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Clinical trial of the non-surgical management of radiotherapy damage to the lower jaw

Submission date 20/09/2022	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 11/11/2022	**Overall study status** Ongoing	
Last Edited 09/04/2025	**Condition category** Oral Health	

Plain English summary of protocol

Background and study aims

Most treatments for head and neck cancer include radiotherapy, and despite advances in planning and doses, this leaves survivors at risk of significant late effects. One of the most severe complications is osteoradionecrosis (ORN), which is bone death caused by irradiation. This can affect any bone or cartilage in the head and neck but is commonest in the lower jaw. ORN is characterized by exposure and crumbling of the jaw, severe pain, repeated infections, weight loss, restricted mouth opening, difficulty in chewing and disfigurement. Existing treatments include supportive and conservative methods such as long-term antibiotics, antiseptic mouthwash and painkillers, and surgery which may be curative but is risky, complex and has unpredictable outcomes. Some studies of osteoradionecrosis suggest that a combination of three medications (pentoxyphylline, tocopherol, clodronate: PENTOCLO) may be capable of complete resolution without surgery. Healing in this way is through lifting off of the dead bone fragments leaving intact skin underneath. Some research suggests that just over half of patients benefit, but this has yet to be proved, particularly in comparison with other treatments. This study proposes to compare PENTOCLO medications against standard supportive medications such as antibiotics, mouthwash and painkillers.

Who can participate?

Patients aged 18 years and over with mandibular ORN

What does the study involve?

Patients will be selected at random for either of the two treatments for at least a year. The trial will also measure pain, side-effects, the need for antibiotics and the instances where deterioration forces the need to resort to surgery instead. Discussion with patients during trial design has resulted in an increased emphasis within the protocol for collection of information on patients' pain and other symptoms, and particularly in providing a 'safety net' for those patients who are deteriorating. As a result, at 4-monthly clinic visits, patients will report their symptoms (pain, eating, mouth-opening, swelling) every 15 days via their smart device using an App.

What are the possible benefits and risks of participating?

Benefits:

Not provided at time of registration

Risks:
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 in the relevant Summary of Product Characteristics.
Vitamin E Suspension (Tocopherol): Diarrhoea and abdominal pain may occur with doses greater than 1 g daily, but are not expected within this trial as the dose is 1 g/day.
Sodium Clodronate: Common side effects include diarrhoea, nausea and vomiting. The comprehensive list of undesirable effects is included in the relevant Summary of Product Characteristics.

Treatment modifications;
Sodium clodronate - Diarrhoea, nausea or vomiting: consider first using a divided dose regimen, rather than a single daily dose, which may improve gastrointestinal tolerance. This is potentially more difficult with regard to compliance for patients in that effective absorption requires an empty stomach (1 hour before and 2 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 C.I., 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 & after discussion with the C.I., 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).

Where is the study run from?
University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
August 2022 to December 2026

Who is funding the study?
National Institute for Health Research Efficacy and Mechanism Evaluation Programme (UK)

Who is the main contact?
1. RAPTOR Trial Team, raptor@liverpool.ac.uk
2. Prof. Richard Shaw, rjshaw@liverpool.ac.uk

Study website
https://raptorstudy.org.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2022-000728-39

IRAS number
1005271

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
UoL001664, IRAS 1005271, CPMS 53806

Study information

Scientific Title
Randomised controlled trial of PENTOCLO (pentoxifylline, tocopherol and clodronate) in mandibular osteoradionecrosis

Acronym
RAPTOR

Study objectives
The primary aim is to determine if PENTOCLO triple therapy (pentoxifylline, tocopherol and clodronate) is effective in the healing of mandibular osteoradionecrosis (ORN).

Secondary Objectives:
To evaluate the impact of PENTOCOLO on:
1. Patients' pain and mouth function
2. Patients' ability to receive treatment and control the disease
3. Patients' analgesia and antibiotic use
4. Patients' anthropological measurements
5. Severity of disease
6. Overall quality of life
7. Mandibular preservation
8. Associated toxicity

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 27/10/2022, North East – Tyne & Wear South Research Ethics Committee (Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 207 104 8286; tyneandwearsouth.rec@hra.nhs.uk), ref: 22/NE/0195

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Osteoradionecrosis (bone death caused by irradiation)

Interventions
Participants are randomised to receive either PENTOCLO (pentoxifylline, tocopherol, clodronate) or standardised supportive care (e.g. antibiotics, mouthwash and painkillers).

