes a number of observational cohorts, all of which were uncontrolled and subject to potential bias. There is a relative paucity of data for patients who are managed conservatively with supportive medical management (including analgesia, antibiotics, antiseptic mouthwash and local removal of any sharp bone); this appears to be effective in 25-44% patients[4], but the data to inform a projected effect size in phase III trial is not yet robust.

5.2 Rationale

The health problem addressed: ORN is a devastating complication following otherwise curative treatment of head and neck cancer, whereby the mandible undergoes necrosis leading to infection, pain and fracture. This results in considerable dysfunction and disfigurement, often requiring very complex reconstructive surgery with composite bone grafts and microvascular techniques.

Unmet health need:
The population at high risk of developing mandibular ORN is rising with the increasing rate of head & neck squamous cell carcinoma (HNSCC) in younger patients and consequent reliance on radiotherapy-based therapy. The changing demographic of HNSCC is at least partly due to cases caused by Human Papillomavirus which has resulted in an increasing proportion of patients cured, and increasing proportion receiving radiotherapy, and even higher risk concurrent chemoradiotherapy, as part of their treatment[15].

Current estimates are that of around 12,000 patients per annum in the UK treated for HN malignancy, approximately 7% of those given radiotherapy will develop ORN[5]. Even using modern fractionation and dose contouring such as IMRT (Intensity Modulated Radiotherapy), which is thought to reduce radiotherapy late toxicity, it appears that ORN remains a major concern. Over 90% of head and neck surgeons frequently manage ORN and most feel that this is an increasing problem in their practice[7]. As such it is estimated that 500-800 new cases of ORN per annum, but the prevalence is higher as many cases persist without resolution.

Proof of concept:
Preclinical research in this field is significantly hampered by the lack of a robust in-vitro or animal model for ORN. The complex tissue architecture and late radiation effects from existing fractionation protocols have so far eluded the construction of a representative laboratory or animal model of ORN. As a result, most of the data has been obtained from clinical observations in various late radiation toxicities from head & neck and other fields, and from cell culture that may not reliably reflect pathophysiology of ORN accurately. Despite these limitations, the pathophysiology and potential therapeutic opportunities in ORN have been reframed in recent years as a fibro-atrophic process mediated by reactive oxygen species (ROS), a progressively more fibroblastic stroma and emphasising the role of TGF-B1[16]. Pentoxifylline, previously used to treat peripheral vascular disease has been shown to have in-vivo anti-TNFa effect, increase erythrocyte flexibility,

vasodilation & anti-inflammatory effects[17]. As a single agent, pentoxifylline has demonstrated some beneficial effects in soft tissue necrosis, trismus and various functional/symptomatic effects after radiotherapy in breast and HN cancer survivors[18].

Tocopherol acts as a ROS scavenger and an inhibitor of TGF-B1 and procollagen gene expression, but alone has proved ineffective in the management of radiation-induced fibrosis. Combining the two agents, and exploiting their apparently synergistic mechanisms, the combination of pentoxifylline and tocopherol has demonstrated benefit in placebo-controlled trials[9] of radiation fibrosis and necrosis, although needing at least 12 months of continuous treatment to avoid rebound. Data on osseous lesions such as mandibular ORN has indicated that the addition of clodronate to inhibit osteoclasts potentiates the effectiveness of the protocol[19] and the current triple regimen of PENTOCLO has been used increasingly since 2005. Clodronate is a first-generation, non-nitrogenous oral bisphosphonate, specifically not associated with drug-induced osteonecrosis, reduces osteoclast activity, decreases fibroblast and macrophage proliferation, and promotes bone formation by osteoblasts. This combination has shown promise in medical management of ORN, with the necrotic bone forming a sequestrum that is eventually shed, revealing intact underlying mucosa.

Sustained Interest:
There is increasing acceptance that cancer survivorship and management of late toxicities is a major consideration worthy of further clinical research. The recent James Lind Alliance (2018) "Living With and Beyond Cancer" (LWBC) priority setting process carried out under direction of the NCRI (National Cancer Research Institute) identified the following: How can the short-term, long-term and late effects of cancer treatments be (a) prevented, and/or (b) best treated/managed? (jla.nihr.ac.uk).

Specifically, NICE (National Institute for Health Care Excellence) in a recent review has recommended against the use of PENTOCLO triple therapy outside of clinical trials (NICE 2016). Despite this, a recent survey of practice has confirmed that in the UK, some of those treating mandibular ORN are already prescribing PENTOCLO[7] despite many admitting knowledge of the NICE position. It is known that many NHS commissioners are reluctant or refusing to fund PENTOCLO, strengthening the case for more robust evidence.

5.3 Risk and Benefits

In order to balance the risks and benefits of the RAPTOR trial, it is necessary to consider expected toxicities of the three individual agents, but also the underlying severity of the clinical condition (mandibular ORN) and the possible morbidities of the alternative treatments for this condition. In addition, it is important to understand that individual clinicians do already prescribe PENTOCLO against clinical guidelines as the alternative treatments appear to be so inadequate.

In summary, therefore it is necessary to consider the considerable morbidity of ORN as well as the risks of standardised supportive care (SSC), of surgery and of all three PENTOCLO medications.

Mandibular ORN: This is a late radiation effect that is frequently accompanied by pain, loss of key oral functions (swallowing, chewing, speech), infection, trismus, bleeding, malnutrition and loss of facial form/aesthetic appearance. ORN causes considerable morbidity and has a documented risk of mortality in more severe presentations, usually as a combination of bleeding, infection or airway compromise.

Standardised Supportive Care: This consists of analgesia (sometimes escalated to opiates), antiseptic mouthwash, alleviation of oral soft tissue trauma by local means, antibiotics (sometimes intermittent, sometimes prolonged course), occasionally antifungal agents and steroids. Such measures are prescribed as titrated to a patient's burden of symptoms. Each of these measures carries its own element of risk, side effects and some drug interactions which are not the subject of the RAPTOR trial but must be borne in mind for context.

Surgery for mandibular ORN: Surgery for ORN is heterogeneous, is proportional to the stage and extent of necrotic bone, and therefore difficult to summarise in brief. The simplest sequestrectomy procedures involved debridement of already loose bone fragments are usually minor day-case procedures. Marginal jaw

resections, or saucerisation, are also carried out in order to take bone back to bleeding/vital margins in an attempt to encourage healing in Notani 1 and 2 cases. Segmental jaw resections, which also involved a varying degree of soft tissue defect are much more significant surgeries accompanied by significant morbidity and occasional mortality. Such procedures usually involve: general anaesthetic, tracheostomy, feeding tube placement, neck access procedures to carotid/jugular vessels, resection of bone, free flap donor site, microvascular anastomosis, osteosynthesis using titanium implanted plates. This surgery has a high complication rate involving significant inpatient admission and frequent infection and wound complications.

5.3.1 Potential Risks

PENTOCLO therapy: A comprehensive list of contraindications, precautions and interactions is available from the relevant Summary of Product Characteristics (SmPCs). Numerous retrospective reports in the peer reviewed literature demonstrate that the combination of drugs is generally well tolerated[14, 20] in the population with ORN. Generally the precise balance of comorbidities and precautions and tolerability is not well documented in these reports, but in Patel et al.[20] (number of subjects - 169) patients were excluded from PENTOCLO if they had a previous history of cerebral or retinal haemorrhage, acute myocardial infarction, severe cardiac arrhythmias or significantly impaired renal or liver function.

A summary of the more important risks and contraindications is as follows:

Pentoxifylline: Common side effects include dizziness and headache associated with vasodilation. Additionally, epigastric discomfort, nausea and diarrhoea are common side effects. The comprehensive list of undesirable effects are listed the relevant SmPC.

Vitamin E Suspension (Tocopherol): Diarrhoea and abdominal pain may occur with doses greater than 1g daily, but are not expected within this trial as the dose is 1g/day.

Sodium Clodronate: Common side effects include diarrhoea, nausea and vomiting. The comprehensive list of undesirable effects are listed in the relevant SmPC.

This trial is categorised as Type B (Somewhat higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the MHRA (Medicines & Healthcare products Regulatory Agency).

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the TMF.

