SPIRIT 2013 protocol recommendations.

Administrative information

1. Prospective randomised assessor blinded pilot study comparing Hyperbaric Oxygen therapy with PENTOCLO for the management of Osteoradionecrosis of the mandible.

2a. Registration – Intended registration is with the clinical trials database of the TGA in Australia as well as the Australian New Zealand Clinical Trials Registry of the NHMRC.

3. Protocol version : 5.1 – Jun 2018

4. Funding: presently unfunded however the costs of the study will be borne by the Oral and Maxillofacial teaching unit in the tertiary hospital in which the study is being carried out.

5. Roles and responsibilities

Dr Vishal M Bulsara BDS – Dentist & Final year medical student, School of Medicine, The University of Notre Dame, Fremantle, Western Australia – Lead writer and investigator

Dr Emma Lewis BDS MBBS FRACDS – Consultant Oral and maxillofacial surgeon – Clinical expert

Professor Mahesh K Bulsara PhD MSc BSc – Professor of Biostatistics, Institute for Health Research, The University of Notre Dame, Fremantle, Western Australia – Consultant, statistics and data analysis methods.

6a. Background and rationale

- The aim of this pilot study is to investigate the management of patients with Osteoradionecrosis (ORN) of the mandible using either a medication regime known as “PENTOCLO” or the traditional “Gold Standard” of hyperbaric oxygen therapy (HBO).

* In patients requiring non-surgical management of Osteoradionecrosis of the mandible has the current “Gold Standard” of Hyperbaric oxygen therapy been compared against a novel Medication regime known as PENTOCLO which has been successfully trialled in several European centres?
* Pilot studies form a crucial step in the research process and fulfil many important functions, they also help to provide valuable insights for other researchers. This pilot study will attempt to generate a hypothesis that can be tested with larger multi-centre randomised controlled trials; as far as we are aware it is also the first time that PENTOCLO has been used in a clinical study an Australian population.
* Osteoradionecrosis of the jaw is a complication said to occur in up to 20% of patients undergoing radiotherapy for the treatment of cancer of the head and neck ([McLeod, Pratt, Mellor, & Brennan, 2012](#_ENREF_9)). Robert Marx proposed in 1983 that Osteoradionecrosis (ORN) of the jaw is due to hypoxia, hypocellular and hypovascular changes to the irradiated tissues after radiotherapy ([Marx, 1983b](#_ENREF_8)). This lead him to propose the use of Hyperbaric oxygen (HBO) in a defined protocol as a therapeutic intervention for patients requiring treatment for ORN ([Marx, 1983a](#_ENREF_7)). Since this time HBO therapy has been extensively researched and is now known to be safe and relatively effective as well as well tolerated by the majority of patients that undergo it ([Bennett, Feldmeier, Hampson, Smee, & Milross, 2012](#_ENREF_1)). The use of PENTOCLO for the treatment of ORN of the mandible was suggested by Delanian *et al* in 2005 ([Delanian, Depondt, & Lefaix, 2005](#_ENREF_4)). Since this time a number of maxillofacial units in France and UK have shifted their treatment protocols for ORN to the use of PENTOCLO as a first line non-surgical option rather than using HBO ([Bennett et al., 2012](#_ENREF_1); [D'Souza, Lowe, & Rogers, 2014](#_ENREF_2); [Delanian, Chatel, Porcher, Depondt, & Lefaix, 2011](#_ENREF_3); [McLeod et al., 2012](#_ENREF_9); [Robard, Louis, Blanchard, Babin, & Delanian, 2014](#_ENREF_12)). It has been claimed by Delanian and others that PENTOCLO offers a faster rate of healing and improvement in SOMA/Notani clinical score for patients on the protocol than the traditional “Gold Standard” of Hyperbaric Oxygen Therapy (HBO) ([Robard et al., 2014](#_ENREF_12)). One of the limitations of the previous clinical trials and literature in this area is that, to date, no centre has undertaken a comparative clinical trial to determine if PENTOCLO is at least equal to HBO therapy for the management of ORN of the mandible. A search of clinical trials registers in the US, UK, Europe and Australia revealed no clinical trials registered to compare PENTOCLO with HBO for the management of ORN of the mandible. It was therefore decided that it would be useful to undertake a pilot study to generate a hypothesis for larger multicentre trials comparing PENTOCLO with HBO for the management of ORN of the mandible.
* Recent literature in this area has also suggested that the only use for PENTOCLO is within a clinical trial environment and recommendations from NICE have suggested a similar position ([Dhanda, Rennie, & Shaw, 2018](#_ENREF_5)). It is therefore imperative that prospective trials are undertaken in this area.

7. Objectives

* To describe time to complete mucosal healing in patients treated with PENTOCLO vs HBO using an accepted clinical and radiographic scoring system.
* To describe the rate of improvement in patients treated with PENTOCLO vs HBO using an accepted clinical and radiographic scoring system.
* To describe the rates of failure of treatment in patients treated with PENTOCLO vs HBO using an accepted clinical and radiographic scoring system.

8. Trial Design

* Pilot Randomised assessor blinded controlled trial 1:1 ratio, exploratory.

9. Study setting – Oral and Maxillofacial surgery outpatient clinic Perth, Western Australia, Australia

10. Eligibility criteria

Patients eligible for the trial will have been referred to the Oral and Maxillofacial surgery outpatient department from a range of sources such as: Dentists (both private practice and public services), General Practitioners, Other medical specialists (such as ENT surgeons, Plastic surgeons, oncologists). Eligible patients will be approached to participate in the study at their first visit with the Oral and Maxillofacial surgery unit where appropriate clinical and radiographic details will be assessed.

Inclusion criteria – Patients diagnosed with ORN by an Oral and Maxillofacial surgeon

- Patients or proxies that are able to give informed consent

Exclusion criteria – Patients that have spontaneously healing ORN

* Patients that have undergone previous treatment for ORN (PENTO, HBO or surgery).
* Patients or proxies that are unable to give informed consent
* Patients that are pregnant at the time of therapy
* Patients that have received previous anti-resorptive or anti-angiogenic medications
* Patients requiring further surgical management for their Head and Neck cancer during the study period
* Patients diagnosed with ORN requiring urgent surgery
* Patients that are unable to be randomised

Medication will be dispensed by clinical pharmacists who are part of the trial and HBO therapy will be performed in a dedicated HBO unit of a major tertiary hospital under the supervision of trained specialist physicians.

11. Interventions.

a. Medication group – 4 weeks of “pre-treatment” therapy to reduce inflammation, infection and pain consisting of 2 grams daily of amoxicillin + clavulanic acid 875/125mg, 50mg Fluconazole daily, 16mg Methyl-prednisolone daily taken orally by the patient. “Therapeutic phase” then commences immediately and consists of 5 days dosing of 800mg Pentoxyphylline and 1000iu Vitamin E (Mon-Fri) taken orally by the patient. If the patient deteriorates (indicated by decrease in clinical and radiographic assessment score at follow-up by consultant) then add Clodronate 1600mg daily orally Mon-Fri) for minimum of 6months but up to 18months if the patient has stable ORN and is not deteriorating further. If the patient experiences any pain or infection then 1gram Ciprofloxacin and Prednisolone 16mg orally on the remaining 2 days (Saturday and Sunday) can be added to help resolve symptoms.

HBO group – 4 weeks of ‘pre-treatment’ therapy as above. “Therapeutic phase” incorporates HBO therapy as prescribed for each individual patient based on Marx’s protocol of 30 dives at 2.4atm for 90minutes per dive. If the patient is stable and not deteriorating after the “therapeutic phase” has ended then they will be reviewed as per the protocol time points. If the patient experiences pain or infection then appropriate medical treatment will be prescribed.

b. Medication group – patients undergoing severe adverse reaction to the medication regime (defined as a reaction affecting quality of life or causing symptoms that the patient comments on) will be removed from the trial and offered HBO therapy.

HBO group – patients undergoing severe adverse reactions (as defined above) to the HBO therapy will be removed from the trial and offered the medication regime.

* Patients requesting to be removed from the trial for any reason will be offered the alternative therapy to which they were assigned.
* Patients with worsening disease (as defined by a change in Notani/Lyons score) will be offered a follow-up visit one month later to assess their status again (after addition of Clodronate in the medication group). Patients showing continued worsening of their condition will be removed from the trial group and offered the alternative therapy or surgical management according to established therapeutic protocols.

c. Patients will be briefed at the beginning of the trial about the importance of attending all visits and adhering to the therapy that they are randomised to. They will also be asked to return any unused medication at follow-up visits so that the clinical pharmacy team can monitor any non-adherence to the medication therapy in this trial group, the data for this will form part of the final analysis for the study.

d. Concomitant monitoring of the patient response to hyperbaric oxygen therapy will be permitted by the HBO unit physicians of the hospital. Patients deteriorating while undertaking HBO therapy will be referred back to the maxillofacial unit for urgent (within 7days) review and a change of treatment if this is warranted, any changes to the protocol will be documented and included in the final analysis.

