

# BMJ Open Protocol for prospective randomised assessor-blinded pilot study comparing hyperbaric oxygen therapy with PENToxifylline+TOcopherol± CLOdronate for the management of early osteoradionecrosis of the mandible

Vishal M Bulsara,<sup>1,2</sup> Max K Bulsara,<sup>3</sup> Emma Lewis<sup>4</sup>

**To cite:** Bulsara VM, Bulsara MK, Lewis E. Protocol for prospective randomised assessor-blinded pilot study comparing hyperbaric oxygen therapy with PENToxifylline+TOcopherol± CLOdronate for the management of early osteoradionecrosis of the mandible. *BMJ Open* 2019;**9**:e026662. doi:10.1136/bmjopen-2018-026662

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-026662>).

Received 14 September 2018  
Revised 4 December 2018  
Accepted 28 January 2019



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For numbered affiliations see end of article.

## Correspondence to

Dr Vishal M Bulsara;  
[vishal.bulsara@gmail.com](mailto:vishal.bulsara@gmail.com)

## ABSTRACT

**Introduction** Osteoradionecrosis (ORN) of the mandible is a painful and debilitating condition occurring after radiotherapy to the head and neck to treat cancer. For decades, hyperbaric oxygen (HBO) has formed the mainstay of the early management of ORN. Literature about the efficacy of HBO is contentious. Recently, Oral and Maxillofacial surgical units in France and UK have trialled a combination of medications to treat ORN, also known as PENTOCLO (PENToxifylline+TOcopherol±CLOdronate). This regime has shown promising results to date however randomised controlled trials in the area comparing HBO against PENTOCLO are lacking and there are no current trials registered in Europe, UK, Australia and the USA. The purpose of this pilot study is to generate a hypothesis that can be tested in large multi-centre controlled trials.

**Methods and analysis** For this pilot study we will recruit 16 patients who will be randomly allocated to one of either HBO or PENTOCLO. After a 4 week period of uniform 'pre-treatment' medication patients will be commenced on their allocated treatment. Standard follow-up examination, imaging and photographs will be taken and de-identified and then presented to two Oral and Maxillofacial surgeons for allocation of a Notani & Lyons classification score. Data for each patient will be tracked over the 18 months of treatment and follow-up. The results will then be analysed using descriptive statistics and all patients included in an intention to treat analysis.

**Ethics and dissemination** Ethical approval for this study has been granted by the South Metropolitan Health Service HREC (PRN RGS0000001193). Data generated by conducting this study will be uploaded to an open access repository in a de-identified form. Results from this study will be disseminated at national and international conferences as well as peer reviewed medical publications.

**Trial registration number** ACTRN12618001099213; Pre-results.

## INTRODUCTION

Osteoradionecrosis (ORN) of the jaw is a complication said to occur in up to 20% of

## Strengths and limitations of this study

- First study to describe the effects of both hyperbaric oxygen and PENTOCLO in the same study.
- First study to use PENTOCLO in an Australian trial environment for osteoradionecrosis
- As this is a pilot study we are assessing the feasibility of the protocol, collecting preliminary data, trialling the data collection tools and we will use the data to perform a sample size calculation for larger trials. We are not assessing treatment outcome measures.
- Small numbers of patients to be treated.
- Blinding of the treating clinicians and patients is not possible at this time.

patients undergoing radiotherapy for the treatment of cancer of the head and neck.<sup>1</sup> Robert Marx proposed in 1983 that ORN of the jaw is due to hypoxia, hypocellular and hypovascular changes to the irradiated tissues after radiotherapy.<sup>2</sup> Consequently, he proposed the use of hyperbaric oxygen (HBO) in a defined protocol as a therapeutic intervention for patients requiring treatment for ORN.<sup>3</sup> Since this time HBO therapy has been extensively researched and is now known to be safe and possibly effective as well as, well tolerated, by the majority of patients that undergo this type of treatment.<sup>4</sup> The use of PENTOCLO for the treatment of ORN of the mandible was suggested by Delanian *et al* in 2005 after a new hypothesis about the pathophysiology of the condition was reported.<sup>5</sup> 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.<sup>1 4 6-8</sup> It has been reported by Delanian and others that PENTOCLO offers a faster rate of healing