5.3.2 Potential Benefits

The principal benefit of PENTOCLO, though uncertain in magnitude, is that of healing or stabilisation of mandibular ORN. This therefore will reduce the symptoms of the condition, reduce or eliminate the prescription of supportive treatments and avoid the need or surgery. From retrospective uncontrolled trials, PENTOCLO may be possibly more effective in early (Notani 1,2 and non-infected) ORN than in late ORN (Notani 3, infected). Retrospective uncontrolled studies suggest that resolution of ORN occurs between 3 to 13 months with 60% of patients showing clinical improvement or total healing. When healing is not achieved, in some cases the regimen appears to be able to stabilise the condition, still avoiding major surgery and limiting subsequent symptoms.

5.4 Objectives

RAPTOR aims to establish the value of the repurposed drug combination Pentoxifylline, Tocopherol & Clodronate (termed PENTOCLO) in treating ORN of the mandible.

Primary Objective: The primary aim is to determine if PENTOCLO triple therapy is effective in healing of mandibular ORN.

Secondary Objectives: To evaluate the impact on PENTOCOLO on:

- Patients pain and mouth function
- Patients ability to receive treatment and control the disease
- Patients analgesia and antibiotic use
- Patients anthropological measurements
- Severity of disease
- Overall Quality of Life
- Mandibular preservation
- Associated toxicity

Translational Objective: To provide genomic DNA from a cohort of patients with ORN for future studies on the genomic determinants of late radiation toxicity.

6 STUDY DESIGN

RAPTOR is a multi-centre, unblinded, randomised, phase II trial, with blinded assessment of primary endpoint, with a 1:1 allocation ratio.

Target population: Patients who have been cured of head and neck cancer who have received radiotherapy and who have ORN of the mandible.

6.1 Blinding

RAPTOR is an unblinded (open-label) trial: neither patients, site investigators or trial site staff are blinded as to allocation.

The integrity and robustness of the primary endpoint measures are however, maintained by assessment of healing and area of exposed bone using clinical photographs. These photographs form the basis of a remote expert panel which is blinded to allocation of trial arm (section 9.1).

6.2 Study Setting

Participants will be identified and recruited from 15 secondary and tertiary NHS hospitals providing care for head and neck cancer patients following radiotherapy in the UK.

6.2.1 Selection of Participating Sites

Sites will be selected on their clinical caseload of ORN and willingness to enter into trial contracts with the sponsor. Criteria for the selection of sites will be determined by the TMG.

Sites fulfilling the trial-specific criteria will be selected to be recruitment sites for the RAPTOR trial and will be opened to recruitment upon successful completion of all global and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

- Positive Capacity and Capability Assessment by Research and Development (R&D) Department
- Approval by Research Ethics Committee (REC) and HRA
- Completed Research Site Agreement
- Completion and return of ‘Signature and Delegation Log’ to LCTC
- All staff contributing to the trial must have valid certified GCP training throughout the conduct of the trial

6.2.2 Selection of Principal Investigators (PIs)

PIs will be required demonstrate equipoise, relevant experience and commitment during early-stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.

A suitable co-investigator should be identified at each site to deputise in case of PI absence.

7 ELIGIBILITY CRITERIA

The RAPTOR trial aims to recruit 120 patients based on sample size calculations described in Section 12.2.11. All patients must provide written, informed consent before any study procedures occur (see Section 10.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

7.1 Inclusion Criteria

Patients eligible for the trial must comply with all of the following at randomisation:

1. A diagnosis of mandibular ORN (as specified in Appendix A)
2. Patients considered suitable for medical management
3. Written and informed consent obtained from participant and agreement of participant to comply with the requirements of the study

7.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

1. Cannot swallow tablets
2. Prior treatment with PENTOCLO or any element thereof within 1 year of the date of randomisation
3. Very early ORN (<20 mm^2 exposed bone) occurring within 12 months of a dental extraction or other dentoalveolar operation ('Minor Bone Spicules' see flowchart below)
4. Mandibular pathological fracture secondary to ORN
5. Extra-oral communicating fistula secondary to ORN
6. Prior surgery/jaw resection
7. Pregnancy
8. Lactation
9. Age <18 years
10. Acute infection at site of the necrotic bone.[1]
11. Contraindications to PENTOCLO medications:
    a. Known hypersensitivity, allergy or anaphylaxis to pentoxifylline, tocopherol or sodium clodronate
    b. Treated hypotension
    c. Severe coronary artery disease, defined as grade IV of the Canadian Cardiology Society Angina Grading (See Appendix B)
    d. Severe atrial fibrillation, defined as grade 4 on modified CCC-SAF[(2)] (See Appendix C)
    e. Myocardial infarction within 6 months
    f. Prior history of extensive retinal haemorrhage
    g. Prior history of intracranial bleeding
    h. Impaired renal function (Creatinine clearance <30 ml/minute, will be formally assessed only if U&E out of reference)
    i. Severe liver failure (class B or C Pugh-Child Score, will be formally assessed only if LFT values, out of reference)

[1] The acute phase of infection should be controlled by appropriate antibiotics and other measures prior to enrolling the patient into the trial

j. Concomitant prescription of anti-platelet agents: clopidogrel, eptifibatide, tirofiban, epoprostenol, iloprost, abciximab, anagrelide, NSAIDs, acetylsalicylates (ASA/LAS) including aspirin >75 mg*, ticlopidine, dipyridamole. (*low dose =<75 mg aspirin is permitted)

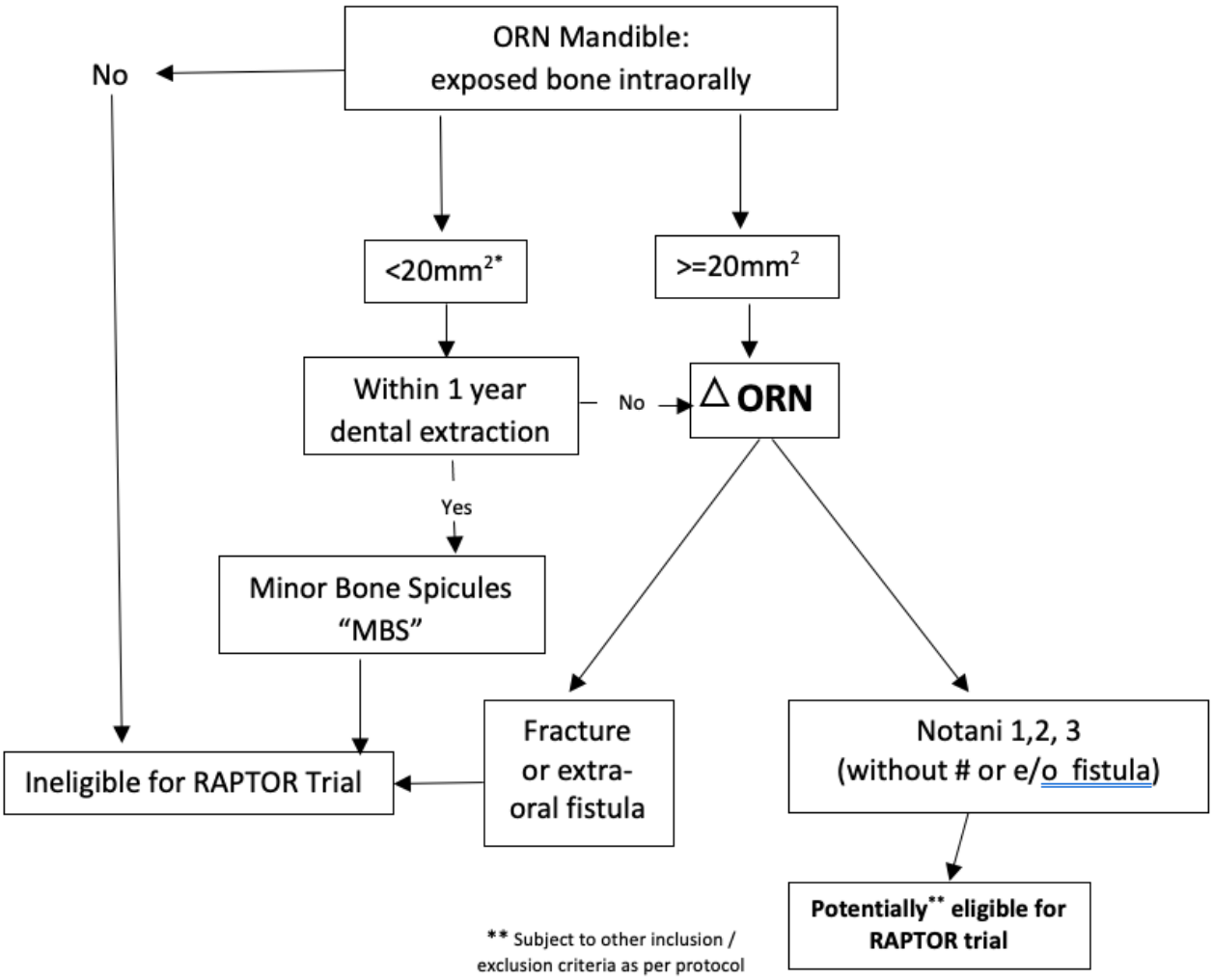
k. Concomitant prescription of ketorolac, cimetidine, ciprofloxacin, theophylline, estramustine phosphate

l. Hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency

m. Concomitant prescription of other bisphosphonates e.g. risedronate, alendronate, aIbandronate, zoledronic acid, pamidronate, etidronate or prescription of denosusamab

n. Concomitant prescription of aminoglycoside antibiotics e.g. gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, paromomycin

