

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

Submission date 20/09/2022	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 11/11/2022	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 28/07/2025	Condition category Oral Health	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

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 (pentoxifylline, 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

Contact information

Type(s)

Scientific

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Type(s)

Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)

2022-000728-39

Integrated Research Application System (IRAS)

1005271

Central Portfolio Management System (CPMS)

53806

Protocol serial number

UoL001664

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

Study type(s)

Treatment

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(s)

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

Key secondary outcome(s)

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/m²)
9. Compliance, gastrointestinal tolerability and toxicity of PENTOCLO measured using the CTCAE

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

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

All

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 mm² 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, albandronate, zoledronic acid, pamidronate, etidronate or prescription of denosumab
 - 11.14. Concomitant prescription of aminoglycoside antibiotics e.g. gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, paromomycin

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 mm² 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
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 - 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

United Kingdom

England

Study participating centre
Aintree University Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

Sponsor information

Organisation
University of Liverpool

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

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?
Protocol article		24/07/2025	28/07/2025	Yes	No
HRA research summary			26/07/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes