Amelioration of Trismus during and beyond a course of Radiotherapy in Head and Neck Cancer Patients

A thesis submitted to the University of Manchester for the degree of PhD
in the Faculty of Biology, Medicine and Health

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School of Medical Sciences
Author Reflections

‘I can’t open my mouth wide like I use to’. This sentiment from a patient participating in a reference group I was leading some 10 years ago was echoed around the group. This was the beginning of a journey which has culminated in the body of work presented in this thesis.
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BMJ Open 2018
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Br J Oral Maxillofac Surg. 2018

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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AR</td>
<td>Action Research</td>
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<td>COM-B</td>
<td>'Capability', 'Opportunity', 'Motivation' and 'Behaviour' model</td>
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<td>CSRI</td>
<td>Client Service Receipt Inventory</td>
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<td>CTCU</td>
<td>Christie Trial Coordination Unit</td>
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<td>EQ-5D</td>
<td>Euroqol-5D questionnaire</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HRQoL</td>
<td>Health Related Quality of Life</td>
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<td>TMJ</td>
<td>Temporomandibular Joint</td>
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<tr>
<td>ICECAP-A</td>
<td>ICEpop CAPability measure for adults</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost-Effectiveness Ratio</td>
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<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiotherapy</td>
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<tr>
<td>MDT</td>
<td>Multi Disciplinary Team</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>NHS R&amp;D</td>
<td>National Health Service Research &amp; Development</td>
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<td>PR</td>
<td>Participatory Research</td>
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<td>RCT</td>
<td>Randomised Control Trial</td>
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<td>RfPB</td>
<td>Research for Patient Benefit</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>TDF</td>
<td>Theoretical Domains Framework</td>
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<tr>
<td>TFA</td>
<td>Theoretical Framework of Analysis</td>
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<td>QALY</td>
<td>Quality-Adjusted Life Year</td>
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Abstract

Introduction: The primary factor limiting jaw movement in head and neck cancer patients is rapid formation of collagen caused by radiation and/or surgery leading to fibrosis and contraction in the muscles used for mastication. Trismus can negatively affect all aspects of Health Related Quality of Life (HRQoL).

Overall Aims: The overall aims of the thesis are to put together a systematic, robust and critically assessed original piece of work concerning amelioration of trismus in head and neck cancer patients and to gain insight into the acceptability of the intervention from the patient perspective.

Methods: To identify risk factors and prevalence for trismus in head and neck patients, mouth opening measurements and HRQoL were monitored in a longitudinal, prospective study. Measurements and questionnaires were completed prior to surgery, after radiotherapy and again at 3 and 6 months post radiotherapy. Subsequently, a randomised feasibility study comparing the efficacy of two approaches to relieve and prevent trismus was undertaken in patients with head and neck cancer who reported subjective tightening of the jaw prior to radiotherapy. Participants received one of two jaw mobilising devices (therabite versus wooden spatulas), commencing a proactive exercise regimen before radiotherapy and continuing for up to 6 months after the start of the intervention. The feasibility of conducting a randomised trial with the two different devices was examined using clinical, HRQoL and health economic assessments. Patient acceptability was explored using qualitative methods, from a sub-sample of fifteen participants.

Results: The longitudinal prospective study (N=87) showed that 47% of patients receiving major surgery for head and neck cancer presented with trismus, 71% had post-surgical trismus and 79% had trismus six months post-surgery/radiotherapy. Males and those with heavy alcohol consumption were less likely to have trismus post-treatment. In the randomised feasibility study, 37 patients received the therabite device and 34 the wooden spatulas for jaw exercises. All patients had some sense of jaw
tightening prior to study entry. Mean mouth opening after 6 months increased in both groups following the exercise intervention, with non-significant differences between the two arms ($p=0.39$). Completion rates of the 3 health economic measures were good. There was no significant difference between the two groups in frequency of contact with care services nor in quality of life between the two groups. Patients did not find either device more acceptable to use, both groups reporting that exercises were stopped temporarily whilst side effects of the radiotherapy were at their worst.

**Discussion:** This novel body of work used an exercise regimen proactively, pre, during and beyond a course of radiotherapy, and the study design also included health economics and a qualitative aspect to gauge acceptability of intervention from patients’ perspectives. The results of both the quantitative and qualitative aspects of the study design will influence healthcare professionals to develop evidence-based decisions about patient management and resource use.

**Conclusion:** This novel work has expanded the knowledge base and can be applicable to the general body of evidence for this intervention in clinical practice. Treatment of objective and subjective trismus should be encouraged prior to radiotherapy and continued post treatment to maintain mouth opening with a jaw mobilising device although this data is not from a definitive Randomised Controlled Trial (RCT). Patients were able to perform proactive exercises throughout radiotherapy and found them acceptable, provided there was a structured break (reduction or cessation of exercises) when the side effects of the radiotherapy were at their worst. This body of work has tentatively shown amelioration in mouth opening in patients who have a subjective tightening of the jaw prior to radiotherapy for head and neck cancer, suggesting that a larger definitive RCT is merited and feasible.
DECLARATION

A declaration stating:

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning;

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Acknowledgements

I would like to express my deepest gratitude to the stellar, Prof Nick Slevin who has supported me throughout my time working with head and neck cancer patients. Many thanks to Mr Brian Musgrove and Prof Craig Barclay for introducing me to the wonderful reference group who I thank unreservedly for their time and honest views. Mr Alf Owen for being my patient representative and supplying me with the patient perspective on the RfPB and patient centred documents. I would also like to thank my past and present supervisors and collaborators on all peered reviewed and published work. Early on my studies, I would like to thank Prof Alex Molassiotis in helping to co-ordinate and for bringing together the world class individuals from the Christie and Liverpool NHS Trusts to conduct the Trismus Trial, namely Prof Nick Slevin and Prof Simon Rogers and their prospective MDTs.

During the latter stages of my studies special thanks to, the dear Prof Ann-Louise Caress for her direct and forthright manner in providing support and advice and Prof Phil Keeley for his kindness and level headed advice.

This work would not have been possible without the support and patience over the many years from my hubby Dr Hai Shiang Lee and our naughty lovable boys, Neo and Kai. To them and my parents (Harbajan and Surjit Dhoot), I dedicate my thesis.
Alternative format

Permission has been granted for this thesis to be presented in alternative format, as each chapter is written in the style of a scientific publication. This was seen as a coherent progression of a single theme (trismus), using several research approaches and independent sub-studies, making the thesis suited to alternative format. The emphasis of my doctoral study was to disseminate the findings to healthcare providers in terms of peer review publications and conference meetings (appendix). The publications follow a cohesive continuous path. A list of the peer reviewed publications which make up the thesis is provided below:

• ‘Inconsistencies in the care of head and neck cancer patients experiencing trismus’
  
  *EJON* (2011)
  
  R.Lee and N.Slevin
  
  This survey information was drafted and collected by R. Lee during a BAHNO conference and written up with contributions from N. Slevin

• ‘Prediction of Post-Treatment Trismus in Head and Neck Cancer Patients’
  
  
  R. Lee, N. Slevin, B. Musgrove, R. Swindell, A. Molassiotis
  
  The concept that trismus was an under reported problem was identified from a patient reference group run by R.Lee who collected all data, and authored the paper with contributions from N.Slevin and A.Molassiotis. R.Lee worked with R. Swindell to analyse the data and to reach the study conclusions.

• *RfPB grant application* (Externally Peer Reviewed by NIHR-RfPB).
  
  N.Slevin owns all rights of the grant application (Chief Investigator). R.Lee wrote the grant application, with insight gained from the patient reference group. Health economics was written entirely by R.T Edwards and the statistical plan was written by D. Ryder. All co-investigators authorised the grant application with sign off by N.Slevin. R.Lee did not contribute to health economics nor to the trial statistical plan apart from data analysis discussions. The financial aspects of the grant application were supplied entirely by the clinical trials unit from the sponsor site.
Protocol for the TRISMUS trial- A Randomised Pilot Study of Therabite versus Wooden Spatula in the Amelioration of Trismus in Head and Neck Cancer Patients’.

*BMJ open* (2018)

*R. Lee, SN Rogers, A. Molassiotis, R.T. Edwards, D. Ryder, N. Slevin*

R. Lee wrote the proactive exercise regimen and the protocol with the aid of a protocol template supplied by the sponsor of the study. The patient information sheet, patient consent form and telephone interview guides were written by R. Lee as well as the completion of IRAS and Ethics submission documents. The nested qualitative section of the protocol was co-authored by A. Molassiotis. Health economics sections were written entirely by R.T. Edwards and the statistical plan was written by D. Ryder. All authors authorised the protocol with overall sign off by R. Lee, who did not contribute to health economics or trial statistical plan.

‘Randomised feasibility study to compare the use of Therabite® with wooden spatulas to relieve and prevent trismus in patients with cancer of the head and neck’.


*R. Lee, ST. Yeo, S.N. Rogers, A.L. Caress, A. Molassiotis, R.T.- Edwards, D. Ryder, P. Sanghera, C. Lunt, B. Scott, P. Keeley, N. Slevin*

R. Lee co-authored the paper, contributing to all sections apart from the health economics sections which were written entirely by T.S Yeo and R.T. Edwards and the statistical results were written by D. Ryder. C. Lunt checked the CONSORT diagram. All authors provided comments on the paper and authorised the publication with overall sign off by N. Slevin. R. Lee did not contribute to health economics or trial statistical sections of the paper.
Perspectives of patients with head and neck cancer on acceptability of undertaking proactive mouth exercises throughout and beyond a course of radiotherapy: a qualitative study.


R. Lee, A.L. Caress, P. Keeley, A. Molassiotis, N. Slevin

R. Lee conceptualised the study, wrote the interview guide and undertook data collection. Transcripts were analysed by R. Lee with contributions from A.L Caress and P. Keeley. The publication was co-authored by R. Lee, A.L Caress and P. Keeley. R. Lee was responsible for the use of Theoretical Framework of Acceptability as an explanatory model. All authors commented and signed off the final version.
Chapter 1: INTRODUCTION

1.1 Overview of Thesis

Trismus can worsen during and beyond a course of radiotherapy. This can lead patients to have a reduced quality of life and increase national healthcare costs to treat this debilitating condition. Therefore a proactive approach to this deterioration in maximum mouth opening would potentially benefit both patients, and NHS expenditure.

The overall aim of this thesis was to enable feasibility testing of proactive exercises throughout and beyond a course of radiotherapy with a view to ameliorate or prevent worsening of trismus in head and neck cancer patients. In order for the overall aim to be achieved, the thesis consists of three substantive pieces of work. First, to understand the extent of trismus and its associated risk factors. Second to investigate, in a scientific robust process, ways to ameliorate trismus. Third, to gauge the acceptability of the intervention from the patients’ perspective. In this introduction, the background to trismus in head and neck cancer is first discussed and a review of the relevant literature on trismus is provided. Finally, the specific objectives of the thesis are introduced.