Flowchart indicating grade of ORN vs eligibility[21]



7.3 Criteria for additional caution

- Patients taking oral anticoagulants should have their INR (international normalised ratio) regularly checked and may need a dose adjustment if taking PENTOCLO. This will only be relevant to patients allocated to the PENTOCLO arm, and is a caution not an exclusion.
- Patients taking any medications to treat diabetes mellitus must have their blood glucose carefully monitored if taking PENTOCLO, and may need a dose adjustment. This will only be relevant to patients allocated to the PENTOCLO arm, and is a caution not an exclusion.

7.4 Co-enrolment Guidelines

Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the RAPTOR trial this must first be discussed with LCTC who will contact the CI.

8 TRIAL TREATMENT/INTERVENTIONS

8.1 Introduction

Eligible patients will be randomised between arm A, the control arm and arm B, the experimental arm. Patients in arm A will receive standard supportive care as described below, and patients in arm B will receive standard supportive care and PENTOCLO (Pentoxifylline, Tocopherol, Clodronate).

IMP will be sourced from usual NHS hospital stock using generic brands prescribed within the NHS, unless advised otherwise by the trial pharmacist.

8.1.1 Duration of Treatment

Treatment is to continue for at least 12 months, up to a maximum of 36 months or until one of the trial endpoints is reached. At 12 months the patient's preference will be sought, irrespective of trial arm, to either conclude the trial, or to continue their allocated trial treatment and procedures. These can be continued for a maximum of 36 months or until one of the trial endpoints is reached. If the patient continues then their trial endpoints will be sought at 3-month intervals and the patient can leave the trial at any subsequent point at their preference.

8.2 Arm A – Control Arm: Standardised supportive care (SSC)

It is not intended to protocolise these interventions listed below, as they are not the trial IMP. A pragmatic approach over the period of the trial is needed, however usage of analgesia and antibiotics is recorded as a secondary outcome measure. All patients should receive adequate SSC to minimise the symptomatic impact of ORN through the trial irrespective of the trial arm allocation.

SSC may include analgesia, mouthwash, antibiotics and alleviation of local trauma, and any other appropriate measures. It specifically excludes hyperbaric oxygen and operations including surgical resection of the mandible (rim or segment).

Analgesia: This will involve analgesia titrated to pain requirements including paracetamol, non-steroidal anti-inflammatory drugs, and opiates as required.

Oral Hygiene/Antiseptic Mouthwash: Patients will receive appropriate support for oral hygiene, chlorohexidine or saline mouthwash.

Antibiotics: Antibiotics will be prescribed as and when infections are clinically evident (erythema, swelling, pain, pus, raised neutrophil count or CRP) and will typically be broad-spectrum antibiotics directed at oral flora. Antifungals may also be prescribed for candidiasis.

Alleviation of local trauma: Patients with loose or sharp bone sequestra or teeth should receive minor debridement or extractions in the outpatient setting in order to alleviate trauma to the oral soft tissues. This may be with the aid of local anaesthetic as needed. (Note: this excludes more major surgery to excise bone that would be carried out in an operating theatre, using saws or drills, or requiring general anaesthetic).

8.3 Arm B – Experimental Arm: SSC and PENTOCLO

The PENTOCLO arm includes SSC as described above *and*:
Pentoxifylline 800 mg daily,
Tocopherol 1000 mg daily,
Clodronate 1600 mg days 1-5 of 7 (Monday through Friday only)

8.3.1 Pentoxifylline: Formulation, Packaging, Labelling, Storage and Stability

Formulation	400 mg Modified release tablet
Active Ingredient Name	Pentoxifylline
Excipients	For a full list of excipients, see SmPC
Prolonged release	Yes
Supplier's name	Site specific brand in use
Storage & stability	Please refer to the SmPC of the brand in use at your site

8.3.2 Tocopherol: Formulation, Packaging, Labelling, Storage and Stability

Formulation[2]	Suspension
Active Ingredient Name	Vitamin E (DL-alpha-tocopherol acetate)
Excipients	For a full list of excipients, see SmPC
Prolonged release	No
Supplier's name	Site specific brand in use
Storage & stability	Please refer to the SmPC of the brand in use at your site

8.3.3 Clodronate: Formulation, Packaging, Labelling, Storage and Stability

Formulation	400 mg Capsules
Active Ingredient Name	Sodium Clodronate
Excipients	For a full list of excipients, see SmPC
Prolonged release	No
Supplier's name	Site specific brand in use
Storage & stability	Please refer to the SmPC of the brand in use at your site

Pentoxifylline 400 mg modified release tablets, Vitamin E suspension and Sodium Clodronate 400 mg capsules will be sourced from usual NHS hospital stock using generic brands prescribed within the NHS, unless advised otherwise by the trial pharmacist.

The hospital pharmacy will label the investigational medicinal product (IMP) in accordance with Annex 13 requirements/regulations[3] at the point of dispensing.

IMP will be dispensed to the patient against a trial specific prescription issued by a delegated prescriber.

[2] There are a variety of concentrations of tocopherol - they are all acceptable to be used, depending on the availability at sites.
[3] EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

8.4 Dosage and Administration

For **Arm B – Experimental Arm: SSC and PENTOCLO:**

Dose regimen;

Pentoxifylline: 1 tablet (400 mg) twice daily, taken with or immediately after meals, and swallowed whole with plenty of water.

Tocopherol (Vitamin E): 1000 mg once daily.

Sodium Clodronate: 1600 mg should be taken as a single dose, but only Monday to Friday, i.e. excluding Saturday and Sunday. This should preferably be taken in the morning on an empty stomach together with a glass of water, then refrain from eating, drinking (other than plain water), and taking any other oral drugs for one hour. Alternatively, between meals, more than two hours after and one hour before eating, drinking (other than plain water).

Route of administration: Oral.
(Note: if patients cannot swallow tablets, inclusion in RAPTOR is contraindicated)

Missed doses: There should not be any 'catch-up' doses, the dose should be missed and the next dose taken as normal.

Duration of treatment: for at least 12 months, up to a maximum of 36 months or until one of the trial endpoints is reached.

8.5 Treatment Modifications

Sodium clodronate
Diarrhoea, nausea or vomiting: consider first using a divided dose regimen, rather than a single daily dose, which may improve gastro-intestinal tolerance. This is potentially more difficult with regard to compliance for patients in that effective absorption requires an empty stomach (one hour before and two hours after eating or drinking anything other than plain water). Dividing the doses therefore requires two such periods in each day. If after trying this and after discussion with the CI, it is possible to halve the dose of Sodium Clodronate to 800 mg daily (in either one or two doses) in the event of gastrointestinal side effects.

Pentoxifylline
Dizziness, headache, epigastric pain or nausea: consider a temporary 2-week dose reduction to 400 mg daily, i.e. a single daily dose, prior to rechallenging with full dose. If after trying this and after discussion with the CI, it is possible to halve the dose of pentoxifylline to 400 mg daily. (In this circumstance, *further* rechallenge at 800 mg is not to be subsequently attempted).

After the patient has entered the trial, the clinician is free to give alternative treatment/intervention to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing further treatment (see section 10.1010).

8.6 Accountability Procedures

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All discrepancies between amounts of study drug dispensed and amounts returned must be documented. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol without prior approval.

If appropriate, drug storage, drug dispensing, and drug accountability should be delegated to the pharmacy of the investigative site.