12. Outcomes

* Primary outcome – improvement or complete healing of ORN of the mandible as defined by Notani/Lyons scoring.
* Secondary outcomes – worsening of ORN

 - complications that arise from treatment

Primary outcome will be measured by two independent assessors in the following way:

* Clinical photographs of the intra-oral status of the tissues will be taken with a standard flash and using a standard intra-oral measurement probe (periodontal probe or disposable surgical ruler) by trained clinical photographers at the tertiary hospital, these photographs will be printed out and combined with the most recent CT still images or panoramic radiographs that have been de-identified to show the boney defect for each patient that has ORN. The independent assessors will then be asked to review the clinical photographs and radiographic images and assign a Notani/Lyons score for each patient ([Lyons, Osher, Warner, Kumar, & Brennan, 2014](#_ENREF_6); [Notani et al., 2003](#_ENREF_10)). This will be repeated at each time point for follow-up (as indicated in the timeline diagram). The treating consultant will also have access to the clinical photographs and radiographic images for the purposes of assigning a score to track the patient’s progress for follow-up. The scores assigned by the independent assessors will be collated in an excel spreadsheet and kept with the patients unique identifier number to track their progress through the study.

Secondary outcome will be measured in the following way:

- A record will be kept by the treating consultant of any serious adverse events that are reported by the patient throughout the treatment. A serious adverse event will be defined as a reaction to treatment that the patient notifies the treating consultant of or a reaction that affects the patient’s Quality of life. Other complications such as worsening of the patient’s condition will be recorded by the treating consultant and these will be de-identified and made known to the lead investigator to be recorded against the patient’s data for the study.

13. Participant timeline – Enrolment will commence in October of 2018 and we estimate that it will take no longer than one year from commencing enrolment in the study to recruiting all participants. Participants will then be commenced on therapy as soon as they are enrolled to minimise the time spent waiting and to ensure that an accurate indication of the relative efficacy of each therapy is gained.

14. Sample size

For this pilot study we will recruit a sample size of 8 patients per treatment arm. As we are not testing a hypothesis the initial results from this pilot study will be used to determine a sample size for a larger trial.

15. Recruitment

Patients will be recruited from those referred to the Oral and Maxillofacial outpatient clinic and having undergone an initial assessment with and Oral and Maxillofacial consultant surgeon. It is estimated that adequate patient numbers will be available for recruitment.

**Methods**

 Allocation:

 16a. Sequence generation – Computer generated random numbers with participants to be stratified by grade of ORN, co-morbidities, sex, age, socio-economic status & smoking status.

 16b. Allocation concealment – Clinical pharmacy department will hold the master unblinded list for the duration of the trial, once participants have been recruited they will be allocated a unique ID number and randomly assigned by computer to one of the two treatment groups. Clinical pharmacy will not have any physical contact with the participants until after they have been assigned.

 16c. Implementation – Clinical pharmacy department will generate the allocation sequence, the lead investigator will enrol participants after clinical assessment has taken place. Interventions will be assigned randomly according to computer-generated list.

 17a. Assessors and investigators will be blinded to the intervention that the participant receives. Clinical photographs will be taken in a dedicated room and de-identified prior to being assessed, radiographs will also be de-identified but coupled with the matching photographs for the purposes of assessment and scoring via the Notani/Lyons index. Investigators will remain blinded during the data collection phase and during the analysis other than knowing which group NUMBER the participants were assigned to and the patients name for the purposes of comparing the two treatments against defined primary and secondary outcome measures and ensuring that the correct imaging results are matched against the correct photographs for the external assessors.

 17b. Unblinding will be permissible if the treating consultant determines that a participant is at risk from a treatment, as defined by an increase in their Notani/Lyons score over two consecutive visits 1 month apart, or if the patient complains of a severe adverse reaction to the treatment that they have been assigned. If this is the case then the participants will be unblinded to offer them the alternative treatment or surgical management. Intention to treat analysis will still be undertaken for these participants.

Methods: Data collection, management, and analysis

18a. – Participants will be assessed by their treating consultant who will complete a standardised form at each follow-up appointment (attached to protocol) to collect the necessary data from trial participants using NHMRC guidelines. At the initial visit baseline information will be collected as part of the patients routine care and utilised for the trial. Throughout the course of the trial information for eventual allocation of SOMA scoring ([Pavy et al., 1995](#_ENREF_11))a will be collected on the standardised forms for inclusion in the eventual analysis at the conclusion of the study. This will enable investigators to also assess patient quality of life during the trial without any potential bias being introduced into the study protocol. The lead investigator will enter the data using the double entry method with built in verification to minimise any data entry errors

18b. as described previously.