1.2 Trismus in Head and Neck Cancer Patients

1.2.1 Definition and Incidence of Trismus

The incidence of trismus varies hugely, ranging from 5% to 42% in head and neck cancer patients post treatment and this has largely been due to variation in patient, tumour and treatment related factors, but also the lack of uniform criteria to define and measure trismus (Dijkstra et al., 2006, Bensadoun et al., 2010, Johnson et al., 2010). In 2006, Dijkstra et al., defined trismus as mouth opening of ≤35mm (either the inter incisor distance or distance between upper and lower alveolus) and this has been widely adopted (Dijkstra et al., 2006, Kent et al., 2008, Bhatia et al., 2009, Lindblom et al., 2014). Prior to this report, trismus definition varied and ranged from a mouth opening of less than 20mm to a mouth opening of less than 40mm (Jen et al., 2002, Nguyen et al., 1988). Severely affected patients may only be able to open their mouths by 5mm or less restricting their oral intake to using a straw (Shulman et al.,
Patients having received radiotherapy to the temporomandibular joint and/or the masseter/pterygoid muscles can experience limitations in jaw opening in 6-86% (Goldstein et al., 1999; Whitmyer et al., 1997). In another small study, it has been shown that 45% of patients who had received curative doses of radiotherapy to the area(s) of the masticatory muscles and/or the ligaments of the temporomandibular joint (TMJ) developed trismus. The same group reported no differences in the incidence of trismus between radiotherapy and chemoradiotherapy or between conventional radiotherapy and intensity modulated radiotherapy (IMRT), although numbers were small (Kent et al., 2008). Gebre-Medhin’s group reported the prevalence of trismus to be 24% at a median of 16 months post radiotherapy. The majority of these patients had stage III-IV oropharyngeal cancers and were treated with IMRT (Gebre-Medhin et al., 2016). In summary, until relatively recently, trismus has not been uniformly defined, but an agreed standard definition is now accepted as equal to or less than 35 mm.

### 1.2.2 Risk Factors for Trismus in Head and Neck Cancer patients

Van der Geer has reported that maximal mouth opening at all times prior to and up to 48 months post radiotherapy is a predictor for developing radiation induced trismus (Van der Geer et al., 2016). Tumours or treatment in the region of the muscles of mastication and temporomandibular joint (TMJ) were the most robust predictors for the development of trismus whilst other studies showed radiation doses to the TMJ and the pterygoids were important (Rao et al., 2016, Van der Molen et al., 2013, Kent et al., 2008). The primary factor limiting jaw movement is rapid formation of collagen caused by radiation and/or surgery leading to fibrosis and contraction in the muscles used for mouth opening/closing/mastication (Ichimura et al. 1993, Goldstein et al., 1999). A comprehensive prospective data registration program collected postoperative external beam radiotherapy information from 788 head and neck cancer patients to ascertain the tumour location to predict trismus. The primary tumour location collected included oral cavity, oropharynx, nasopharynx, salivary glands, ear, hypopharynx, supraglottic larynx, glottis, subglottic larynx, nasal cavity and maxillary sinus. The findings pointed to tumours in the oropharynx and nasopharynx being the most likely to develop post radiotherapy trismus (Kamstra et al., 2016). Agarwal reported that the use of flaps for reconstruction, delay in radiotherapy post-surgery and non-compliance of patients to
physiotherapy were risk factors for developing post operative trismus in primary surgical patients (Agarwal et al., 2016). Immobilised joints show rapid degenerative changes which can make remobilisation difficult, particularly for patients who require feeding tubes or limit their intake to mostly liquids during treatment, and who may not realise progressive onset of trismus until food intake is resumed (Goldstein 1999). There is a suggestion that irradiation of the pterygoid muscles is a critical factor in the development of post radiation trismus. It appears that although the TMJ region may be excluded during radiotherapy, it is difficult to exclude the pterygoid muscles (Hague et al, 2018) if tumours are close by.

1.2.3 Functional and Health Related Quality of Life (HRQoL) Impairment from Trismus in Head and Neck cancer

Trismus can further lead to secondary problems, such as with chewing, swallowing, and weight loss in mouth cancer patients, requiring input from specialists such as speech and language therapists, dieticians and orthodontic surgeons. Patients who can only intake small amounts of food may experience significant weight loss and nutritional defects. Limited mouth opening may result in compromised airway clearance. Patients with limited tongue movement due to restricted mouth opening may not be able to form a bolus which may result in residual food remaining after swallowing and food aspiration. Speech can be compromised when the mouth is unable to open sufficiently to create sounds. Muscle damage leads to compromised swallowing as the larynx cannot be properly elevated. In patients who have received radiation to the mandible, poor oral hygiene may lead to dental cavities as a result of hypo salivation which can lead to infection. In extreme cases this may lead to osteoradionecrosis of the jaw, requiring major surgery (Noone and Barclay 2017). Restricted mouth opening also leads to difficulty fitting dentures and dental implants, leading to further problems with chewing (Kumar et al., 2018). These problems negatively impact on quality of life. These patients may also suffer from lack of intimacy due to loss of kissing function, lack of self-esteem, depression, suicide tendencies and altered body image with nearly 60% of patients feeling discounted or stigmatised because of their cancer-related appearance (Zeller 2006, Misono et al., 2008, Fingeret et al., 2009, Cam et al., 2015). What is clear is that trismus can be adversely associated with physical and mental well being
1.3. Treatment Options for Trismus

Historically, the simplest method to treat trismus was to use the thumbs and forefingers between the incisors to physically push the jaws further apart. A trismus screw has also been used by inserting the smallest end of the screw between the molar teeth and then rotating the Christmas tree shaped device to crank open the jaw. This device had great potential for damaging tooth enamel as it was made of acrylic plastic with spiralling threads. (Giuliano et al., 1995). The most commonly used treatment is thought to be wooden spatulas (Figure 1)(Lee and Slevin 2011).

![Figure 1. Use of wooden spatulas.](image)

The wooden spatulas are stacked lengthways and used to force open the mouth over time. Wooden spatulas can be geared to meet individual patient needs as they can be adapted to small incremental changes. They are also easy to use and inexpensive and simply cause static stretching of the fibrosed area (Gibbons and Abulhoul, 2007).

![Figure 2. The therabite system being used.](image)

Figure 2 shows the Therabite jaw motion rehabilitation system being used ([http://www.atomsmedical.com](http://www.atomsmedical.com)). The therabite is a patient controlled, handheld device with an upper and lower tray and a leverage system that utilises repetitive passive motion to stretch the fibrosed area.

1.4. Overview of Current Evidence Regarding Interventions for Trismus.

Only a few small-scale studies have been reported in the literature on interventions for trismus. Buchbinder et al., conducted a very small randomised clinical trial with patients who had radiation-induced trismus. At the end of the ten week intervention period, the
group of patients using the therabite system (n=7) had shown the greatest improvement in mouth opening (mean of 13mm), whilst the group using tongue depressors (n=7) showed only a slight improvement of less than 5mm on average (Buchbinder et al., 1993). Maloney reported a randomised trial of 46 patients with TMJ disease comparing the use of therabite and an intraoral appliance (n=17), the use of tongue depressors in combination with an intraoral appliance (n=12) and an intraoral appliance only (n=17). All patients were provided with manual manipulation of the mandible with flat bite plane therapy for four weeks prior to randomly being assigned to the three groups. They showed that patients using the therabite experienced improved mobility and decreased pain compared to the group using the intraoral appliance alone (Maloney et al., 2002). Cohen studied the use of therabite for trismus in the early postoperative period in 7 patients who had surgical excision and reconstruction for head and neck cancer. It was reported that the use of therabite increased the range of motion and decreased pain in both muscle and joint disorders (Cohen et al., 2005). A systematic review carried out by McNeely on the effectiveness of physical interventions for TMJ disorders concluded that the results support active and passive oral exercises as effective interventions to reduce trismus (McNeely et al., 2006). These few studies show that the use of therabite after radiotherapy and/ or surgery may potentially improve maximum mouth opening, but only a couple of publications had used a control group for comparison. All studies had small sample sizes and power calculations were not reported suggesting no statistical information could be elucidated. A randomised clinical trial by Loorents (2014), looked at prevention of trismus during radiotherapy. The average maximum mouth opening prior to intervention was 45.7mm in both the therabite and control samples with an average increase in maximum mouth opening after intervention up by 3mm. The maximum opening achieved by the therabite is stated to be 45mm which is smaller than the average maximum mouth openings reported by this group prior to intervention. Loorents et al, concluded that patients with trismus should not be burdened with an intense prophylactic training programme during radiotherapy and 12 months beyond. However, this study also had a small sample size (N=66) and a high dropout rate (36%). This group also concluded that high risk patient (Stage 3/4) would benefit from a prophylactic training programme (Loorents et al., 2014). See table 1 for summary of RCTs for trismus exercise interventions. It is very difficult to compare these studies, as various exercise regimens have been used as well as timing of the exercises before or after radiotherapy. Follow up duration also varies between the studies from 10 weeks to
12 months and also compliance rates are not stated, which are important considerations in these studies.

Table 1. Summary of RCT of trismus exercise interventions.

<table>
<thead>
<tr>
<th>Author of trismus RCTs</th>
<th>Type of intervention</th>
<th>1. Mean MMOmm before:</th>
<th>Start of intervention: (Follow up FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2. Mean MMOmm after:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Mean MMOmm change:</td>
<td></td>
</tr>
<tr>
<td>Buchbinder et al., (1993)</td>
<td>Active range of motion (N=5)</td>
<td>1. 22.6mm</td>
<td>&lt;5 years RT (10 weeks FU)</td>
</tr>
<tr>
<td>Tumour stage: not reported</td>
<td>6-10</td>
<td>2. 27.0mm</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: HNC</td>
<td>10</td>
<td>3. 4.4mm</td>
<td></td>
</tr>
<tr>
<td>Drop out: Not reported</td>
<td>Active range of motion &amp; tongue depressors (N=7)</td>
<td>1. 21.1mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-10</td>
<td>2. 27.1mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5x30secs</td>
<td>3. 6.0mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>therabite (N=9)</td>
<td>1. 21.3mm</td>
<td></td>
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<tr>
<td></td>
<td>6-10</td>
<td>2. 34.9mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5x30secs</td>
<td>3. 13.6mm</td>
<td></td>
</tr>
<tr>
<td>Van der Molen et al., (2011)</td>
<td>therabite (N=27)</td>
<td>1. 50.0mm</td>
<td>2 weeks before start of CCRT (-)</td>
</tr>
<tr>
<td>Tumour stage: III-IV</td>
<td>3</td>
<td>2. 47.0mm</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: HNC, SCC</td>
<td>6-10x10-30secs</td>
<td>3. -3.0mm</td>
<td></td>
</tr>
<tr>
<td>Drop out: 6 from both groups.</td>
<td>Active range of motion (N=28)</td>
<td>4. 50.0mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5. 47.0mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5x5</td>
<td>6. -3.0mm</td>
<td></td>
</tr>
<tr>
<td>Tang et al., 2011</td>
<td>Active &amp; passive range of motion &amp; therabite (N=22)</td>
<td>1. 18.9mm</td>
<td>1.8 years after RT (3 months FU)</td>
</tr>
<tr>
<td>Tumour stage: not reported</td>
<td>3</td>
<td>2. 17.0mm</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: NPC</td>
<td>15</td>
<td>3. -1.9mm</td>
<td></td>
</tr>
<tr>
<td>Drop out: 3 from intervention group.</td>
<td>Control (N=21)</td>
<td>1. 18.0mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>2. 11.0mm</td>
<td></td>
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<td></td>
<td></td>
<td>3. -6.9mm</td>
<td>1.6 years after RT (3 months FU)</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>MMO</td>
<td>1.</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td><strong>Van der Molen et al., (2014)</strong></td>
<td>therabite</td>
<td></td>
<td>53.7mm</td>
</tr>
<tr>
<td>Tumour stage: III-IV</td>
<td>(N=15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis: HNC, SCC</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drop out: Not reported</td>
<td>6-10x10-30secs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active range of motion</td>
<td></td>
<td>49.7mm</td>
</tr>
<tr>
<td>(N=14)</td>
<td>5x5</td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Loorents et al., (2014)</strong></td>
<td>therabite</td>
<td></td>
<td>45.4mm</td>
</tr>
<tr>
<td>Tumour stage: I-IV</td>
<td>(N=33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis: HNC</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total drop out: 24</td>
<td>5x15secs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention (10)</td>
<td>Control</td>
<td></td>
<td>45.4mm</td>
</tr>
<tr>
<td>Control (14)</td>
<td>(N=33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Li et al., 2018</strong></td>
<td>EZ Bite</td>
<td></td>
<td>15.7mm</td>
</tr>
<tr>
<td>Tumour stage I-IV</td>
<td>(n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis: Various HNC &amp; (Oral Submucous fibrosis) OSF</td>
<td>Warm up exercises first</td>
<td>5x30sec</td>
<td></td>
</tr>
<tr>
<td>Drop out: Not reported.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conventional Group</td>
<td></td>
<td>14.8mm</td>
</tr>
<tr>
<td></td>
<td>Wooden spaulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warm up exercises first</td>
<td>5x30sec</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control Group</td>
<td></td>
<td>14.2mm</td>
</tr>
<tr>
<td></td>
<td>Non-compliant from above 2 groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warm up exercises first</td>
<td>5x30sec</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used in Table above: MMO (Maximum mouth opening), HNC (Head and Neck cancer), RT (radiotherapy), N (number of patients), SCC (Squamous Cell Carcinoma), CCRT (Concomitant ChemoRadiotherapy), NPC (Nasophyngeal Carcinoma).

A Cochrane protocol was compiled by Carvalho et al., 2016, to examine interventions for preventing and treating trismus in patients with head and neck cancer, but results are not
yet published. The stated objectives of the review were to assess the effects of a) interventions for preventing trismus in patients with head and neck cancer before its onset and b) interventions for treating trismus after its onset (Carvalho et al., 2016). Previously published work by Van der Molen and Carnaby-Mann (2012) in the area of proactive jaw exercises for head and neck patients receiving chemoradiotherapy have shown less of a decline in mouth opening compared to standard post treatment rehabilitation techniques; however both studies had small numbers, only 10 week follow up and no economic evaluation (Van der Molen et al., 2011, Carnaby-Mann et al., 2012). Recently Li’s group have reported on a new device called a EZBite which was shown in 20 patients over a 10 week intervention period to improve average mouth opening when compared with wooden spatulas and control groups, with or without radiotherapy (Li et al., 2018). However, the authors report that this device cannot be used for patients with soft tissue trauma and would cause high risk to patients with compromised teeth. Patients using this hand operated device also reported the short term force applied to the hands after manipulation of the device to be troublesome (Li et al., 2018).

In summary, current post-treatment interventions such as wooden spatulas, therabite, Dynasplint, swallowing therapies and recently the EZBite have only shown a modest effect once trismus is established (Van der Molen et al., 2011, Carnaby-Mann et al., 2012, Carvalho et al., 2016, Rapidis et al., 2015, Scherpenhuizen et al., 2015, Loorents et al., 2014, Kamstra et al., 2013, Kamstra 2016, Li et al., 2018). There is, consequently a need for a larger controlled study to provide clearer evidence whether devices such as wooden spatulas or therabite are helpful in preventing and improving trismus. Furthermore, as the literature showed that trismus was likely to be more of a problem during and after radiotherapy and was difficult to treat once established, a novel approach investigating the use of proactive exercises before, during and beyond radiotherapy is called for. This will be addressed in chapters four and five of this thesis.

1.4.1 MRC Guidance on Research Involving Complex Interventions.

The proposal presented in this thesis has been designed based on the framework of the MRC complex intervention (www.mrc.ac.uk/complexinterventionsguidance). The definition of complex interventions has been given by Campbell et al., 2000 and the MRC. These groups cite that complex interventions are ‘built up from a number of components, which may act both independently and interdependently’ (Campbell et al.,
The 2000 MRC framework consists of a stepwise approach starting at Phase 0 – Preclinical or theoretical (why should this intervention work?), Phase 1 – Modelling (how does it work?), Phase 2 - Exploratory or pilot trial (optimising trial measures), Phase 3 – Definitive randomised controlled trial and finally Phase 4- Implementation. The guidance suggests that feasibility and piloting the intervention is a crucial step to ensure that the intervention is successfully implemented into routine clinical practice.

### 1.5 Rationale and Objectives.

A full-scale trial (phase 3, above) was not appropriate at this stage due to the small number of high risk patients (necessitating a trial to be multicentred and thus increasing research costs) as well as having an intervention for which there is insufficient scientific evidence of effectiveness. Lack of patient compliance with interventions has been problematic in past studies. Hence, a trial to establish feasibility and acceptability was deemed necessary as a first step (phase 2).

Furthermore, medical teams are reluctant to introduce therabite or even wooden spatulas as routine (phase 4) without scientific evidence of improvement in mouth opening and in quality of life. Additionally, there is a need to prove both the patient acceptability and cost effectiveness of therabite as opposed to wooden spatulas to prevent and ameliorate trismus before they can be adopted as standard. To this end, the overall aim of the work reported here was to investigate a proactive intervention to relieve and prevent trismus which is acceptable for patients undergoing proactive exercises throughout a course of radiotherapy and beyond. In order to meet this aim, the following objectives were identified:

1. To better understand how healthcare professionals were identifying and currently treating trismus (Chapter 2).
2. To determine the prevalence of trismus in head and neck cancer patients treated with primary surgery and attending the head and neck cancer clinic of a tertiary referral cancer centre in the UK (Chapter 2).
3. To develop a protocol to assess the feasibility and cost-effectiveness of therabite use compared with wooden spatula in ameliorating trismus in patients
treated with stage 3 and 4 oral and oropharyngeal cancer with radiotherapy as part of their management (Chapter 3).

4. To conduct a randomised, open-label, feasibility study, to assess the feasibility and cost-effectiveness of therabite use compared with wooden spatula in ameliorating trismus in patients treated for stage 3 and 4 oral and oropharyngeal cancer treated with radiotherapy (Chapter 4).

5. To explore patients’ perspectives on feasibility of proactive exercises throughout a course of radiotherapy and beyond (Chapter 5).
1.6 Thesis structure

This thesis has been constructed, with permission, in line with institutional guidance on ‘alternative format’. Each of the projects is well suited to being presented as a standalone document, but collectively these lead to a coherent thesis. This section outlines how the individual objectives of the thesis have been addressed.

Chapter two identified the extent of trismus in surgical patients attending a tertiary referral cancer centre which addresses objective two. These patients were followed up longitudinally and maximum mouth readings were taken during their treatment pathway. Factors predicting trismus were identified and this also addresses objective two. This prospective study showed that 47% of patients presented with trismus, 71% had post surgical trismus and 79% had trismus 6 months post surgery/radiotherapy. Several HRQOL variables showed that pain, eating, chewing, taste, saliva, social functioning, social contact and dry mouth were significantly more impaired in the trismus group compared to the non-trismus group. Post surgery HRQOL differences between the trismus and the non-trismus group highlighted problems with social and role functioning, fatigue, activity, recreation, and overall reduction in QOL. Since, a trend of increased trismus was shown after radiotherapy, it was hypothesised that starting proactive exercises during radiotherapy may prevent or relieve trismus.

Consulting the literature on restricted mouth opening or trismus it was found that in a small number of patients the ‘therabite’ was able to modestly increase maximum mouth opening of head and neck cancer patients if used after radiotherapy (See Table 1). It was evident from the review of the existing published literature that there was a need for a more scientifically robust study to establish the overall benefits of using an intervention to potentially reduce trismus. The literature did not show any study trial design conducted with the appropriate power calculations to address the fundamental question of whether proactive intervention of any treatment will reduce trismus in patients treated for head and neck cancer. Therefore, there is an unmet need to conduct this research in accordance with clinical scientific methodology in the form of a randomized feasibility study. Securing funding from the NIHR-RfPB (see appendix) enabled objectives three and four to be addressed and reported in chapters three and four. The protocol for the
study (Chapter 3) has been published in BMJ open and the results of the feasibility study (Chapter 4) are summarised below and have been published in *BJOMS*.

37 patients were randomised to therabite, 34 to wooden spatulas. Mean post intervention mouth opening increased in both groups. After adjustment for baseline MO, centre, surgery and chemoradiation, there was no difference (T – WS) in average mouth opening at the ‘6 month’ assessment. (p=0.39). Feasibility of exercises’ in both groups were comparable.

At 6 months, Client Service Receipt Inventory showed no significant difference (p>0.05) in the frequency of both primary and secondary care contacts between the two groups. Therabite costs were £385 per patient higher than wooden spatulas and had a Quality Adjusted Life Years loss of 0.0137 (equating to a difference of 5 quality-adjusted days over a year in favour of the WS.