8.7 Concomitant Medications/Treatments and Specific Restrictions

8.7.1 Precautions Required:

- Anti-platelet agents: clopidogrel, eptifibatide, tirofiban, epoprostenol, iloprost, abciximab, anagrelide, NSAIDs, acetylsalicylates (ASA/LAS) including aspirin >75mg*, ticlopidine, dipyridamole. (*low dose =<75 mg aspirin is permitted)
- Ketorolac, cimetidine, ciprofloxacin, theophylline, estramustine phosphate
- Any Aminoglycoside antibiotics e.g. gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, paromomycin
- Any other Bisphosphonates e.g. risedronate, alendronate, aIbandronate, zoledronic acid, pamidronate, etidronate

If an indication for bisphosphonates emerges while the patient is on trial (irrespective of the trial arm), this needs to be discussed with the CI.

If any medications listed above are taken then adverse events related to this must be reported as per section 11 Safety Reporting.

8.7.2 Data on Concomitant Medication

Concomitant medication information should be collected on a specific CRF regarding any usage of:

- Antibiotics
- Analgesia

8.8 Overdose

Overdose is defined for trial purposes here as more than double the recommended daily dose, and any AE/AR/SAE resulting should be reported with the relevant CRF.

There are specific recommendations regarding pentoxifylline and sodium clodronate.

Pentoxifylline: The treatment of overdosage should be symptomatic with particular attention to supporting the cardiovascular system.

Sodium Clodronate: Management of overdose should be symptomatic. Adequate hydration should be ensured, and renal, hepatic function and serum calcium should be monitored. Serum calcium should be monitored, and oral or parenteral calcium supplementation may be needed.
Sodium clodronate is normally taken 5 days a week (Mon-Fri). If it's taken 6 or 7 days a week, this would be classed as an overdose.

9 OUTCOMES

9.1 Primary Outcome

Objective: The primary outcome measure is time to healing, measured as the time from randomisation to confirmed healing (without the need for surgery).

Outcome measure: Time from randomisation to healing of ORN as measured by:

- clinical examination by confirming completely healed oral mucosa
- intra-oral clinical photographs.

Conversely, patients who demonstrate failure of treatment, either:

- deterioration of ORN (Appendix A), including fracture or extra-oral fistula)
- a clinical indication to intervene with mandibular resection & reconstruction

will be treated as censored observations.

To avoid any potential risk of bias due to unblinded site investigators, clinical photographs taken with an in-field ruler (Puritan stick) are subject to a central blinded review. In cases of trismus, clinical photographs are facilitated by intra-oral cameras which are available with disposable single use covers. Digital copy of the clinical photographs (with in-field rulers) will be securely uploaded to the study database by the site staff. At the end of the trial, the central review panel will be provided with the anonymised clinical photographs by the LCTC from baseline and end of trial for blinded assessment.

Time point: Every 3 months (+/- 1 month) following randomisation until end of trial for that patient

9.2 Secondary Outcomes

Table 1: Secondary Outcomes

Objectives	Outcome Measures	Time point(s) of evaluation
Efficacy:		
1. Patients pain and mouth function	• Pain • eating • mouth opening • swelling self-reported.	Every 15 days until end of trial for the patient (collected remotely on a custom App i.e. “ePROM”)
2. Patients ability to receive treatment and control the disease	Time from randomisation to worsening of ORN as measured: • Extent of exposed bone measured in two dimensions as mm^2 (and for some trial visits supported by clinical photograph with in-field ruler) and • Notani grade (Appendix A)	At baseline and 12 months (and at study completion for the patients that stay in the study for over 12 months)
3. Patients analgesia and antibiotic use	• Drug and dose taken for pain relief in the 24-hour period leading up to appointment	Every 3 months following randomisation until end of trial for that patient

	• Days of antibiotic usage. Systemic antibiotics taken since last trial appointment (type: dose & and number of days for each type)	
4. Patients anthropological measurements	Patient BMI (kg/m^2) where kg is a patient weight in kilograms and m^2 is their height in metres squared	Every 3 months following randomisation until end of trial for that patient
5. Severity of Disease	Grade by "Osteonecrosis of jaw" within CTCAE v 5.0 2017 (Appendix D - within Musculoskeletal and connective tissue disorders)	Every 3 months following randomisation until end of trial for that patient
6. Overall Quality of Life	Quality of Life (EORTC QLQ-C30 and QLQ-H&N35)	Every 3 months following randomisation until end of trial for that patient
7. Mandibular preservation	Mandibular preservation rate measured as the removal of mandibula following surgery (segmental resection, with or without reconstruction)	Every 3 months following randomisation until end of trial for that patient
Toxicity:		
8. Associated Toxicity • Gastrointestinal tolerability of PENTOCLO regimen 2 weeks after commencing (Only in Arm B: PENTOCLO) and • To determine toxicity of PENTOCLO regimen	Gastrointestinal tolerability of Adverse Event reporting	2 weeks after commencing trial medications +/- 5 working days, (may be by telephone)

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

Identification of patients will be dependent on the site arrangements for follow-up of head and neck cancer patients who have received radiotherapy and may include:

- Joint Head & Neck Oncology MDT and Clinics
- Oral & Maxillofacial Surgery Clinics
- ENT Clinics
- Clinical Oncology Clinics
- Oral Surgery Clinics
- Dental Hospital Clinics
- Specialist Osteoradionecrosis Clinics

Thus, potentially eligible patients are identified from secondary and tertiary hospital sites within the NHS in the UK.

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all participants. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent, they do not have to give a reason.

10.2.1 Prospective Informed Consent Process

Written informed consent will be sought from patients who will be approached by the study team and invited to consider participation.

Patients will be approached by a member of the local research team during their initial referral appointment or during routine follow-up. A written information sheet that forms part of the ethically approved Patient Information Sheet and Consent form will be provided. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ensure that the patient has fully understood all the information and will ask if they are happy to consent to participation in the trial.

Where this is the case, written informed consent will be obtained by means of a dated patient's signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the patients for their information,
- One copy transferred to LCTC via secure transfer methods,
- One copy filed in the participant's medical records paper/electronic.

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

10.3 Screening Procedures

Blood tests: Liver function tests (LFT) and Urea & electrolytes (UE) are used to assess liver and renal function. The specific thresholds in RAPTOR for recruitment (Renal: Creatinine clearance <30ml/minute, Liver: Child-Pugh B or C) are only calculated where relevant LFT and UE (creatinine) values are out of reference range.
Pregnancy test in female patients.

Research Blood test: Blood is collected at the same venepuncture (ideally) and will form the basis of the associated bioresource for radiogenomic studies.

Medication and Medical History Check: Against a list of excluded conditions and concomitant medications as specified in the exclusion criteria.

Radiographs: An orthopantomogram* is required prior to randomisation to define the stage of ORN using Notani – under the relevant IRMER guidance: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/ionising-radiation/.

Consent is required for screening procedures and this will explicitly detail the DNA to be extracted and stored from the research blood test for radiogenomic research.
Randomisation must be carried out within **56 days (8 weeks)** of the initial screening visit.

**NB: Suitable orthopantomograms taken within 4 months may be used to reduce unnecessarily repeated exposure to ionising radiation.*

Screening log
A screening log will be maintained of all the patients who undergo screening, regardless of whether they decide to participate in or are deemed eligible for the trial, to provide important information for monitoring purposes. Reasons for not being eligible and reasons for declining to participate will be asked routinely but it will be made clear that patients or their legal representatives do not have to provide a reason unless happy to do so.

10.4 Eligibility Assessment and Confirmation

Trial specific screening assessments must only be performed after patients have consented to trial participation and signed the informed consent form.

Eligibility can only be confirmed by an appropriately qualified medical or dental professional who is named on the delegation log and must not occur until all eligibility assessments have been performed and results reviewed. Eligibility criteria are described in detail in Section 7.

Eligibility confirmation must be documented in the participant's medical notes and then on the trial's eligibility CRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was randomised.

Screening data will be used to assess and confirm eligibility. Screened patients deemed ineligible will have the reasons for this recorded on the screening log.

The time allowed between screening and randomisation will be limited to 56 days (with the exception of orthopantomogram where 4 months will be the maximum period). >56 days after the screening, patients must be re-screened and reconsented if they wish to be recruited.

10.5 Baseline Assessments

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.88) in order to accurately complete the Baseline CRF and collect the necessary information for the trial analyses.