19. Master unblinded list will be held securely in a spreadsheet on a password locked computer that is only accessible within the clinical pharmacy office of the hospital. A copy of the patients name and intervention NUMBER as well as any data collected for the trial will be held on a password-protected computer in the office of the maxillofacial department of the participating hospital. The data will also be backed-up on an encrypted external hard drive that will be kept in a locked filing cabinet of the maxillofacial office and only accessed periodically to update the data held on it.

All data will be held on the external hard drive for a period of 10 years after the conclusion of the study after which the hard drive will be securely destroyed. The master unblinded list will be held by the clinical pharmacy department for the same length of time as the external hard drive to enable identification of the participants if this is required.

20a Descriptive statistics will be utilised to define the time point during follow-up at which the patient is completely healed or in the event of improvement without complete healing at 18months descriptive statistics (estimates of the mean and standard deviation for each treatment group for continuous measurements and proportions in each treatment group for categorical variables) will be used to quantify the degree of improvement for each patient within both groups. At the conclusion of the trial all participants will be included in an intention to treat analysis

20b N/A

20c Given the sample size of participants in each treatment arm and the clinical contact that the participants are subjected to during follow-up, it is unlikely that any data will be missing.

**Methods: Monitoring**

21a An independent data monitoring committee is not required as each participant will be under the care of an Oral and Maxillofacial consultant surgeon who will be able to access their prior medical records for the treatment and determine if they have deteriorated and act as per the study protocol to offer a different treatment in consultation with the research team in order that no part of the protocol is violated.

21b N/A

22 As per normal hospital protocol any patient experiencing an adverse event (defined as a reaction affecting Quality of life) will contact the maxillofacial outpatient department at the hospital and be booked with their treating consultant at the next available clinic to be reviewed. Any urgent or life threatening emergency will be treated in the Emergency department of the same state health service and the patient will be asked to report visits of this type at their next appointment or directly to the research team via a dedicated mobile telephone number.

23 The research team will meet on a monthly basis with the data to that point provided in a blinded form. The data will not be unblinded for the meeting until completion of the trial and data analysis has concluded.

**Ethics and Dissemination**

24. Research ethics approval – Ethics and Governance approval will be sought from the relevant participating institution via the national ethics application form.

25. Any modification of the protocol will need to be agreed by the research team, if this involves the collection of data, patient treatment, safety or data analysis this will be communicated to the Co-ordinating principal investigator who will then disseminate the information to the relevant parties, for example if the change in protocol requires participants to be notified then the clinical pharmacy team who are holding the master list will be notified by the CPI and they will then go about notifying each of the participants via the agreed format which the participant will indicate on their PICF. In the case of investigative staff requiring notification of protocol changes, this will be communicated with the team and if required then re-training or re-writing of protocol forms and an ethics amendment will be sought via the institutional ethics committee, this will need to take place prior to any further data collection occurring.

**Consent or Assent**

26a. Informed consent or assent will be gained by the consultant who undertakes the initial clinical assessment with the patient to quantify their ORN and ensure that the patient is able to ask any questions that they may have. Patients will also be provided with an information and consent form (PICF) which will allow them to contact via telephone or email one of the investigative team to ask any further questions that they may have as well as providing a space for the patient to sign the consent form and provide the required information so that written consent is gained.

26b. N/A

27. **Confidentiality –** Personal information will be collected on a secure form (electronic or paper) that will be stored in the Tertiary hospital site record of the patient. The investigative team will be notified that there is new data by the collecting unit and this data will be retrieved electronically via a secure and encrypted connection to the data source. Once data analysis begins all data for the trial will be stored on secure servers for the duration of the analysis and for a period of five years after this according to Health department protocols.

28. No conflicts or interest are known of or declared by the investigative team either financial or otherwise.

29. Only members of the investigative team that have undergone ethics approval to be involved in the trial and signed a confidentiality agreement will have access to the trial data and only the CPI will have access to the raw data set after data analysis has been completed.

30.Post trial care will be carried out according to standard maxillofacial unit recall schedules for the participating site. If participants are in need of further more intensive surgical management then this will be offered to them by the treating consultant, if they are healed then they will be followed up according to the protocol of the unit to ensure that this change is permanent and that resolution of pain and infection has occurred.

31a. Once trial data has been analysed the outcome of the trial will be communicated via the participants preferred mode of contact, clinicians will be informed of the outcome of the trial via a dedicated meeting that will be held at the participating site. Data will be written up and published in peer-reviewed journals regardless of outcome in the trial and presented at national and international meetings of clinicians interested in the area of research (ORN).

31b. Authorship will be decided amongst the participating investigators according to the NHMRC guidelines for authorship of scientific papers. Write up of the data analysis will be completed by the investigative team.

31c. N/A

**Appendices**

32. See attached.

33. N/A

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