Chapter five addresses objective five with presentation of the participants’ perspective on the acceptability of carrying out proactive exercises during a course of radiotherapy and beyond. The findings of this piece of work concluded the following comments:

Allow patients to have more of a say in the exercise regimen to aid compliance.

Exercises three times a day rather than five. Also to take a variable break of up to five to six weeks when side effects from radiotherapy are at their worst. Prolong study/exercises to 9-12 months post intervention to capture late effects.

The culmination of the work presented in this thesis addresses the overall aim which adds to the growing body of evidence to recommend a proactive, acceptable exercise regime to prevent or relieve trismus in head and neck cancer patients in order to improve patients health related quality of life.
Chapter 2
Letter to the Editor

Inconsistencies in the care of head and neck cancer patients experiencing trismus

Patients receiving radiation to the temporomandibular joint and/or the masseter/pterygoid muscles can experience limitations in jaw opening or trismus (Whitmyer et al., 1997). The deleterious effect of trismus on the quality of life of head and neck cancer patients is well established (Kent et al., 2008; Scott et al., 2008; Bensadoun et al., 2010), but the definition and options for treating trismus are far from being standardised. A survey was conducted to identify the current practice for defining and treating trismus in head and neck oncology patients. This was undertaken in order to determine if patients from different UK centres were receiving different interventions.

Delegates attending the British Association of Head and Neck Oncology (BAHNO, www.bahno.org.uk) 2009 conference were approached and 39 questionnaires were evaluated from 35 different centres throughout the United Kingdom.

In relation to the criteria used to define trismus, 21 (53.8%) delegates used only one method to define trismus. Ten of 39 (25.6%) delegates reported that they defined trismus from only a functional point of view, with 4 (10.3%) indicating access to the oral cavity as the only criterion they used. Seven (17.9%) indicated that they only used an inter-incisor distance of ≤35 mm as the criterion to define trismus. 17 (43.6%) delegates used more than one method to define trismus. Two of 39 (5.1%) delegates indicated ≤35 mm and function, 9 (23.1%) reported functional and access to oral cavity and 5 (12.8%) delegates opted for all three methods including ≤35 mm cut-off, functional and access to oral cavity as their criteria. One (2.6%) delegate used a questionnaire and the ≤35 mm cut-off and 1 (2.6%) delegate did not respond to this question. Together, the function only and function and access to oral cavity made up 50% of responses and using the ≤35 mm cut-off was only used by less than a third of the delegates. Therefore, there does not appear to be a consensus on the criteria to define trismus.

There was not a specific time point when mouth opening was being measured, which would suggest that problems associated with reduced maximum mouth opening are not being prospectively assessed and some patients are not receiving the appropriate treatment when required. This survey also highlights differences in practice and follow-up regimes for patients from different centres within the UK. The treatments given for trismus also vary considerably with tongue depressors being the most favoured (41%) followed by the therabite (35%), manual manipulation (17%), and others (7%) including drugs (not specified), and surgery. This survey has shown that not all patients identified as having trismus are being treated for this very debilitating condition. The results from the questionnaire suggest that a clear formalised plan needs to exist for the recognition, treatment and follow up for patients suffering from trismus. Patients are not given the same treatment options throughout the country which needs to be addressed by evidenced based clinical research in order to establish consistent care to all head and neck cancer patients.

Conflict of interest

None declared.

References


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Prediction of post-treatment trismus in head and neck cancer patients

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Available online 26 July 2011

Abstract

Our aim was to establish the incidence of trismus over time, together with risk factors (including quality of life (QoL)) for the prediction of trismus after treatment in patients with cancer of the head and neck. It was a longitudinal study of 152 patients accepted for primary operation who attended the head and neck cancer clinic of a tertiary referral cancer centre in the United Kingdom. A total of 87 patients was studied prospectively. Our results showed that 41/87 (47%) of patients presented with trismus, 57/80 (71%) had postoperative trismus, and 41/52 (79%) had trismus 6 months after operation or radiotherapy (trismus defined as a maximum mouth opening of ≤35 mm). Men and those who drank a lot of alcohol were less likely to have trismus after treatment. QoL variables showed that pain, eating, chewing, taste, saliva, social functioning, social contact, and dry mouth were significantly more impaired in the trismus group than among those without trismus. Postoperative differences in QoL between the two groups highlighted problems with social function and role-playing, fatigue, activity, recreation, and overall reduction in QoL. Women, and those who do not drink alcohol, are at particularly high risk of developing trismus, and, to prevent it and treat it, patients may benefit from multidisciplinary management at an early stage during treatment.

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Keywords: Trismus; Quality of life; Head and neck cancer; Risk factors

Introduction

Restricted mouth opening (trismus) in patients with cancer of the head and neck may result in difficulties with daily activities such as eating, chewing, swallowing, breathing, and speaking. It can lead to further problems such as severe pain, weight loss, and poor oral hygiene.1 In the light of these problems it is not surprising that 30–40% of these patients develop depression after treatment,2 and their rehabilitation may require treatment from a multidisciplinary team including speech and language therapists, dietitians, physiotherapists, counsellors, dentists, and orthodontic specialists.

Risk factors for trismus after treatment of cancer of the head and neck include tumours in the region of mouth-closing muscles, and disruption of the temporomandibular joint (TMJ) or the muscles of mastication, particularly the medial pterygoid muscle. The primary factor that limits movement of the jaw is rapid formation of collagen caused by radiation,3 or operation, or both, leading to fibrosis and contraction in the muscles used for closing the mouth and mastication.4

The variations in the reports of trismus5,6 have largely been caused by differences in sites of treatment, types of treatment, stage of tumour at the time of presentation, and a lack of a uniform definition of trismus. Dijkstra et al.7 defined it as mouth opening of ≤35 mm (either the interincisal distance or the distance between the upper and lower alveolus), and they were supported by Scott et al.8 Before these reports trismus was defined as mouth opening of less than 20 mm,9 or less than 40 mm.10

Some patients may be able to open their mouths by only about 5 mm, which restricts them to a liquid diet using a
straw. Publications about trismus have largely focused on patients being given radiotherapy (RT) as their primary treatment, or as an adjunct to resection. There is no consensus on the incidence of trismus. In one study, it was reported that 45% of 40 patients who had been given curative doses of RT developed trismus, with no differences in the incidence between RT and chemoradiotherapy or between conventional RT and intensity-modulated RT. However, a recent systematic review of trismus induced by cancer treatments concluded that the weighted prevalence for patients given conventional RT was 25.4% compared with 5% for those patients given intensity-modulated RT. There is no mention in this review, however, of the prevalence of trismus after primary surgical treatment. The published data on trismus is essentially cross-sectional in design, often with small numbers of patients.

The purpose of the study was to assess the incidence of trismus over time, to pinpoint the associated risk factors in patients treated by primary surgery with or without postoperative RT, and to assess its impact on the quality of life (QoL).

**Patients and methods**

We designed a prospective, observational study of patients with cancer of the head and neck referred to the oromaxillofacial and ENT clinics of a major cancer centre in the northwest of England.

**Inclusion and exclusion criteria**

Patients who presented with cancer of the head and neck and were treated by primary radical surgery alone, or primary radical surgery plus RT, or chemoradiotherapy (no distinction was made between these latter two groups), were included. Patients who had laser treatment of cancers of the tongue or larynx were excluded as were those with cancers of the thyroid or skin. Patients who were edentulous or whose incisors were partly missing were also excluded.

**Participants and procedures**

Patients who consented to participate in the study provided maximum readings of mouth opening and QoL measures at their preoperative assessment, 6 weeks after their primary operation, and again more than 6 months after treatment (including those given adjuvant RT or chemoradiotherapy).

**Assessments**

Maximum mouth opening was measured using a Platon motion scale (manufactured by Atos Medical), which was inserted between the maxillary and mandibular incisors while the patient was sitting upright. A threshold of ≤35 mm (incisor to incisor) was used to define trismus.

Initially two independent readings of maximum mouth opening were taken by the research worker and the specialist nurse from 20 patients, and these showed no significant interobserver differences. We concluded that the research worker alone could take all future readings. Additional readings from the bottom of the nose to the chin with the mouth closed and open were taken using Willis bite calipers.

QoL was assessed using the University of Washington Quality of Life Questionnaire version 4 (UWQoL v4), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and its head and neck module (EORTC QLQ H&N C35). Because of the many problems faced by patients with cancer of the head and neck we thought that a combination of these scales was appropriate.

Data were collected using a touch screen. The raw data from the QoL scales were converted to scores ranging from 0 to 100 using linear transformation according to the standard scoring procedures outlined by Fayers et al.

**Analysis of data**

Descriptive statistics were used, and variables reported as number (%). The following were used to assess comparisons between groups: continuous variables – Student’s *t* test or the non-parametric Mann–Whitney *U* test as appropriate; ordinal variables – the Wilcoxon rank-sum test; and dichotomous variables – Fisher’s exact test, which was used to assess the significance of differences between subgroups of patients. The Mann–Whitney test was used to assess the significance of differences in the QoL variables between the groups with and without trismus before treatment, postoperatively, and more than 6 months after RT. Logistic regression was used to identify any independent predictors of trismus. All analyses were made with the help of the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Details of patients and treatments in the larger sample**

A total of 152 patients (none of whom had had any intervention or treatment for limited mouth opening within the study period) were available for assessment; this is the number of patients who had had trismus measured postoperatively and had completed either the 6-week or the 6-month assessment. Eighty-seven subjects were followed prospectively to assess the incidence of trismus, whereas the data from all 152 patients were used for the predictive analysis. Two thirds were men, and primary sites were oral cavity 70 (46%), pharynx 41 (27%), and larynx 21 (14%). Sixty-two patients (41%) presented with stage 2, 46 with stage 4 (30%), 31 with stage 1 (20%), and 14 with stage 3 disease (9%). Seventy-three (48%) were current smokers, 47 were ex-smokers (31%), and
Table 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Total number of patients</th>
<th>No. (%) with trismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>87</td>
<td>41 (47)</td>
</tr>
<tr>
<td>After operation</td>
<td>80</td>
<td>57 (71)</td>
</tr>
<tr>
<td>After operation and radiotherapy</td>
<td>52</td>
<td>41 (79)</td>
</tr>
</tbody>
</table>

32 (21%) had never smoked. Fifty-nine patients were current or past heavy drinkers (39%).

Incidence of trismus over time (n = 87)

Eighty-seven of the 152 patients were included in this prospective longitudinal analysis because these patients were seen in clinic by the research worker at all three time points: preoperatively, postoperatively, and more than 6 months after treatment. It was not possible to collect postoperative maximum mouth openings for those seven of the 87 patients seen in clinic, because three patients had surgical complications with flaps, two patients’ mouths did not open sufficiently to insert the Platon motion scale, one said that his mouth was too sore, and one left the clinic after completing the QoL questionnaires. Sixty-five patients had one or more missing readings for maximum mouth opening, were not seen at one of the three time points specified, and were therefore excluded from this analysis, although used for the QoL analysis.