Dose:
Pentoxifylline 800 mg daily
Tocopherol 1000 mg daily
Clodronate 1600 mg days 1-5 of 7 (Monday to Friday)

Route of administration: oral

Duration of treatment: minimum 1 year

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Pentoxifylline, tocopherol, sodium clodronate

Primary outcome measure
Time to healing (defined as the complete elimination of exposed bone without the need for surgery), measured every 3 months following randomisation until the end of the trial for that patient

Secondary outcome measures
Measured every 3 months following randomisation until the end of the trial for that patient unless otherwise noted:
1. PROMs (patient-reported outcome measures) of symptoms related to ORN recorded every 15 days: pain, eating, trismus, swelling
2. Time to treatment failure/progression, measured as the time from randomisation until worsening ORN or the clinical need for mandibular resection and reconstruction
3. Analgesia and antibiotic usage recorded at 3-monthly appointments
4. Mandibular preservation rate measured by general head and neck and intra-oral examination every 3 months
5. Notani grade of ORN recorded at 3-monthly appointments
6. Dimensions of exposed bone between baseline and primary endpoint measured using clinical photograph with in-field ruler
7. Severity of disease and overall quality of life measured using Common Toxicity Criteria for Adverse Events (CTCAE)/Subjective, objective, management and analytic (SOMA)/Quality of Life (QOL) scores
8. Patients' weight and height measurements recorded at 3 monthly visits to calculate the BMI (kg/m^2)
9. Compliance, gastrointestinal tolerability and toxicity of PENTOCLO measured using the CTCAE

Overall study start date
05/08/2022

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. A diagnosis of mandibular ORN
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
4. Aged 18 years and over

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
120

Key exclusion criteria
Current exclusion criteria as of 09/01/2024:

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')
4. Mandibular pathological fracture secondary to ORN
5. Indication for mandible resection - i.e. patient for whom the severity of their ORN symptoms already constitute an indication for mandible resection and reconstruction. Typically, these symptoms will include severe pain, repeated infections, significant mobile pathological fracture or distressing fistula)
6. Patient has had definitive resection / reconstruction for mandibular ORN -i.e. no longer has exposed necrotic bone present.
7. Pregnancy
8. Lactation
9. Age <18 years
10. Acute infection at site of the necrotic bone.
11. Contraindications to PENTOCLO medications:
11.1. Known hypersensitivity, allergy or anaphylaxis to pentoxifylline, tocopherol or sodium clodronate
11.2. Treated hypotension
11.3. Severe coronary artery disease, defined as grade IV of the Canadian Cardiology Society Angina Grading
11.4. Severe atrial fibrillation, defined as grade 4 on modified CCC-SAF
11.5. Myocardial infarction within 6 months
11.6. Prior history of extensive retinal haemorrhage
11.7. Prior history of intracranial bleeding
11.8. Impaired renal function (Creatinine clearance <30 ml/minute, will be formally assessed only if U&E out of reference)
11.9. Severe liver failure (class B or C Pugh-Child Score, will be formally assessed only if LFT values, out of reference)
11.10. 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)
11.11. Concomitant prescription of ketorolac, cimetidine, ciprofloxacin, theophylline, estramustine phosphate
11.12. Hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency
11.13. Concomitant prescription other bisphosphonates e.g. risedronate, alendronate, aIbandronate, zoledronic acid, pamidronate, etidronate or prescription of denosusamab
11.14. Concomitant prescription of aminoglycoside antibiotics e.g. gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, paromomycin

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Previous 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:
11.1. Known hypersensitivity, allergy or anaphylaxis to pentoxifylline, tocopherol or sodium clodronate
11.2. Treated hypotension
11.3. Severe coronary artery disease, defined as grade IV of the Canadian Cardiology Society Angina Grading
11.4. Severe atrial fibrillation, defined as grade 4 on modified CCC-SAF
11.5. Myocardial infarction within 6 months
11.6. Prior history of extensive retinal haemorrhage
11.7. Prior history of intracranial bleeding
11.8. Impaired renal function (Creatinine clearance <30 ml/minute, will be formally assessed only if U&E out of reference)
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11.10. 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)
11.11. Concomitant prescription of ketorolac, cimetidine, ciprofloxacin, theophylline, estramustine phosphate
11.12. Hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency
11.13. Concomitant prescription other bisphosphonates e.g. risedronate, alendronate, aIbandronate, zoledronic acid, pamidronate, etidronate or prescription of denosusamab
11.14. Concomitant prescription of aminoglycoside antibiotics e.g. gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, paromomycin

Date of first enrolment
27/04/2023

Date of final enrolment
26/04/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Aintree University Hospital
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Sponsor information

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University of Liverpool

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Sponsor type
University/education

Website
http://www.liv.ac.uk/

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research Efficacy and Mechanism Evaluation Programme

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Submission to regulatory authorities
6. Registration on a public database

Intention to publish date
31/12/2026

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No