and improvement in SOMA/Notani clinical score for patients on the protocol compared with the traditional 'gold standard' of HBO.<sup>8</sup> One of the limitations of the previous clinical trials and literature in this area is that, to date, there are no published reports on a comparative clinical trial to determine if the efficacy of PENTOCLO is at least equal to HBO therapy for the management of early ORN of the mandible. A search of clinical trials registers in the USA, UK, Europe and Australia revealed no clinical trials registered to compare PENTOCLO with HBO for the management of ORN of the mandible. As a consequence, we therefore decided that it would be useful to undertake a pilot study to generate a hypothesis for larger multicentre clinical 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 recent recommendations from the National Institute for Health and Care Excellence have suggested a similar position.<sup>9</sup> It is therefore imperative that prospective trials are undertaken in this area.

## METHODS AND ANALYSIS

Detailed methods with regards to the intervention and analysis are available with the full pilot study protocol included with this summary.

Patients will be recruited from those referred to the Oral and Maxillofacial outpatient clinic and having undergone an initial assessment with an Oral and Maxillofacial consultant surgeon who will not be a member of the investigating team. Patients agreeing to participate in the study will be block randomised via computer generated random numbers with participants to be stratified by grade of ORN, co-morbidities, sex, age, socio-economic status & smoking status. Enrolment will commence in January of 2019 and we estimate that it will take no longer than 1 year from commencing enrolment in the study to recruit all participants. Participants will 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.