Of the 87 patients, 52 went on to have adjuvant treatment after the operation and maximum mouth opening readings were obtained more than 6 months after (chemo)radiotherapy. Maximum readings at all three time points were obtained for all 52 of these patients, so no data were lost. Thirty-five patients had no adjuvant treatment postoperatively. The results are shown in Table 1.

Comparison of personal and clinical characteristics of the groups with and without trismus (n = 76 in each group)

A Wilcoxon matched pairs signed ranks test showed no significant difference (p = 0.19) between the trismus values after operation and those measured more than 6 months after treatment. To assess the late effects of trismus, therefore, we thought that it was a reasonable assumption to use the postoperative trismus value as a surrogate for the final assessment value.

Based on the criterion of a maximum mouth opening of ≤35 mm, 76 patients were assigned to the trismus group and another 76 to the non-trismus group. Gender and whether or not they drank alcohol differed significantly (p < 0.05) between the trismus and non-trismus group. Fisher’s exact test showed that women were significantly more likely to present with trismus than men (p = 0.02). The site of the primary tumour did not predict trismus (p = 0.29). Those patients who consumed more than the weekly allowance of 40 units of alcohol for men and over 30 units for women had a significantly lower rate of trismus, and were significantly less likely to develop trismus after treatment (p = 0.01). Having chemo/radiotherapy did not predict that the patient would develop trismus after treatment (p = 0.68).

Comparison of QoL variables in those who did and did not develop trismus

QoL data were available for all 152 patients assigned to either the trismus or non-trismus group. All QoL questions were fully completed, as the electronic tablet did not allow patients to skip questions. Table 2 shows differences in QoL variables through the patients’ treatment based on whether they had trismus or not.

Discussion

One of the strengths of this study is its prospective design, and the fact that we collected baseline data about maximum mouth opening and QoL before treatment began. These data ensured that the differences evaluated were attributed to the treatment given and not to the tumour. To date we know of no published research into trismus that has taken the form of a prospective design with QoL variables.

Clinical and personal characteristics of patients with and without trismus

A comparison of these characteristics ensured that valid predictions could be made to find out which patients were more likely to develop trismus after treatment. We found that female sex had a significant effect, because women are more likely to have smaller maximum mouth opening (50.4 (5.9) mm) than men (53.8 (6.5) mm); perhaps separate criteria should be used to define trismus in women, as has been suggested elsewhere.

We noted that current or previous heavy drinkers had a substantially smaller chance of developing trismus or presenting with trismus before treatment. Being intoxicated may reduce the sense of pain during movement of the jaw, leading to wider opening of the mouth than among those who do not drink so much. Perhaps the alcohol also acts as a muscle relaxant, and counteracts the laying down of collagen.

Postoperative chemo/radiotherapy did not predict the development of trismus after treatment. Our results suggested that a large proportion of patients with trismus after chemo/radiotherapy (as we have not differentiated between them and those patients who had radiotherapy alone) already had trismus postoperatively. Adjuvant treatment could underm...
Table 2
Comparison of QoL variables in the two groups before treatment, after operation, and more than 6 months after radiotherapy, using univariate analysis.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>p value</th>
<th>After treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trismus (n = 29)</td>
<td></td>
<td>No trismus (n = 41)</td>
<td></td>
</tr>
<tr>
<td>UWQOLv4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>29</td>
<td>0.04</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Chewing</td>
<td>29</td>
<td>0.03</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Taste</td>
<td>29</td>
<td>0.02</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Saliva</td>
<td>21</td>
<td>&lt;0.001</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Activity</td>
<td>–</td>
<td></td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Recreation</td>
<td>–</td>
<td></td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>EORTC-QLQ-C30:</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>29</td>
<td>0.009</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Pain</td>
<td>29</td>
<td>0.02</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Constipation</td>
<td>29</td>
<td>0.02</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Role functioning</td>
<td>–</td>
<td></td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Fatigue</td>
<td>–</td>
<td></td>
<td>40</td>
<td>14</td>
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<tr>
<td>Overall QoL</td>
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<td>40</td>
<td>14</td>
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<tr>
<td>EORTC-QLQ-C35:</td>
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<tr>
<td>Pain</td>
<td>29</td>
<td>0.03</td>
<td>40</td>
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<tr>
<td>Eating</td>
<td>29</td>
<td>0.003</td>
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<tr>
<td>Social contact</td>
<td>29</td>
<td>0.02</td>
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<tr>
<td>Dry mouth</td>
<td>29</td>
<td>0.01</td>
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<tr>
<td>Mouth openinga</td>
<td>29</td>
<td>&lt;0.0003</td>
<td>40</td>
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a More than 6 months after treatment 23/23 (trismus) and 12/12 (no trismus) had problems with mouth opening (p = 0.007).

we have presented prospective data about trismus and QoL that were recorded before and after treatment, unlike many cross-sectional studies in the past.

QoL variables in patients with and without trismus

The QoL variables that are significant for the group of patients with trismus before treatment are centred around functional deficits. Examples of these include, eating, chewing, having a dry mouth, and not being able to taste food. Our results also imply that an appreciable proportion of patients with trismus have a lot of pain, which remains constant and presents an unmet need. Patients who have limited mouth opening before treatment, and who have severe pain, may be reluctant to open their mouths and this makes their trismus worse. Pain has been reported by 48% of 50 patients with cancer of the head and neck before treatment, and this needs alleviation to improve their QoL.19

Our data have also shown that patients with trismus have greater problems with social contact and social functioning before treatment, and that scores for social functioning deteriorated further after treatment.20 Bozec et al.21 showed similar trends in these QoL variables for postoperative patients, and reported that difficulties with social eating, speech, trismus, and salivary problems increased significantly postoperatively.

Our data reflect the published evidence, which supports the premise that QoL of patients with cancer of the head and neck returns to preillness levels by 6 months after treatment. They imply that the worst problems faced by patients with trismus were experienced before treatment and after operation, and these variables had returned to normal 6 months after treatment. The evidence also supports the finding that there is no significant difference between QoL variables between 6 months and 12 months after treatment.22

A key limitation in this study was incomplete data, because only one research worker was collecting it. These data have been considered to be missing at random, and were not expected to bias the results, although they may limit their generalisability. The distinction between postoperative radiotherapy and chemoradiotherapy should be addressed in future studies. We believe consistent early intervention is important in the amelioration of trismus.23,24

Acknowledgements

We would like to acknowledge the help received from the Christie/Central Manchester MDT, in particular Dr Barclay for use of the touch screen computer tablet, Mr Homer and Mr Loughran for access to ENT patients.

References

Chapter 3
BMJ Open

Protocol for the trismus trial—therabite versus wooden spatula in the amelioration of trismus in patients with head and neck cancer: randomised pilot study

Rana Lee,1 Alex Molassiotis,2 Simon N Rogers,3 Rhiannon Tudor Edwards,4 David Ryder,5 Nick Slevin1

ABSTRACT

Introduction Patients can develop trismus from their head and neck cancer or as a result of treatment. Trismus affects the jaw muscles and makes mouth opening difficult. To potentially combat trismus, patients could undertake proactive jaw stretching exercises prior to, during and after radiotherapy, although currently these are not the standard of care.

Methods and analysis This is a randomised, open-label, controlled, two-centre feasibility study, to assess the objective and subjective effectiveness and cost-effectiveness of therabite use compared with wooden spatula in ameliorating trismus in patients treated for stage 3 and 4 oral and oropharyngeal cancer, managed either by primary surgery followed by (chemo)radiotherapy or primary (chemo)radiotherapy. The principal objective assessment is measurement of maximum jaw opening. Assessments in all cases will be performed preradiotherapy and again at 3 and 6 months postintervention. Secondary aims of the study will be (1) to assess whether therabite or the wooden spatula intervention improves patients’ quality of life, (2) reduce the level of post-treatment clinical management/healthcare use and (3) a nested qualitative study will explore the experience of the patient taking part in the intervention; data will be transcribed verbatim and analysis will be based on content analysis methods using the interview questions as the framework for examination.

Ethics and dissemination North West Greater Manchester granted ethical approval (REC Reference 11/NW/0744). Good Clinical Practice and the Declaration of Helsinki have been adhered to. The results will be presented internationally and submitted to a peer-reviewed journal. Head and neck cancer charities and information websites will also be approached.

Trial registration number NCT01733797.

INTRODUCTION

Patients with head and neck cancer can experience a variety of complications following surgery and/or radiation/chemoradiation, including limited mouth opening or trismus.1 Trismus will affect the ability to chew food, speak coherently, brush completely the lingual or palatal surfaces of the teeth, have routine dental assessment and oral examination to detect possible cancer recurrence. This can lead to malnutrition and lack of energy, chronic periodontal disease, caries, dental integrity with risk of osteoradionecrosis of the jaw.2-5 These patients may also suffer from lack of intimacy due to lack of kissing function, lack of self-esteem, depression, suicide tendencies and altered body image with nearly 60% of patients feeling discounted or stigmatised because of their cancer-related appearance.6,7

Only a few studies exist in which the effects of interventions on trismus have been investigated. Buchbinder conducted a randomised clinical trial (RCT) with 21 patients who had radiation-induced trismus. At the end of the 10-week period, the group of patients using the therabite system (n=7) had shown the greatest improvement (mean of 13 mm), while the group using tongue depressors (n=7) only showed a modest improvement...
of less than 5mm on average.\textsuperscript{8} Maloney conducted a RCT with 46 patients with temporomandibular joint (TMJ) disease comparing the use of therabite and an intraoral appliance (n=17), the use of tongue depressors in combination with an intraoral appliance (n=12) and an intraoral appliance only (n=17). It showed that patients using the therabite experienced increased mobility and decreased pain compared with the group using intraoral appliance alone.\textsuperscript{9} Cohen studied the use of therabite in the early postoperative management of trismus in only seven patients who had surgical treatment and reconstruction for head and neck cancer. The authors report that the use of therabite increased the range of motion and decreased pain in both muscle and joint disorders.\textsuperscript{10} Finally, a systematic review carried out by McNeely et al\textsuperscript{11} on the effectiveness of physical interventions for TMJ disorders concluded that the results support the use of active and passive oral exercises as effective interventions to reduce trismus.\textsuperscript{11} This handful of studies shows that the use of therabite after radiotherapy and/or surgical treatments can improve maximum mouth opening, but some publications had not used a control group with which to compare maximum mouth opening readings. Also, all studies had small sample sizes and power calculations were not reported.