This includes the following assessments:

- Clinical photograph of ORN, with in-field ruler
- Assessments of Notani grade of ORN and of severity by CTCAE v5.0
- Initiation of ePROM – assessment of pain, eating, mouth opening, swelling
- Assessment of medical history
- List of current medications
- Height
- Weight
- Quality of Life using EORTC QLQ-C30 and QLQ-H&N35
- Blood test: UE, LFT, Pregnancy test in females
- Orthopantomogram

Routinely collected information can be transcribed from the patient's medical notes into the CRF once appropriate consent has been obtained. The patient can proceed to randomisation once all the baseline assessments have been completed.

10.6 Randomisation

10.6.1 Randomisation Process

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by LCTC to receive either arm A, SSC; or arm B, PENTOCLO + SSC, (in a ratio of 1:1). Randomisation should occur no more than once and:

a) Fully informed written consent has been obtained (and appropriately documented).
b) Eligibility criteria have been fulfilled (and eligibility confirmed).
c) Baseline assessments have been completed.

Designated research staff will be issued with a personal login and password.

When the system requirements (i.e. consent, eligibility) are confirmed the participant treatment allocation and a unique study number (randomisation number) will be displayed on a secure webpage. An automated email confirmation will be sent to the authorised randomiser, PI, trial manager and pharmacy.

Randomisation web page can be accessed on https://rand.lctc.org.uk/raptor/.

10.6.2 Randomisation System Failure

ORN is a chronic condition, so in the event of being unable to complete randomisation due to some technical deficiency in the randomisation system, it would be expected to re-appoint the patient and carry out randomisation at such a time that this issue had been resolved.

10.7 Intervention

Once the research team are made aware of the treatment allocation participants will receive their allocated treatment within 2 weeks. This will be administered as described in Section 8.4.

10.8 Schedule for Assessments and Follow-up

All assessments and follow-up are to be conducted in line with the Schedule of Assessments below:

Schedule of Assessments:

Assessment	Screening	Randomisation	Baseline[4]	2-week check by telephone	Clinic Visit Schedule *(in months)*				*Optional Clinic Visits[5] (in months)*							Study Completion
					3	6	9	12	15	18	21	24	27	30	33	
Clinic Visit Numbers					1	2	3	4	5	6	7	8	9	10	11	
Accepted Variance				*+/- 1 week*	*+/- 1 month*											*+/- 1 months*
Informed Consent	X															
Assessment of Eligibility Criteria	X															
Confirmation of Eligibility	X															
Review of Medical History	X		X													
Review of Concomitant Medications (including analgesia and antibiotic usage)	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Demographics[6]	X															
General oral/head and neck examination	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Intra-oral examination and assessment of ORN by Notani and CTCAE grade	X		X		X	X	X	X	X	X	X	X	X	X	X	X
UE	X															
LFT	X															
Research Blood Sample	X															
Pregnancy test[7]	X															
Radiology: Orthopantomogram	X							X[8]								X[9]
Patient Completes training for 15-day return of ePROM[10]			X													
Height & Weight measurement & BMI calculation			X		X	X	X	X	X	X	X	X	X	X	X	X

[4] At baseline, all procedures should be done before randomisation.
[5] These visits only apply to the patients who chose to continue the study after 12 months. For the rest of the patients, 12 months will be considered as study completion.
[6] Gender, ethnicity
[7] As appropriate
[8] May use OPT if taken for other clinical reason and within 4 months of study visit.
[9] Only repeat OPT at completion if there is mora than >4 months after the last OPT.
[10] ePROM to be completed every 15 days (or facilitated using website/research staff every 30 days)

Assessment	**Screening**	**Randomisation**	**Baseline[4]**	**2-week check by telephone**	**Clinic Visit Schedule *(in months)***				***Optional Clinic Visits[5] (in months)***							**Study Completion**
					3	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	
Clinic Visit Numbers					1	2	3	4	5	6	7	8	9	10	11	
Accepted Variance				*+/- 1 week*	*+/- 1 month*											*+/- 1 months*
Special Assay: Clinical Photograph with in-field ruler			X					X								X
PROM: EORTC QLQ-30 and H&N35			X		X	X	X	X	X	X	X	X	X	X	X	X
Randomisation		X														
Dispense Study Medication		X			X	X	X	X	X	X	X	X	X	X	X	
Collection of Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X

Types of Follow-up:

Remote recording of self-reported symptoms using RAPTOR App:
At baseline, patients are given training in initiating the ePROM data collection. This is used continuously to their study completion visit and will trigger collection of symptoms every 15 days.
Participants that do not report via ePROM, have the option of:

i. completing the ePROM via webpage or if this is not possible,
ii. via telephone facilitated by the site research staff.

Telephone follow-up:
A single telephone appointment is conducted 2 weeks after randomisation and once study medication has been started. The purpose is to check compliance with using the App, to reconfirm contact details, and for patients in Arm B remotely record the four target GI symptoms likely related to PENTOCLO overall tolerability (Abdominal Pain, Diarrhoea, Nausea, Vomiting).

Clinic Visits type 1 (at 3, 6, 9, …, max 33 months):
3-monthly trial visit to:
Review medications and medical history
Examine patient generally from head and neck perspective i.e. to exclude recurrence
Assess index ORN for progression or regression: assess Grade by Notani and CTCAE
Record antibiotic and analgesia usage
Measure BMI
Assess GI symptoms (only patients in Arm B)
QoL questionnaire using EORTC QLQ30 and QLQHN 35
& Arm B only - dispense trial medications

Clinic Visits type 2 (at 12 months and at study completion for patients who continue beyond 12 months):
As per type 1 with:
An orthopantomogram carried out (may use one carried out for any reason if within 4 months)
Photograph of exposed bone with in-field ruler

10.9 Translational Samples

The research samples being taken from participants in the trial, as described below, will be collected and stored for future translational/exploratory, ethically approved studies. The participant trial consent will cover the use of the samples for translational research. The translational aspects of the study are exploratory and are not included in the trial endpoints. The translational work will be subject to a separate statistical analysis plan and translational study report and not be part of the RAPTOR trial SAP or trial report.

10.9.1 Sample Collection

The details of the sample collection processes will be provided in a separate RAPTOR sample collection and laboratory manual. In addition to the participant's routine haematology blood samples, one EDTA blood sample is collected at the screening appointment. The purpose of the sample is to create a bioresource for subsequent radiogenomic studies.

10.9.2 Sample Storage and Handling

The EDTA blood sample will be delivered to University of Liverpool GCPLab Facility, who will remain custodian.

10.9.3 Custodianship

All samples will remain the responsibility of the PI until a representative from the University of Liverpool GCPLab Facility have confirmed receipt.

10.10 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of trial intervention and treatment and follow-up assessments/visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.10.1 Premature Discontinuation of Trial Intervention

Participants may discontinue treatment for reasons including, but not limited to:

- Participant-led i.e. request by the participant
- Unacceptable toxicity, although dose reductions are a possible mitigation that should be explored (see Section 11 for Adverse Event reporting)
- Intercurrent illness preventing further treatment
- Pregnancy
- Death
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion
    - Reasons of non-adherence or non-compliance with treatment or other trial procedures
    - Participant meets an exclusion criterion (either newly developed or not previously recognised)

Discontinuation from trial intervention does not mean discontinuation of the study altogether, and the remaining study procedures, follow-up assessment/visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn). The exception for this is for surgical resection of ORN, and when this is performed, it will trigger a Study Completion Visit irrespective of timepoint.

Data to be collected at the time of discontinuation will constitute a **Study Completion Visit**:
Examine patient generally from head and neck oncology perspective
Assess index ORN for progression or regression: assess Grade by Notani and CTCAE
Record antibiotic and analgesia usage
Measure BMI
Assess GI symptoms (only patients in Arm B)
Photograph of ORN with in-field ruler
QoL questionnaire using EORTC QLQ30 and QLQ HN35
Orthopantomogram if not already completed for any reason within 4 months

10.10.2 Participant Withdrawal from Follow-up

Participants are free to withdraw from follow-up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study and LCTC should be informed via email to LCTC and via completion of a Withdrawal CRF to be returned to LCTC within 7 days.

In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SAEs will be notifiable to LCTC via processes detailed in Section 11 even if a participant has withdrawn from follow-up.

10.10.3 Participant Transfer

If a participant moves from the area, every effort should be made for the participant to be followed-up at another participating trial site and for this trial site to take over responsibility for the participant or for follow-up via GP.

A copy of the participant CRFs should be provided to the new site. The participant remains the responsibility of the original site until the new site PI has signed the Transfer CRF.