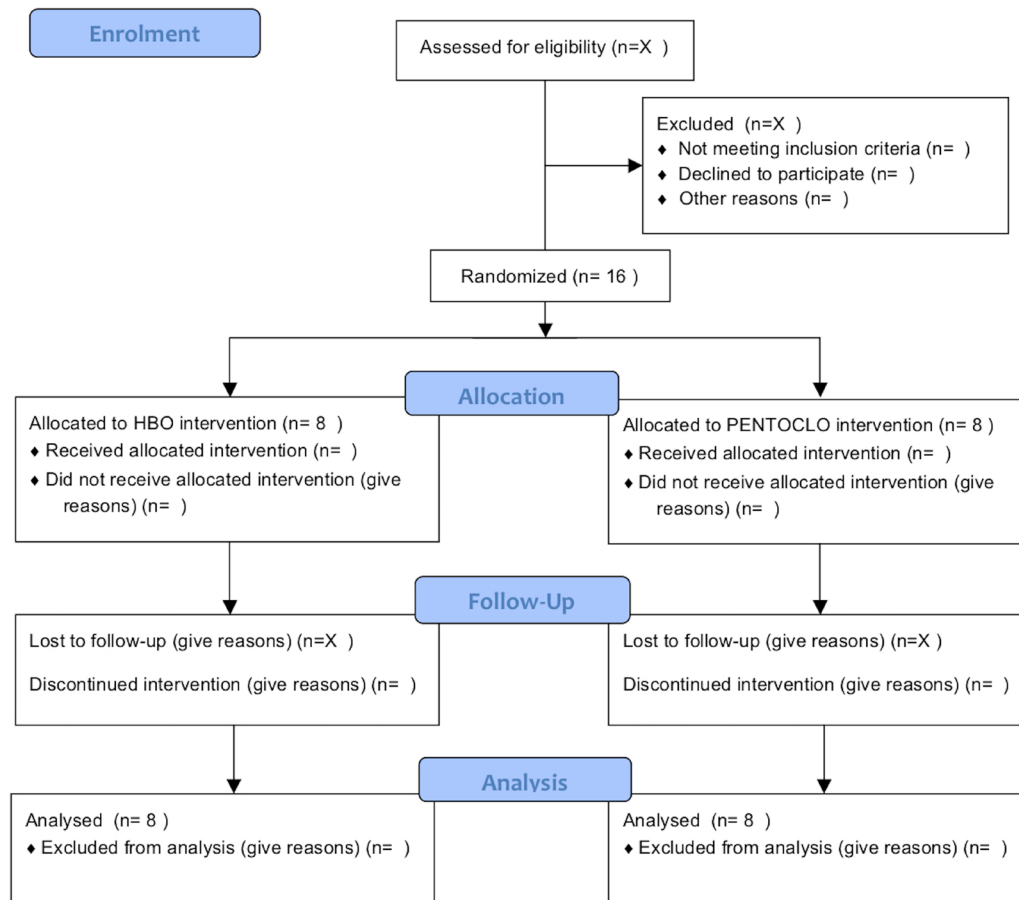
## Interventions

Medication group – 4 weeks of 'pre-treatment' therapy to reduce inflammation, infection and pain consisting of 2 g daily of Amoxicillin+Clavulanic acid 875/125 mg (1 g morning and night), 50 mg Fluconazole daily (morning), 16 mg prednisolone daily (morning) taken orally by the patient. 'Therapeutic phase' then commences immediately and consists of 5 days dosing of 800 mg pentoxifylline (400 mg morning and night) and 1000 IU vitamin E (morning) (Monday to Friday) taken orally by the patient. If the patient deteriorates (defined as a negative change or worsening in either Notani or Lyons score at follow-up by consultant) then add clodronate 1600 mg daily (orally morning, Monday to Friday, tablet to be swallowed intact and not crushed per clinical pharmacists involved with the

trial) for a minimum of 6 months but up to 18 months if the patient has stable ORN and is not deteriorating further (defined as an ongoing negative change in either Notani or Lyons score for two consecutive appointments 1 month apart). If the patient experiences any pain or infection then 1 g ciprofloxacin (500 mg morning and night) and prednisolone 16 mg (morning) orally on the remaining 2 days (Saturday and Sunday) can be added to help resolve symptoms for as long as the patient is symptomatic, if this fails to be effective then a short course of 7 days per week therapy of either the same steroid or antibiotic will be added to help alleviate symptoms, this will be recorded against the patients data for the trial. Patients that have fully healed (defined by complete mucosal coverage of the bony defect excepting minor bone spicules of less than 20 mm<sup>2</sup> present for 6 months or more and that have no ongoing pain) will continue to take the medication and be reviewed up to the 18-month follow-up point at which time they will cease. Patients that are not fully healed will also continue to take the medication and be reviewed up to the 18-month follow-up point at which time a decision will be made in conjunction with their treating consultant about whether to continue with the medication or to offer an alternative treatment. Note will be made in the final analysis about what the patient decides.

HBO group—4 weeks of 'pre-treatment' therapy as above. 'Therapeutic phase' incorporates HBO therapy prescribed for each patient based on Marx's protocol of 30 dives at 2.4 atm for 90 min per dive, the treatment will be monitored and administered by specialist physicians who are not part of the trial team in a dedicated HBO unit and will be the same for all patients in the HBO arm. If the patient has healed after this treatment (defined by complete mucosal coverage of the bony defect excepting minor bone spicules of less than 20 mm<sup>2</sup> present for 6 months or more and that have no ongoing pain) then they will be reviewed as per the protocol time points to 18 months after which they will undergo normal follow-up according to established oral and maxillofacial unit protocols. If the patient still has exposed bone meeting Notani grade 1 scoring criteria then they will undergo a surgical procedure to remove the exposed bone and then a further 10 dives of HBO at 2.4 atm for 90 min per dive again as per Marx' protocol.<sup>3</sup> If the patient experiences pain or infection during the course of treatment then appropriate medical treatment will be prescribed according to the same protocol outlined in the medication intervention but without the addition of any of: pentoxifylline, tocopherol or clodronate.