METHODS AND ANALYSIS

Design
This is a randomised, controlled two-centre pilot study, to assess the feasibility of therabite use compared with wooden spatula in ameliorating trismus in patients treated for stages 3 and 4 oral and oropharyngeal cancer.

Settings
Christie Hospital National Health Service (NHS) Trust (with MRI/Wythenshawe/Pennine NHS Trust hospitals) and Aintree Hospital NHS Trust.

Sample
The cohort will comprise previously untreated patients with stage 3 and 4 oral and oropharyngeal cancer managed either by chemoradiotherapy or surgery followed by (chemo)radiotherapy. Disruption of the TMJ, the pterygoid muscles or the masseter muscle is likely to result in trismus, and hence patients having surgery or radiotherapy in the vicinity of these joints/muscles will form the sample of this study.

The inclusion of patients in stages 3 and 4 comes from the evidence that T3/4 patients are most likely to develop trismus.\textsuperscript{12} The use of the therabite may prevent deterioration by maintaining or improving range of movement.

Inclusion/Exclusion criteria

Inclusion
\begin{itemize}
  \item Provision of signed, written informed consent.
  \item Aged 18 years and older.
\end{itemize}

Exclusion
\begin{itemize}
  \item <12 mm mouth opening (cannot use therabite).
  \item Anatomically unable to use therabite for example patients who may only be partially dentate and to use the therabite would place extreme stress on the existing teeth).
  \item Cognitive impairment as judged by the clinicians.
  \item Some patients with mouth cancer present at an advanced stage, and the treating consultant will use clinical judgement as to their inclusion or exclusion to the study.
  \item All patients who the treating consultant deems too unwell to use the therabite instrument will also be excluded. This may also include patients whose alcohol dependency may result in their non-compliance with future assessments.
  \item International patients treated at The Christie or Aintree Hospital who may not have routine follow-up at these sites.
\end{itemize}

Intervention
The Therabite Jaw Motion Rehabilitation System (Platon Medical) will be used.\textsuperscript{13} This is a patient-controlled jaw mobilisation device which employs anatomically correct, repetitive passive motion and stretching to help restore proper jaw opening. The suggested improvement in jaw function comes about via a combination of stretching of connective tissues, mobilisation of joints and strengthening muscles across their full range of motion. Patients will be trained on the safe use of therabite or wooden spatula and recording procedure prior to commencement of primary chemoradiotherapy or after primary surgery. This at their prechemoradiotherapy assessment day, whichever visit is more convenient for the patient.

No known adverse effects have been documented or reported from patients using the therabite. General and user information for the therabite will be given with the device to patients.

Therabite protocol
For patients randomised to therabite use, they will be asked to follow the 5-5-30 protocol which is:
\begin{itemize}
  \item Five sessions per day.
  \item Five openings/closing per session.
  \item 30s stretch for each opening.
\end{itemize}

This regime has been selected after consultation with Platon medical who manufacture the equipment and has worldwide experience of using the device. The
importance of motion in the rehabilitation of patients with mandibular hypomobility is also supported by the literature. Israel and Syrop’s review highlights the point that the TMJ is a synovial joint and as such functions as the same as other synovial joints in the body. Therefore, lack of mobility of the TMJ may lead to restrictions in maximum mouth opening fairly rapidly. 14

Patients will commence therabite use approximately 3/4 wks post surgery. Based on the literature, it is imperative that therabite use is encouraged as early as possible and maintained to achieve maximum benefit for patients with mandibular hypomobility. 15 This is further supported by Melchers who performed a qualitative study of positive and negative aspects influencing adherence when using the therabite device, reporting that goal setting, belief and self-discipline were all positive factors. 16

Control group: wooden spatula

Wooden tongue depressors or‘spatulas’ have been demonstrated to be ineffective in the management of established trismus in patients with head and neck cancer, 6 although at present form the basis for best supportive care for the management of trismus. This treatment is also a passive form of exercise designed to increase mouth opening range. Standard wooden tongue depressors will be used, measuring approximately 1.25 mm in thickness and 14 mm in width.

The use of the wooden tongue depressors will commence at randomisation and patients will be asked to complete the 5-5-30 regime. Patients will be instructed to place a maximum number of wooden spatulas in between their front teeth.

An additional spatula will be placed in between the already stacked spatulas. The number of spatulas placed for each treatment will be recorded by the patient.

Assessment scales

Post surgical maximum mouth opening and health-related quality of life (HRQoL) assessments will take place at 3 to 4 weeks. This is the optimal time prior to the start of radiotherapy treatment. Follow-up assessments will take place at 3 and 6 months following start of intervention. More specifically, patients will undergo the following assessments.

Primary outcome

Maximum mouth opening using the Willis Gauge (primary outcome).

Secondary outcomes

*Interincisor maximal mouth opening measured using the therabite motion scale*

Mouth opening measurements will be recorded using the Willis Bite Gauge (SS White Group, Gloucester, UK) and measured in millimetres (mm) for both dentate and edentulous patients. These measurements are taken from the top of the philtrum to the under surface of the mandible.

A chart will be used to record which teeth were used to record the measurements using the Therabite Motion Scale. This is so that subsequent recordings will use the same landmarks for each individual patient.

*HRQol*

QoL will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C 30) and head and neck (H&N) module (EORTC QLQ H&N 35). These questionnaires have been validated and have been shown to be reliable in detecting QoL changes in patients with H&N cancer 17–20 Data will be collected using a touchscreen data collection method. Patients will be encouraged to complete questionnaires on their own to help reduce bias.

*Use of secondary health services*

Costs will be identified, measured and valued using a microcosting approach, by which each component of resource use is identified, estimated and a unit cost derived from market prices and national estimates. The cost analysis will be performed from the perspective of the health service provider and from a societal perspective. Included in the healthcare provider costs will be those accrued by the acute trusts. Costs to the patients and their families, including social care, will be considered as the additional costs for society. It will be in the form of a structured interview documenting which healthcare professionals the patient have visited. Structured interview will take place at the 3 months and 6 months post intervention, covering the previous 3 months. Patients will also be asked which secondary healthcare services they have been referred to. Such services may include speech and language therapy, dietary and nutritional advice and/or artificial feeding and orthodontic interventions including surgery. Patient notes will be also be audited; however, as records may not always be complete, patient interviews are deemed to be a more accurate assessment of use of healthcare resources. Study patients will be monitored and any clinical interventions recorded. An estimate of costs of interventions will be made, an average cost per patient calculated, and this will be compared between study and control patients. The aim of this is to assess whether the potential economic benefit of therabite offsets its cost of £250 per patient.

Patient characteristics will include age, gender, treatment, dentate, site of cancer, stage of tumour, alcohol use and radiotherapy dose and will be obtained from the medical records.

*Nested qualitative study*

All patients will be approached by the medical team at the 6-month time schedule to be included in the nested qualitative study. Telephone interviews will be conducted with patients in their own home by the researcher RL within 3 months of completing the exercise regime and will explore the experience of the patient taking part in the intervention, any issues that participants found difficult.
during the intervention, any problems with the terabite or wooden spatula and the mouth exercises, issues around compliance with the protocol or interference of the intervention with their lives and whether pain has been an issue in their compliance with the intervention. Hence, these interviews will aim to explore any practical issues that make the delivery of the intervention less feasible to control or consider such variables in a future phase III trial. A blank copy of interview schedule is available. Data will be tape-recorded and transcribed verbatim; data analysis will be performed by RL and researchers with expertise in qualitative methods, based on content analysis methods using the interview questions as the framework of analysis by Richie and Spencer. Field notes will be taken during the interview, and all data coding and emergent themes will be provided as well as participant quotations to illustrate the findings and divergent themes in a transparent and reproducible manner. The Consolidated Criteria for Reporting Qualitative Research checklist will be used to report important aspects of the research team, reflexivity of the researchers, study design, data analysis and reporting.

Sample size
Since we are measuring the difference within each patient from their baseline to 6 months post intervention, we are not going to adjust for gender or dentate state (each person acts as their own control). This pilot will give us information on whether we need to adjust for these in a future phase III study. From published literature, we estimated that the SD of the differences in each of the treatment groups could be as high as 10 mm being the worse case scenario.

In our prevalence study, median mouth opening was 40 mm when the patient could chew as well as ever, 30 mm when soft solids could be eaten but some foods could not be chewed and 24 mm when even soft solids could not be chewed. We estimate that if we want to detect a minimum of 5 mm improvement from the background difference, which is our control arm (no intervention), the common SD is 8 mm (patients that have had no intervention and have had radiotherapy). Based on our prevalence study data, if we wish to detect a difference between the two arms of 5 mm change with an SD of 8 mm with 80% power, we would require 42 cases per group. With an additional 25% attrition rate (as we have seen in our prevalence study), 112 patients will be required.

Recruitment rate
The planned recruitment rate will be two patients per week across the two centres at Liverpool and Manchester (catchment population is approximately 5 million). On average, Christie and Aintree Hospital will see 1000 patients with head and neck cancer a year. Of these, approximately half will be oral and oropharyngeal patients. Of these 500 patients, 60% will be stage 3 and 4, giving a potential pool of 300 patients. Of these, 100 may not be suitable on account of clinical factors.

The following factors may affect compliance (with both regimes):
- Pain.
- Anxiety.
- Radiation induced mucositis.
- Alcohol dependency.

A recent study by Melchers et al indicated that pain due to radiation-induced mucositis had a negative effect on adherence when using the terabite device. Other factors such as anxiety, ill-fitting terabite pads and the lack of goal setting during treatment also had a negative effect. It is our intention therefore to monitor for these symptoms/problems during the patients’ course of treatment and manage accordingly. However, there have been reports that patients with higher initial pain and jaw use limitation levels were more compliant with treatment recommendations.

Patients who are alcohol dependent prior to randomisation may be excluded following clinical assessment by both the patients’ consultant and the researchers.

Randomisation
Randomisation will be by the minimisation method. Allocation will be equal between the two arms of the trial and will be administered centrally by the Manchester Academic Health Sciences Centre Trials Co-ordination Unit (MAHSC-CTU). There will be no replacement of patients who fail for whatever reason to take part in the trial.

Patient identification (ID) will be by trial ID which will be a sequential number from 001 to the total number of patients in the trial. Any patient who fulfils the criteria for inclusion and takes part will be evaluable, unless there is a serious deviation from the protocol. For example, patients who do not receive radiotherapy or who do not have measurements of mouth opening at 3 and 6 months would not be evaluable, though they would remain in the study.

Analyses plan
Descriptive statistics will be used to identify prevalence of trismus between the two groups and mouth openings. Similarly, descriptive statistics will be calculated for number of patients completing the study and amount of data missing from the questionnaires. The analysis would further involve a two-tailed unpaired t-test at the 5% significance level. The change from baseline to 6 months for each case would be compared between treatment group 1 and treatment group 2. Power calculations will take place to assess the number of patients required for a phase III trial.