10.10.4 Loss to Follow-up

A participant will be considered lost to follow-up if s/he fails to return for 3 scheduled visits and is not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow-up, site research staff will make every effort to regain contact with the participant (i.e. 3 telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes.
- If the participant continues to be unreachable, they should be considered withdrawn from the study with a primary reason of lost to follow-up and this should be recorded on the appropriate CRF.

10.11 End of Trial

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the TSC, on the recommendation of the IDSMC.

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and MHRA
- Trial-related materials reconciled and returned/disposed of as appropriate
- All site data entered onto the study database, discrepancies raised, and satisfactory responses received
- Quality Control checks of the Investigator Site Files, Pharmacy Files and TMF as appropriate

10.11.1 Study Discontinuation

In the event that the study is discontinued, sites will make arrangements for suitable ongoing care, including that of ORN, by conventional means.

11 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

11.1 Terms and Definitions

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR)
Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Serious Adverse Event (SAE)
Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR)
An adverse reaction which meets the definition of serious (see Section 11.22) is a Serious Adverse Reaction. A Serious Adverse Reaction event that has been assessed as 'expected' (see Section 11.55 Expectedness) according to the Reference Safety Information (see below) will remain classified as a Serious Adverse Reaction only, however some Serious Adverse Reactions that are considered 'unexpected' will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An adverse reaction that is classed in nature as serious and "unexpected" (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Reference Safety Information (RSI)
The information used for assessing whether an adverse reaction is expected (see section 11.55). This is contained in the Summary of Product Characteristics (SmPC) for the product and must be approved for use by the MHRA. The RSI used to assess the expectedness of a SAR must be the current approved version at the time of onset of the SAR. The RSI for this trial is defined in section 11.5.1.

11.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

An adverse event/adverse reaction is assessed as serious if it:

- Results in death;
- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure

for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE);

- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis);
- Other important medical events (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

11.3 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 2: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.
Life-Threatening	
Death	

A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 11.22. Hence, a severe safety event need not necessarily be a "serious" safety event.

11.4 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assignment of the causality should be made using the definitions in the table below:

Table 3: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on known safety profiles of IMP from the SmPC. If any doubt about the causality exists, the local investigator should inform the LCTC who will notify the CI. In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded, and the MHRA/REC will be informed of both points of view.

11.5 Assessment of "Expectedness"

The CI for the RAPTOR trial is responsible for determining whether a safety event is expected or unexpected, however a Chief Investigator will not assess their own patients, these patients will be assessed by the Medical Reviewer. There is no requirement for a reporting investigator to make an assessment of expectedness.

An event will be considered unexpected if it is not listed within the current and approved RSI (see section 11.5.1) for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI the event should be assessed as unexpected.

There won't be an expectedness assessment for the patients in Arm A – control arm, as they will not be receiving any IMPs, and any treatment they receive as part of SSC will vary from patient to patient.

11.5.1 Reference Safety Information/Information used to Assess Expectedness

The Reference Safety Information (RSI) for RAPTOR will be one document created to comprise of section 4.8 of each of the following SmPCs:

- Trental 400 mg Modified release Tablets (pentoxifylline)
- Clasteon 400 mg Capsules (sodium clodronate)
- Vitamin E Suspension (tocopherol)

SmPCs will be used in conjunction. If an SAE is listed in any of the three SmPCs, it will be considered expected.

11.6 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the below described "active monitoring" period which meet the definition of serious (see section 11.22) and are recorded for this study (see section 11.77) must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in section 11.111. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be from the period of randomisation until 30 days from last administration of IMP.

11.7 Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment

- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

Do not record:

- Medical or **surgical*** procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication **without signs or symptoms****
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

***Surgical procedures related to ORN of the mandible are reported as endpoints elsewhere, rather than as AE/SAEs.**

N.B. If overdose occurred **with resulting signs and symptoms that meet the protocol criteria for AE/AR/SAE/SAR/SUSAR then they should be reported accordingly (see section 8.8 for more information) and the overdose highlighted to the LCTC team.

The events above do not need recording as aligns with the overall risk profile of the trial.

11.8 Reporting of Pregnancy

If pregnancy occurs during either the intervention or follow-up period of the trial this must be notified to the LCTC using the appropriate CRF within 24 hours of the research team becoming aware. The pregnancy must be followed up by the site research team until outcome and reported to LCTC.

Any pregnancies which result in a safety event assessed as "serious" (e.g. birth defect) must also be reported separately on the appropriate Safety Event CRFs in accordance with processes described in section 11.100. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

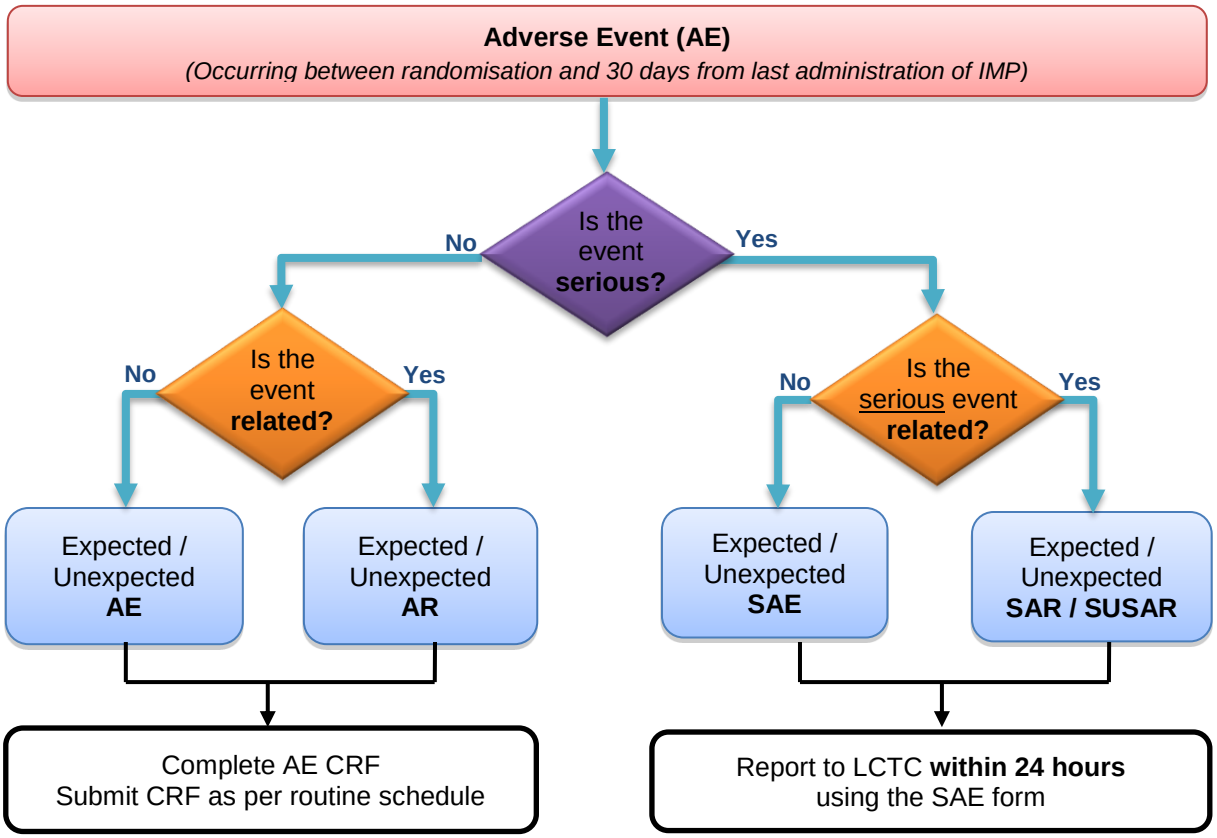
11.9 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the appropriate CRF within 24 hours of becoming aware.

11.10 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events.

11.10.1 Flowchart for Site Reporting Requirements of Adverse Events



11.10.2 Reporting Safety Events to the LCTC

All safety events (whether or not assessed as serious/related/expected) should be recorded on an Adverse Event (AE) CRF; multiple events can be recorded on one form.

Safety events which are assessed as "serious" must **also** be recorded in more detail on Serious Adverse Event (SAE) CRF; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. Each SAE should have a corresponding record on the participant's AE CRF. Where additional information is received by site after initial submission to LCTC, this should be provided on a follow-up form within 5 days. SAE CRFs collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the CI or Medical Reviewer, and assessed for causality and expectedness.