For this pilot study, we will recruit eight patients per treatment arm (figure 1). demonstrates the planned enrolment and randomisation. As we are not testing a hypothesis the initial descriptive results on efficacy of the two treatment arms will be used to determine an adequately powered sample size for a larger clinical trial. Assessors and investigators will be blinded to the treatment that the study participants receive. Clinical photographs will be taken in a dedicated room and de-identified prior to being assessed,

**CONSORT 2010 Flow Diagram – Planned enrolment beginning January 2019**


**Figure 1** Planned enrolment CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; HBO, hyperbaric oxygen.

radiographs will also be de-identified but coupled with the matching photographs for the purposes of assessment and scoring via the modified Notani and Lyons classifications. 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 unique identifier number 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.

### Objectives

- ▶ To describe time to complete 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.

### Outcomes

- ▶ Primary outcome—successful healing, improvement or worsening of ORN of the mandible.
- ▶ Secondary outcome—complications that arise from treatment.

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

- ▶ Successful healing will primarily be defined by complete mucosal coverage and absence of pain over

the previously involved area. In the event of partial healing or worsening a Notani and Lyons score will be assigned with Notani score taking precedence in the event of a discrepancy between the two scores. For the purposes of this study Minor bone spicules of less than 20mm<sup>2</sup> present for 6 months or more that remain after treatment with no radiographic abnormalities will be considered fully healed and not Notani grade 1.<sup>10</sup>

- ▶ Clinical photographs of the intra-oral status of the tissues will be taken with a standard flash by trained clinical photographers at the tertiary hospital, these photographs will be de-identified and printed out with the unique identifier number sticker on them. An authorised Maxillofacial registrar not participating in the trial or the clinical team but who is aware of the methodology and which patients are on the trial will be asked to select, de-identify, add the unique identifier sticker and print out the most recent CT still images or panoramic radiographs that demonstrate the largest extent of the boney defect by the treating consultant at each visit. The two sets of images will then be combined and double checked by the trial investigators and then provided to the independent assessors. If the patients have trismus and cannot have clinical photographs taken then a digital intra-oral scanner will be used with measurements of the mucosal defect made using the images. If the patients have absolute trismus and cannot open their mouth at all then soft tissue windows on the most recent CT scan will be used to measure the defect. Images will show the boney and soft tissue 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 and Lyons score which are the validated scoring systems for ORN chosen to be used in this study.<sup>10-12</sup> This will be done for each patient presented to the assessors shortly after the various different time points for follow-up for each patient. The treating consultant will also have access to the clinical photographs and radiographic images for the purposes of assigning a score to track the patients 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:

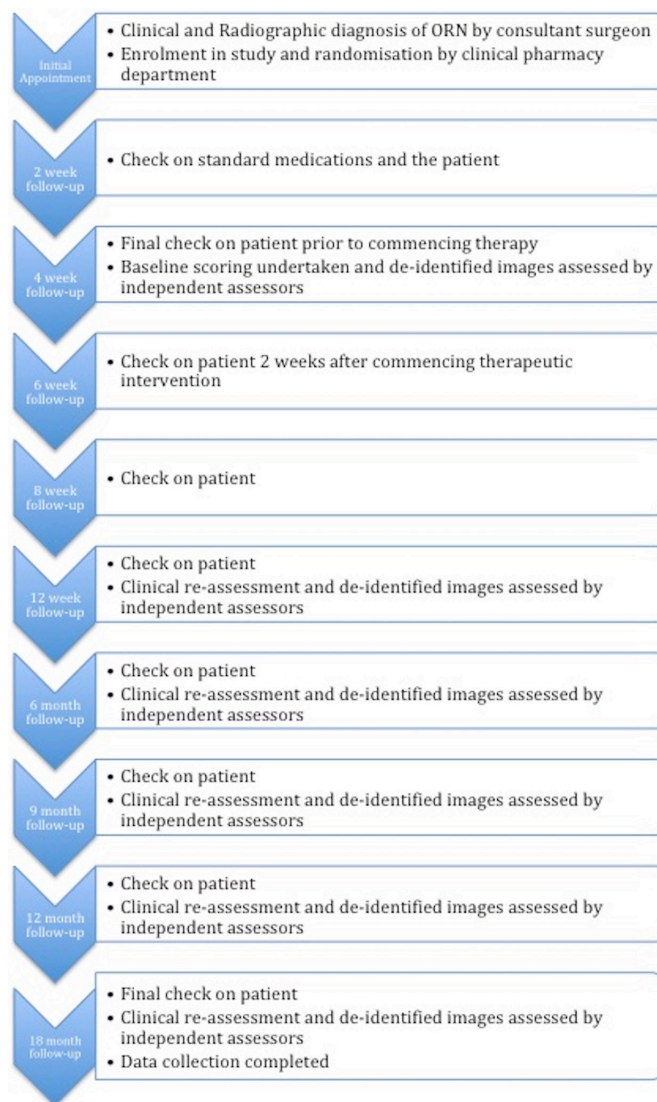
- ▶ A record will be kept by the treating consultant of any serious adverse events that are reported throughout the treatment. A serious adverse event will be defined as per the U.S. Food and Drug Administration.<sup>13</sup> Other complications such as worsening of the patient's condition will be recorded 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.