The effect of missing values will be assessed by comparing the numbers and percentages of participants with missing values in the two arms of the study; differences in baseline variables between participants with observed and missing outcomes in each arm and for participants with observed outcomes, differences in baseline variables between the two arms. Logistic regression models will be used to assess potential factors affecting dropout.
Analysis of economic data: the total cost of each arm of the trial will be calculated by combining the resource use and unit cost data. No discounting is necessary given the time period of data collection (less than 1 year); sensitivity analysis will be carried out to account for uncertainty where estimates in cost data are used. Differences in costs between the two arms will be tested for using independent t-tests. Analysis will be carried out by a health economist.

HRQoL
QoL will be assessed using the EORTC QLQ-C 30 and H&N module (EORTC QLQ H&N 35). These questionnaires have been validated and have been shown to be reliable in detecting QOL changes in patients with H&N cancer. Patients will be encouraged to complete questionnaires on their own to help reduce bias. It is expected that some of the QOL subscales will be more sensitive to change than others (these are likely to be subscales around ‘eating’, ‘weight loss’, ‘pain’, ‘taste’, ‘chewing’ as we have seen in our recently completed longitudinal observational study) and will establish the appropriate scales to be used in the phase III trial but also required sample sizes.

Health economics assessments
EQ-5D questionnaire. This is a validated generic, health-related, preference-based measure comprising five domains: mobility; self-care; usual activities; pain and discomfort; anxiety and depression. Each domain has three levels (no problems, some problems and a lot of problems). The questions are complemented by a visual analogue scale on which respondents are asked to indicate their current health.

ICEpop CAPability measure for adults (ICECAP-A). This is a more encompassing quality of life measure. There are five domains: attachment, security, role, enjoyment and independence. There are four levels of capability ranging from a lot to none.

Measurement of costs for health economics analysis
Overall economic question for the planned full RCT
What is the incremental cost-effectiveness of therabite in the management of trismus in patients with H&N cancer as compared with treatment as usual?

Feasibility study questions
We will explore how well generic HRQoL measures, that is, EQ-5D and ICECAP-A perform in this patient group—for the purpose of quality-adjusted life year (QALY) calculation in the planned full RCT.

We will explore the sensitivity of these measures, comparing patient responses with cancer-specific HRQoL measures in this feasibility study.

We will explore the extent to which an interview-based client service receipt inventory (CSRI) can capture frequency and type of service contracts based on patient recall over 3 months.

For this patient group, we will be particularly interested in asking patients about their contacts with such services as speech and language therapy, dietary and nutritional advice and/or artificial feeding and orthodontic interventions including surgery. Patient notes will be also be audited, as records may not always be complete. Patient interviews are deemed to be a more accurate assessment of use of healthcare resources in this patient group.

Preliminary incremental cost-effectiveness ratio calculation to explore power issues in an economic analysis alongside the planned full RCT.

From an NHS perspective, the following health economic analysis will be performed:
1. Undertake a microcosting of the therabite intervention.
2. Record study participant primary and secondary care health service use, social care and voluntary sector use (using an interviewer administered CSRI, costed using national unit costs).
3. Explore whether it is feasible for the main planned full RCT to adopt a cost-utility approach, calculating cost per QALY, which has more meaning for patient QoL than for example, cost-effectiveness analysis using the Willis gauge as a measure of maximum mouth opening.
4. Using pilot data from the feasibility study, we will explore how bootstrapping enables us to generate cost-effectiveness acceptability curves to communicate to policy-makers the probability that the therabite intervention is cost-effective.
5. Suggest appropriate sensitivity analysis and subgroup analysis strategies to explore uncertainties in the planned full RCT.

Data analysis
Descriptive statistics will be used to identify prevalence of trismus between the two groups and mouth openings. Similarly, descriptive statistics will be calculated for number of patients completing the study and amount of data missing. The primary analysis would further involve a two-tailed unpaired t-test at the 5% significance level. The change from baseline to 6 months for each case would be compared between treatment group 1 and treatment group 2. Power calculations will take place to assess the number of patients required for a phase III trial.

The secondary analysis will be an analysis of compliance. This will be a normal distribution test of the proportion of the log completed by each patient, taking into account that some patients might not complete the full 6 months of the log.

Probable/possible outputs
This is a feasibility trial progressing to a phase III trial; if results are positive in the phase III trial, our intervention can be recommended for use in the NHS. The need for lengthy and expensive operations to try and correct trismus can also be reduced and patients may see improvements in all aspects of quality of life. We anticipate that
this research will lead to alleviation of symptoms including restriction/pain with mouth opening, inability to eat in front of friends/family or in public, poor oral hygiene or inability to have dentures fitted. Restrictions in mouth opening will also hamper access for clinical assessment of local recurrence. This evidence base may also benefit the wider NHS by reducing the levels of post-treatment clinical, dental and psychological management required by these patients.

**Primary and secondary analysis**

Analysis will be done by commercially available statistical software, SPSS V.16 or S plus. The key variables in the primary and secondary analyses will be presented using the appropriate tables which show means, SD and CIs.

The null hypothesis for the primary analysis will be that there is no difference in the amount of mouth opening at 6 months between the two arms of the trial. The alternative will be two sided: it is unspecified which arm will result in more or less mouth opening.

The null hypothesis for the secondary analysis will be that there is no difference between the two arms in the proportion of the log completed by each patient. As before the alternative will be two sided: it is unspecified which arm will result in a higher proportion of the log each patient has to complete.

Patients who withdraw or do not receive any assessment of mouth opening after they enter the trial will be missing with regards to the primary analysis. With regard to the secondary analysis, if patients do not enter any data into the log but are assessed after they enter the trial then the proportion completed will be zero.

**ETHICS AND DISSEMINATION**

The trial was approved by the Research Ethics Committee and each participating site R&D department prior to study start-up at the site. Great care will be taken to fully explain the study to the patients before fully informed consent is taken.

Sponsorship and clinical governance will be the responsibility of The Christie NHS Foundation Trust Research and Development Division. The trial will be conducted in accordance with the principles of good clinical practice.

**Trial monitoring and oversight**

The Clinical Trials Unit of The Christie will be responsible for scientific, financial and administrative management of the project in association with relevant trust departments.

The research team consisting of six members will form the basis of the trial management group and will meet formally every 2 months to assess progress of the project against agreed milestones, present results and address any delays or problems. An independent monitoring committee will not be formed as there is no drug involvement and no risk to patients entering this study. The trial will be monitored by the Christie Trials Coordination Unit on the basis of a trial risk assessment.

**Criteria for discontinuation**

- Voluntary discontinuation by the patient.
- Severe non-compliance to the protocol as judged by the investigators.
- Patients lost to follow-up.
- Recurrence of tumour.
- Intercurrent illness.
- Withdrawal of consent to radiotherapy treatment or death of the patient.
- Participants are to be replaced to account for discontinuation/withdrawal of participants while the study is still open to recruitment.
- The follow-up for withdrawn subjects will take place as standard, lead by the consultant supervising their radiotherapy treatment.

If discontinuation or withdrawal of participants takes place, then The Christie Clinical Trials Unit (CTU) will be informed.

All patients' will only complete the procedures if they are able to. If they are unable to continue to participate in the study then their data will be collected up to that point. If the patient is physically too weak to continue with the therabite or the tongue depressors, then data will be collected up to that point and included in the analysis. These data will be retained by the CTU for audit purposes. Patients may still be asked to complete the validated questionnaires if they are able.

A sentence will be included in the patient information sheet to inform them that all data from the maximum mouth opening and completed questionnaires will still be used.

**Expected toxicity**

None has been reported in the literature of either intervention.

**Serious adverse events**

All serious adverse events occurring during radiotherapy will be faxed to the MAHSC-CTU, with the following exceptions:

- Serious adverse events (SAEs) representing an expected change or progression of the neoplastic condition that was the cause of treatment.
- Any grade of acute radiation toxicity (mentioned above) not requiring inpatient hospitalisation for specific treatment.
- Hospitalisation due to mucositis.
- Standard chemotherapy toxicities.

SAEs will be collected until 6 months after intervention which will be end of study.

**Compliance issues and loss to follow-up**

Melchers indicated that pain due to radiation-induced mucositis had a negative effect on adherence when using the therabite device. Other factors such as anxiety, ill-fitting therabite pads and the lack of goal setting during
treatment also had a negative effect. Our intention is to monitor for these symptoms/problems during the patients’ course of treatment and manage accordingly. Compliance of each intervention will be monitored using a patient log book and allow us to calculate the compliance rate. Such a log book has been used in a previous trial from our team based at The Christie, examining the tolerability of Manuka honey for oral mucositis. Compliance will be enhanced by identifying key factors and addressing them during the study (ie, setting up with patients a clear goal from the exercise, addressing oral pain more effectively to allow exercises to take place, provide patients with reminders particularly as the time from enrolment increases).

In other studies of non-pharmacological interventions, we have carried out with this population, attrition from enrolment increases).

Trial closure

► After recruiting the desired number of patients into the study, the study will stop recruiting further patients.
► When all the recruited patients have completed their 6 months of jaw exercises and the necessary data has been collected, the study will close.
► There is no planned follow-up period for the participants.

Dissemination

The Macmillan Cancer Relief organisation will be approached to enhance patient dissemination. In keeping with previous clinical research by the authors, we intend to present at national and international meetings, such as the British Association of Head and Neck Oncologists, International Association of Oral and Maxillofacial Surgery and Quality of Life conferences in Head and Neck Cancer. Efforts will be made to update web-based information sites with the outcomes of our study including www.mouthcancerfoundation.org and www.headandneckcancer.co.uk. Hospitals. All these efforts are aimed at giving patients with head and neck cancer with this debilitating condition, some hope that a scientifically robust study is aimed at helping them improve their overall quality of life.

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Contributors NS and RL conceived the study design. NS is the grant holder and CI of the study, AM, SNR and RTE are coinvestigators. DR provided statistical expertise in clinical trial design. RTE provide the Health Economics input entirely. All the authors approved the protocol.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval North West Greater Manchester which granted ethical approval (REC Reference (11 /NW/0744). ‘The Christie NHS Foundation Trust Hospital acknowledges the support of the National Institute of Health Research Clinical Research Network’ (NIHR CRN: Trismus RPB trial (portfolio ID 13415).