11.10.3 Follow-up After Adverse Events

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting "serious" safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown

11.11 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study (see section 11.77) which the local research team becomes aware of are reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events. When documenting any adverse events, the correct medical terminology **must** be used.

All safety events must be recorded on an AE CRF and transferred to LCTC **within seven days of the site team becoming aware of the event**.

Safety events which meet the definition of "serious" must be reported in more detail to the LCTC on an SAE CRF and reported **immediately and in no circumstances later than 24 hours from becoming aware** where they will be appropriately processed.

The SAE CRF should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person/dentist. Minimum reporting information must be provided in initial reports for all studies.

Minimum information required for reporting:

- Study site number
- Patient study number
- A description of the event
- Date of onset
- The reason why the event is classified as serious
- Suspect IMP (including active substance name)
- Investigator assessment of the association between the event and study treatment

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE CRF, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the site R&D team in accordance with local policy.

REPORTING AN INITIAL OR FOLLOW-UP SAE

The investigator should ensure the actions below are completed for all reportable SAEs:

1) Research sites should telephone the appropriate trial manager on telephone number **0151 7951728** to advise that an SAE report has been submitted as soon as possible.

2) **The SAE form should be emailed securely to the LCTC Central Safety Team via email to lctcsafe@liverpool.ac.uk (within 24 hours of site becoming aware).**

3) The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).

4) The patient must be identified by trial number, age and initials **only**. The patient's name **should not** be used on any correspondence.

5) SAEs must be subsequently followed up in line with the processes below:
   - Follow-up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. N.B. Follow-up may continue after completion of protocol treatment if necessary.

- Follow-up information is noted on a new SAE form to be transferred securely to the LCTC as soon as more information becomes available.
- Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up/final.

6) Extra, annotated information and/or copies of pseudonymised test results may be requested by LCTC if required.

11.12 LCTC Responsibilities

The trial Sponsor, University of Liverpool have delegated to LCTC the duty of onward reporting of safety events to REC and MHRA. SOPs will be followed to ensure appropriate reporting as detailed below.

All SAEs will be forwarded to the CI or Medical Reviewer by LCTC within 24 hours of receiving the minimum information from site. The CI/Medical Reviewer will review information provided by site and for all events assessed as "related" will provide an assessment of "expectedness".

Safety events which are assessed as "serious", "related" and "unexpected" will be expedited to the REC and MHRA as a SUSAR within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of the LCTC first becoming aware of the event.

Additionally, SUSARs will be reported to the trial Sponsor and PIs of participating within the agreed timelines.

Any concerns raised by the TSC or IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported AEs/ARs and SARs/SAEs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

11.12.1 Safety Reports

Safety reports will be generated during the course of the trial which allows for monitoring of safety event including reporting rates and safety events. The LCTC will produce annual reports and submit to the MHRA and REC. Additionally, safety events will be included in reports to the IDSMC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

11.12.2 Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

LCTC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence

until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

11.13 Contact Details and Out-of-hours Medical Cover

As this IMP is in some cases standard NHS practice, and has well established safety profile, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for RAPTOR participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, sites should contact LCTC in the first instance, who can then forward this information to the CI or delegate to provide medical advice in relation to participation.

12 STATISTICAL CONSIDERATIONS

12.1 Introduction

Details are provided on the statistic considerations including all details of the sample size calculations, randomisation procedures and details for analysis. Please note that a separate Statistical Analysis Plan (SAP) will provide detailed instructions of all analytical procedures to be followed.

12.2 Sample Size

12.2.1 Sample Size Calculation

The primary endpoint is the time-to-healing measured as a time-to-event outcome. The definition is time from randomisation to healing of ORN.

Current estimates of the use of PENTOCLO give a 12-month healing rate of approximately 60% and it is considered that this would have to demonstrate an improvement over a 40% rate in the control arm (equivalent to a hazard ratio of 0.56). Using a one-sided alpha level of 0.1 and a Power of 90% then a total of 78 events are required. Including a 5% rate for patient attrition and based on estimated recruitment rates, it is estimated that 120 patients are required to obtain the events required.

12.3 Method of Randomisation

12.3.1 Allocation Sequence Generation

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by LCTC to receive either arm A, SSC or arm B, PENTOCLO + SSC (in a ratio of 1:1).

Randomisation lists shall be produced by a statistician at the LCTC prior to the recruitment of the first patient. Patients shall be randomised using a 1:1 ratio. Lists will be stratified by study site.

12.3.2 Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all baseline measurements have been completed.

12.4 Interim Analyses

There are no formal stopping rules based on efficacy or futility of the primary endpoint. Analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an IDSMC. These analyses will be performed at the LCTC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

12.5 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Patient Groups
The primary analysis will be carried out on the full analysis set which will be defined on the intention to treat principle retaining patients in their initially randomised groups irrespective of any protocol violations.

Exposure to Treatment
Exposure to treatment will be assessed by mean dose/patient, mean planned dose, no. of completed cycles, and proportion of patients with dose omission.

Levels of Significance
Analysis of the primary outcome will be assessed using 1-tailed 0.1 level as is consistent with the type I alpha level used in the study design. All analyses of secondary outcomes will use the nominal $p<0.05$ level to determine statistical significance.

Missing Data
Missing data are expected to be small and final analyses are planned to be carried out on a complete case basis. As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

If substantial missing data (>10%) are observed and it is considered appropriate upon review, then multiple imputation using chained equations will be applied.

Analysis of the Primary Outcomes
The primary outcome is time to healing. Healing rates will be estimated using the method of Kaplan and Meier. Comparisons across treatment groups will be performed using a log-rank test. Further analysis adjusting for key demographic/clinical covariates will be performed using a Cox proportional hazards model. Further sub-group and sensitivity analyses are defined in the SAP.

13 DATA MANAGEMENT AND TRIAL MONITORING

For the RAPTOR trial the responsibilities for Data Management and Monitoring are delegated to LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

13.1 Source Documents

CRF will be considered the source document for data where no prior record exists, and which is recorded directly in the bespoke CRF. A RAPTOR source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes RAPTOR-specific source data.

Date(s) of informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

13.2 Data Collection Methods

Participant CRF folders will be provided to sites for local completion by members of the research team trained and delegated the duty. Study staff named at each site will enter data from source documents corresponding to a participant's visit onto the relevant CRF in the participant's folder. The CRF is the primary data collection instrument for the study so all data requested on the CRF **must** be recorded and all missing data must be explained. A copy of all CRFs should be retained at site. Any corrections should be made in accordance with GCP.

Questionnaires are a source document and **sites should photocopy them** in order to retain a copy at site before posting originals to LCTC.

Data entered into the ePROM is considered source data. A copy of the data will be provided to sites on appropriate media to be stored with the ISF at the end of trial for archiving.

13.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed in conjunction with the trial risk assessment to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.

13.3.1 Central Monitoring

There are a number of monitoring features in place at LCTC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be returned to the site in the form of data queries. Data query

forms will be produced at LCTC from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to LCTC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

13.3.2 Clinical Site Monitoring

In order to perform their role effectively, the trial manager and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the Participant Information Sheet and Consent (PISC) form. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

13.4 Risk Assessment

In accordance with the principles of GCP and legislation applicable to research, this trial has undergone a risk assessment to mitigate the risks and assure the safety, well-being and rights of participants, and the credibility of study results. This risk assessment has been completed in partnership between:

- Sponsor representative/s
- CI
- Trial Manager and Senior/Supervising Trial Managers
- Trial statistician and Supervising Statistician
- Information Systems (IS) team
- Data Management team

In conducting this risk assessment, the contributors considered potential participant safety, participant rights, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

This level of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial.

13.5 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial screening and/or randomisation number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.

N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioner's Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

13.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each site will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated.
- The Trial Manager at the LCTC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual site.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between sites and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

13.7 Records Retention

The retention period for the RAPTOR data and information is 25 years from the official End of Trial date (defined in section 10.11 above).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File, the applicable participant medical records and Pharmacy Site File, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the LCTC.

The PI is also responsible for archiving 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). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories etc.).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 REGULATORY AND ETHICAL CONSIDERATIONS

14.1 Statement of Compliance

The study will be carried out in accordance with:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (and amendments)
- The principles of Good Clinical Practice
- The World Medical Association Declaration of Helsinki
- UK General Data Protection Regulation
- LCTC Liverpool Clinical Trials Centre SOPs
- The template content is structured consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013)
- UK Policy Framework for Health and Social Care Research

14.2 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent REC and has received a favourable opinion.