### Inclusion criteria

- ▶ Patients diagnosed with grade 1 Notani score ORN by an Oral and Maxillofacial surgeon, ORN will be defined as “an area of exposed devitalized irradiated bone that fails to heal over a period of 3 to 6 months in the absence of local neoplastic disease”<sup>14</sup> and is greater than 20mm<sup>2</sup> in size.<sup>10</sup>
- ▶ Patients 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 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.



**Figure 2** Timeline describing the planned follow-up for each patient after the initial ‘screening’ visit where the treating consultant will collect baseline data. ORN, osteoradionecrosis.

- ▶ Patients requiring further surgical management for their head and neck cancer during the study period.
- ▶ Patients diagnosed with ORN requiring surgery as first line management (Notani grade 2 or 3 or those with grade 1 who have an acute infection which requires surgical curettage).
- ▶ Patients who are unable to be randomised either because they cannot swallow medication or because they cannot undergo HBO therapy (eg, they have optic neuritis, chronic obstructive pulmonary disease or congenital pulmonary blebs).

Descriptive statistics will be calculated and summarised 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 18 months, descriptive statistics (estimates of the mean, SD and 95% CIs, 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. Patients worsening while on the trial will be analysed up to the point at which they were removed from the treatment they were originally assigned to. At the conclusion of the trial all participants will be included in an intention to treat analysis. The results of this study will be used to inform the numbers of participants needed for each trial arm in a large multicentre controlled trial that will follow.

Figure 2 demonstrates the follow-up schedule for the patients recruited to the study. Each participant will be commenced on 'pre-treatment' immediately after their initial appointment to minimise the time spent waiting and decrease any pain or infection that they may have.

### Patient and consumer involvement

Patients and consumer representatives have had input into the trial design via the ethics committee that has given approval for this study. The committee has several patient and consumer representatives among its constituents. We have planned to disseminate the results of the study to the trial participants via their indicated preferred method of contact which will be a part of the information collected at their initial appointment with the treating consultant Oral and Maxillofacial Surgeon. We have also planned to include a patient representative on the data monitoring committee that will form part of the large multi-centre controlled trial to follow this pilot study.

### Ethics and dissemination

Any modification of the protocol during the study 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.

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 5 years after this according to Health department protocols

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.

### Author affiliations

<sup>1</sup>School of Dentistry, Oral Health Centre of Western Australia, Crawley, Western Australia, Australia

<sup>2</sup>Ear, Nose and Throat Surgery, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

<sup>3</sup>The Institute for Health Research, The University of Notre Dame, Fremantle, Western Australia, Australia

<sup>4</sup>Oral and Maxillofacial Surgery, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

**Acknowledgements** Dr Abdullah Kanbour for his ongoing input into the pilot study.

**Contributors** VMB wrote the protocol using SPIRIT 2013 recommendations. Statistical input and sample size estimates were made by MKB and clinical expertise in the area was provided by EL. All authors meet the four criteria for authorship listed by the ICMJE.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Ethical approval for this study has been granted by the South Metropolitan Health Service Human Research Ethics Committee (PRN RGS0000001193).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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### REFERENCES

1. McLeod NM, Pratt CA, Mellor TK, et al. Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the Portsmouth experience. *Br J Oral Maxillofac Surg* 2012;50:41–4.

2. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg* 1983;41:283–8.
3. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 1983;41:351–7.
4. Bennett MH, Feldmeier J, Hampson N, *et al*. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2012;5:CD005005.
5. Delanian S, Depondt J, Lefaix JL. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. *Head Neck* 2005;27:114–23.
6. Delanian S, Chatel C, Porcher R, *et al*. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO): a phase II trial. *Int J Radiat Oncol Biol Phys* 2011;80:832–9.
7. D'Souza J, Lowe D, Rogers SN. Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible: experience from a regional head and neck unit. *Br J Oral Maxillofac Surg* 2014;52:356–62.
8. Robard L, Louis MY, Blanchard D, *et al*. Medical treatment of osteoradionecrosis of the mandible by PENTOCLO: preliminary results. *Eur Ann Otorhinolaryngol Head Neck Dis* 2014;131:333–8.
9. Dhanda J, Rennie L, Shaw R. Current trends in the medical management of osteoradionecrosis using triple therapy. *Br J Oral Maxillofac Surg* 2018;56:401–5.
10. Shaw R, Tesfaye B, Bickerstaff M, *et al*. Refining the definition of mandibular osteoradionecrosis in clinical trials: the cancer research UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis). *Oral Oncol* 2017;64:73–7.
11. Lyons A, Osher J, Warner E, *et al*. Osteoradionecrosis—a review of current concepts in defining the extent of the disease and a new classification proposal. *Br J Oral Maxillofac Surg* 2014;52:392–5.
12. Notani K, Yamazaki Y, Kitada H, *et al*. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck* 2003;25:181–6.
13. ADMINISTRATION USFD. What is a serious adverse event. 2018 <https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm>
14. Rivero JA, Shamji O, Kolokythas A. Osteoradionecrosis: a review of pathophysiology, prevention and pharmacologic management using pentoxifylline,  $\alpha$ -tocopherol, and clodronate. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2017;124:464–71.
15. Batstone MD, Cosson J, Marquart L, *et al*. Platelet rich plasma for the prevention of osteoradionecrosis. A double blinded randomized cross over controlled trial. *Int J Oral Maxillofac Surg* 2012;41:2–4.
16. Churchill-Davidson I, Sanger C, Thomlinson RH. High-pressure oxygen and radiotherapy. *Lancet* 1955;268:1091–5.
17. Lubek JE, Hancock MK, Strome SE. What is the value of hyperbaric oxygen therapy in management of osteoradionecrosis of the head and neck? *Laryngoscope* 2013;123:555–6.
18. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. *Br J Oral Maxillofac Surg* 2008;46:653–60.
19. McCaul JA. Pharmacologic modalities in the treatment of osteoradionecrosis of the jaw. *Oral Maxillofac Surg Clin North Am* 2014;26:247–52.
20. Nabil S, Samman N. Risk factors for osteoradionecrosis after head and neck radiation: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;113:54–69.
21. Rice N, Polyzois I, Ekanayake K, *et al*. The management of osteoradionecrosis of the jaws—a review. *Surgeon* 2015;13:101–9.
22. Sawhney R, Ducic Y. Management of pathologic fractures of the mandible secondary to osteoradionecrosis. *Otolaryngol Head Neck Surg* 2013;148:54–8.
23. Shaw RJ, Butterworth C. Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part II: prevention. *Br J Oral Maxillofac Surg* 2011;49:9–13.
24. Shaw RJ, Dhanda J. Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part I: treatment. *Br J Oral Maxillofac Surg* 2011;49:2–8.
25. Silvestre-Rangil J, Silvestre FJ. Clinico-therapeutic management of osteoradionecrosis: a literature review and update. *Med Oral Patol Oral Cir Bucal* 2011;16:e900–4.