The study procedures outlined in section 10 are standard, non-invasive, well tolerated clinical procedures with minimal associated risk.

14.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate REC, MHRA, Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

14.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical e.g. MHRA and REC requirements are handled based on their nature and severity.

14.4.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

14.4.2 Serious breaches

A breach of the protocol or GCP is ‘serious’ if it meets the definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within 7 days by LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

15 INDEMNITY

University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

16 PUBLICATION AND DISSEMINATION

16.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's CI, Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

16.2 Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the RAPTOR Consortium which will also be named at the manuscript head.

16.3 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA and a summary provided to REC. The results of RAPTOR will be published regardless of the magnitude or direction of effect.

Outputs would include publication of data in relevant journals and to present at the most impactful international meetings such as ASCO, AACR, NCRI as well as key head and neck / dental meetings such as International or American Head and Neck Associations/ International Academy of Oral Oncology.

We also plan to report the findings back to the NCRI committees where RAPTOR was developed (principally the Head and Neck Cancer Clinical Studies Group and Living With and Beyond Cancer (LWBC)).

The findings of the trial will be summarised on the study web pages which are regularly visited by patients. Additionally, summaries of the main findings will be provided to those patients who participated in the trial.

16.4 Data Sharing

All requests for access to the IPD will be reviewed by the Sponsor and discussed with the CI in accordance with the Sponsor's policy on data sharing.

17 CHRONOLOGY OF PROTOCOL AMENDMENTS

17.1 Version 1.0 (02/Aug/2022)

Original Approved version

18 REFERENCES

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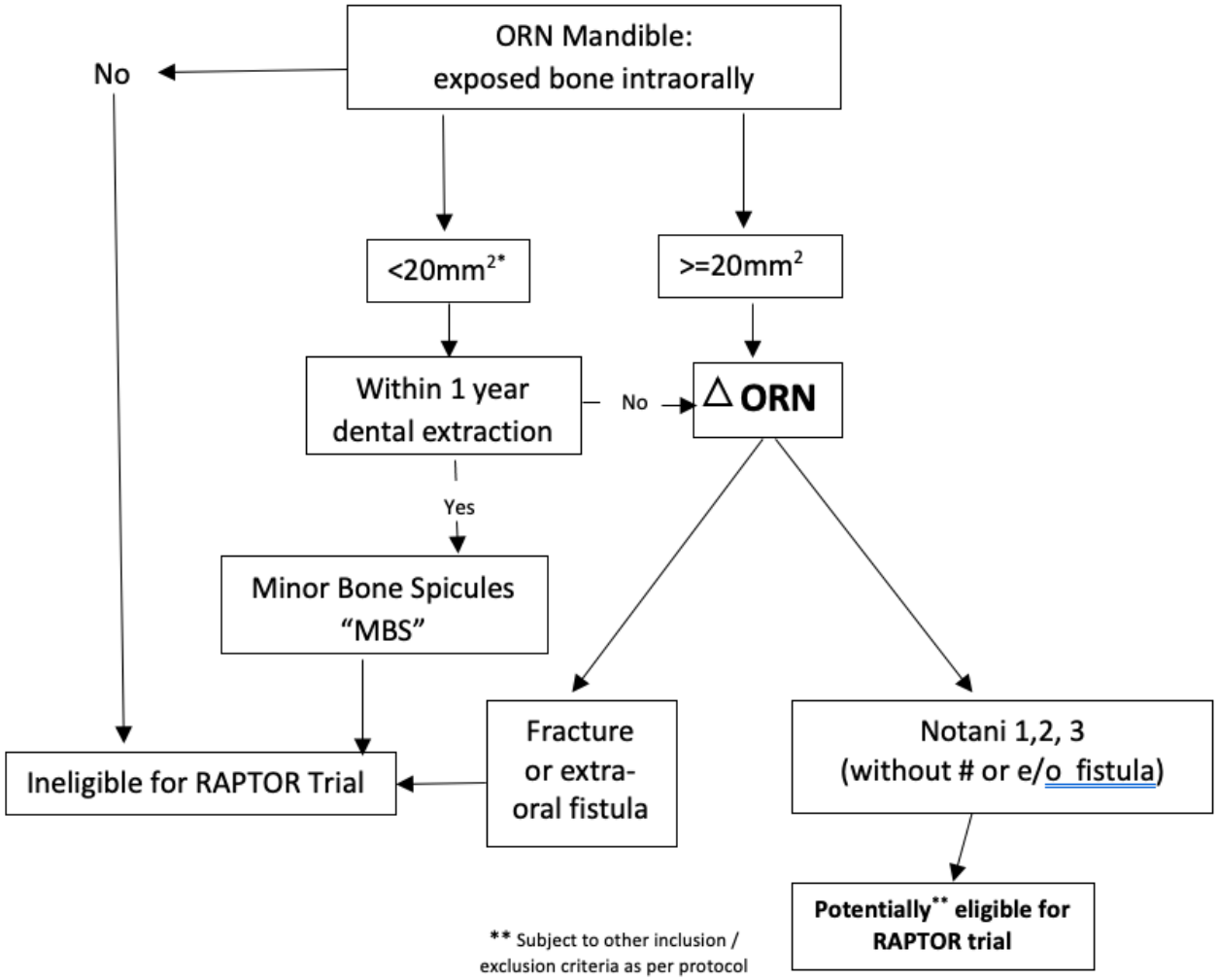
19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and/or Ethical review are submitted as separate version-controlled documents.

20 APPENDICES

Appendix A: Classification of ORN for the purposes of the RAPTOR Trial



Appendix B: Canadian Cardiology Society Angina Grading[(1)]

Higher grade indicates higher severity of angina:

Grade	Description
I	Angina with strenuous/rapid/prolonged exertion at work or recreation only; no angina with ordinary physical activity, e.g. walking, climbing stairs
II	Ordinary activity slightly limited: angina with walking/climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold/wind, under emotional stress, during few hours after awakening, walking >2 blocks on level ground, or climbing >1 flight of stairs at normal pace and normal conditions
III	Marked limitation of ordinary physical activity: angina with walking 1-2 blocks on level ground or climbing 1 flight of stairs at normal pace and normal conditions
IV	Inability to carry on any physical activity without discomfort; anginal syndrome may be present at rest

Appendix C: Scale for Assessing the Symptom Severity of Atrial Fibrillation[2]

Step 1 – Symptoms

Identify the presence of the following symptoms:

A. Palpitation
B. Dyspnea
C. Dizziness, presyncope, or syncope
D. Chest pain
E. Weakness or fatigue

Step 2 – Association

Is AF, when present, associated with the above-listed symptoms (A-E)?

For example: Ascertain if any of the above symptoms are present during AF and likely caused by AF (as opposed to some other cause).

Step 3 – Functionality

Determine if the symptoms associated with AF (or the treatment of AF) affect the patient's functionality (subjective quality of life).

Class 0

Asymptomatic with respect to AF

Class 1

Symptoms attributable to AF have ***minimal*** effect on patient's general QoL.

- minimal and/or infrequent symptoms, or
- single episode of AF without syncope or heart failure

Class 2

Symptoms attributable to AF have a ***minor*** effect on patient's general QoL.

- mild awareness of symptoms in patients with persistent/permanent AF, or
- rare episodes (eg, less than a few per year) in patients with paroxysmal or intermittent AF

Class 3

Symptoms attributable to AF have a ***moderate*** effect on patient's general QoL.

- moderate awareness of symptoms on most days in patients with persistent/permanent AF, or
- more common episodes (eg, more than every few months) or more severe symptoms, or both, in patients with paroxysmal or intermittent AF

Class 4

Symptoms attributable to AF have a ***severe*** effect on patient's general QoL.

- very unpleasant symptoms in patients with persistent/paroxysmal AF and/or
- frequent and highly symptomatic episodes in patients with paroxysmal or intermittent AF and/or
- syncope thought to be due to AF and/or
- congestive heart failure secondary to AF

Appendix D: CTCAE Classification of Osteonecrosis of jaw (CTCAE Version 5.0 Nov 27 2017)

CTCAE Term: Osteonecrosis of the jaw
Grade 1: Asymptomatic; clinical or diagnostic observations only, intervention not indicated
Grade 2: Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL
Grade 3: Severe symptoms; limiting self-care ADL; elective operative intervention indicated
Grade 4: Life-threatening Death consequences; urgent intervention indicated
Grade 5: Death