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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Chapter 4
Randomised feasibility study to compare the use of Therabite® with wooden spatulas to relieve and prevent trismus in patients with cancer of the head and neck

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Abstract

Our aim was to compare the efficacy of the Therabite® jaw motion rehabilitation system (Atos Medical) with that of wooden spatulas to relieve and prevent trismus in patients who have had radiotherapy for stage three and four oral and oropharyngeal cancer. Secondary aims were to assess the feasibility and the impact of exercise on health-related quality of life (QoL), and the use of health services after treatment. We designed a randomised, open-label, controlled, three-centre feasibility study to compare the effectiveness and cost of the Therabite® and wooden spatulas. We studied compliance with exercises and health-related QoL, assessed cost using three health economics measures, and conducted semistructured interviews with patients. Patients were randomised into two groups: the Therabite® group (n = 37) and the wooden spatula group (n = 34). All patients had some sense of jaw tightening before the study started. Mean mouth opening after six months increased in both groups, but the difference between the groups was not significant (p = 0.39). Completion rates for the three economic measures were good. There was no significant difference between the two groups in frequency of contact with care services or in QoL. Exercises during and after radiotherapy can ameliorate trismus in patients with stage three and four oral and oropharyngeal cancers, but differences between groups in efficacy, compliance, QoL, or use of hospital or community health services, were not significant.

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Keywords: Trismus; Head and Neck cancer; Randomised trial; Feasibility; Health economics; Exercises

Introduction

Around 7600 patients were diagnosed with cancer of the lip, oral cavity, or oropharynx in the UK in 2013. Trismus, which can develop as a result of the disease or its treatment, is under-reported as a serious complication, and radiotherapy is been reported as one of the most common causes. The definition

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of trismus by Dijkstra et al as a maximum mouth opening of 35 mm or less is now widely accepted. Trismus can impair the ability to chew, swallow, and speak, and can be detrimental to oral health, dental integrity, and overall quality of life (QoL). Psychological difficulties can include low self-esteem, depression, and suicidal tendencies.

Studies by van der Molen et al and and Carnaby-Mann et al on jaw exercises in patients treated with chemoradiotherapy for cancer of the head and neck showed less of a decline in mouth opening than standard rehabilitation techniques after treatment. However, both studies were small with only a 10-week follow up, and there were no economic evaluations. Current treatments such as the use of wooden spatulas, Therabite® (Atos Medical), Dynasplint® (Dynasplint Systems Inc), and swallowing therapies, have shown only a modest effect once trismus is established. However, Scherpenhuizen et al suggested that jaw exercises can improve mouth opening in patients with established radiotherapy-induced trismus. In view of these conflicting opinions, there is consensus about the need for a rigorous, controlled study to provide clearer evidence of the value of exercise devices in patients who have trismus before radiotherapy or who have a high risk of developing it afterwards.

This feasibility study was designed to find out whether exercises are beneficial and to inform the design of a larger study, in line with the Medical Research Council framework for complex interventions.

Our main aim was to compare the efficacy of the Therabite® with that of the current standard treatment with wooden spatulas to relieve or prevent trismus. Secondary aims were to assess the feasibility and the impact of exercise on health-related QoL, the need for additional treatment, and completion rates of three health economics outcome measures: the Client Service Receipt Inventory (CSRI), EQ-5D-3L (EuroQol), and ICECAP-A (ICEpop CAPability measure for Adults).

**Material and methods**

This randomised, open-label, controlled, three-centre feasibility study was designed to compare the use of Therabite® with wooden spatulas to treat and relieve trismus in patients with stages three and four oral and oropharyngeal cancer. The study was approved by the North Manchester Ethics Committee (12/NW/0414) and all patients gave written informed consent before the study started.

Patients treated by primary chemoradiotherapy, radiotherapy, or operation followed by chemoradiotherapy or radiotherapy, were recruited from three tertiary referral centres in England. Those who had tightening of the jaw before radiotherapy were invited to participate. They were all prescribed a dose of 60-70 Gy in 30-35 fractions to the jaw over six to seven weeks using intensity-modulated radiotherapy (IMRT).

To detect a minimum mean (SD) difference in mouth opening of 5 (8) mm from baseline (previously estimated from patients who had radiotherapy without operation) with 80% power, required 42 patients/group. With a predicted 25% attrition rate, 112 patients were required in total.

Patients were randomised using the minimisation method with a random element (allocation was with a 0.75 probability to the arm yielding a lower imbalance score or 0.5 if scores were tied). Controlled factors were operation or no operation, centre, and synchronous chemotherapy given or not given. Patients were then instructed to do their exercises according to a set protocol.

Those whose mouth opening was less than 12 mm (not wide enough for the Therabite®), or who were anatomically unable to use the Therabite® because they were partially dentate, and those with a past history of operation or radiotherapy to the head and neck, were excluded.

**Protocol for use of Therabite® or wooden spatula and measurement of mouth opening**

Patients randomised to either group were asked to follow the 5-30 protocol, which comprised five sessions/day for six months. At each session they had to open their mouths for 30 seconds then close it. They had to do this five times. They started the exercises about three weeks postoperatively or one to three weeks before radiotherapy, and recorded the maximum mouth opening at the end of each day using a Platon Therabite® range of motion scale (Atos Medical) to show compliance. They also used a Willis bite gauge to measure from the bottom of the nose to the chin with the mouth closed and open at baseline and again three and six months after treatment.

Table 1 shows the patients’ details.

**Quality of life**

Quality of life (QoL) was assessed at baseline, and at three and six months after treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C 30) and the Head and Neck (H&N) module (EORTC QLQ H & N 35). Data were collected on a pro forma.

**Health economics assessments**

To assess health economics we used the EQ-5D-3L (European Quality of Life - 5 Dimensions - 3 Levels) at baseline and three and six months after treatment. This is a validated, generic, health-related, preference-based measure that comprises five domains: mobility; self-care; usual activities; pain and discomfort; and anxiety and depression. Each domain has three levels (no problem, some problems, and major problems) giving a total of 243 possible health states. We converted these into EQ-5D-3L index scores (single utility
scores anchored at 0 for death and one for perfect health), which can be “negative” if patients consider their health to be worse than death.\(^{20,21}\) We then translated the index scores into quality-adjusted life years (QALY) by weighting them with quantity of life (the aggregated number of years lived), using the area-under-the-curve method.\(^{22,23}\) Quality-adjusted life years is a common unit of effect (a measure of utility) that has been advocated by the National Institute for Health and Care Excellence (NICE) in the UK for the evaluation of cost-effectiveness.\(^{24}\)

ICECAP-A (ICEpop CAPability measure for Adults) (baseline, and at three and six months) is a measure of QoL with five domains: attachment, security, role, enjoyment, and independence.\(^{25}\)

At three and six months we interviewed patients using the Client Service Receipt Inventory (CSRI) to find out how often they had used primary and secondary care services\(^{26}\) such as speech and language therapy; dietary and nutritional advice or artificial feeding, or both, and orthodontic interventions including surgery.

Nested qualitative study

We used semistructured telephone interviews up to six months after completion of the study to find out about the patients’ experiences of the study and how trismus affected their daily lives. To plan possible variables for a future phase III trial, patients were asked about compliance with the protocol and whether pain had affected it. Data were transcribed verbatim and were analysed according to the framework analysis reported by Ritchie and Spencer.\(^{27}\)

Data analysis

Statistical analysis was done with the help of Stata statistical software, release 13 (StataCorp LP, College Station, USA) and SPSS for Windows, version 16 (SPSS Inc, Chicago, USA). The null hypothesis for the primary analysis was that there would be no difference between the groups in the amount of mouth opening at six months.

Descriptive statistics were used to report the prevalence of trismus and mouth opening. Similarly descriptive statistics were used to calculate the number of patients who completed different parts of the study and the amount of missing data.

The original power calculation was based on a \(t\) test of change in scores, but the analysis of covariance (ANCOVA) is more efficient. An ANCOVA model was fitted with the six-month measurement of mouth opening as the response, and the trial arm as the variable of primary interest after adjustments had been made for baseline, centre, operation, and chemoradiation.

Economic analysis was done using Microsoft Excel 2013 and SPSS Statistics for Windows, version 22 (IBM Corp, Armonk, USA). Confidence intervals (CI) for costs and health-related QoL were estimated using non-parametric bootstrapping methods.\(^{28,29}\) A simulation of 5000 non-parametric bootstrapping iterations was run to construct 95% CI around estimates of costs and QoL scores using Microsoft Excel 2013.

Results

Of the 237 patients screened, 71 were included. Most of those not included had had no subjective tightening of the jaw or had declined participation.

There were 37 patients in the Therabite\(^{®}\) group and 34 in the wooden spatula group (Fig. 1). Median (range) maximum mouth opening at baseline was 24.0 (12.0–58.0) mm for the Therabite\(^{®}\) group and 21.8 (12.5–48.0) mm for the spatula group. Recorded baseline characteristics (age, sex, previous operation, radiotherapy or chemoradiotherapy, site and stage of disease, use of alcohol, and smoking status) were broadly similar in both groups. This was made possible by using prior stratification factors to minimise differences at baseline (Table 1).

Maximum mouth opening

Measurements of mouth opening at six months were supplied by 41/71 participants, which may indicate that mouth opening in both groups had not deteriorated. The difference between the two interventions was not significant although

<table>
<thead>
<tr>
<th>Centre:</th>
<th>Wooden spatulas</th>
<th>Therabite(^{®})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liverpool</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Birmingham</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Manchester</td>
<td>23</td>
<td>22</td>
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<table>
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<tr>
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<td>14</td>
<td>11</td>
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<td>T1/2</td>
<td>20</td>
<td>26</td>
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<td>14</td>
</tr>
<tr>
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<td>25</td>
<td>23</td>
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<td>25</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
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<th>Previous heavy</th>
<th>Never heavy</th>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>Previous heavy</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Never heavy</td>
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<td>19</td>
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<th>Current smoker</th>
<th>Ex smoker</th>
<th>Never smoked</th>
</tr>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>Ex smoker</td>
<td>17</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>13</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Site of disease:</th>
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<th>Oropharyngeal</th>
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</thead>
<tbody>
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<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage:</th>
<th>T1/2 N+ M0</th>
<th>T3/4 N0 M0</th>
<th>T3/4 N+ M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 N+ M0</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>T3/4 N0 M0</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>T3/4 N+ M0</td>
<td>15</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. Consort diagram.
the power of the study was low because we failed to achieve the target recruitment and the attrition rate was higher than anticipated. The estimated difference in mean mouth opening at six months after adjustment for baseline, centre, operation, and chemoradiation in an analysis of covariance model was -2.43 mm (95% CI -8.15 to 3.29). This was not significant ($t_{135} = -0.86$, 2-tail $p = 0.39$). There was no formal evidence against two key assumptions of the fitted model: normality of the residuals (Shapiro-Wilk test, $Z = 0.6$, 1-tail $p = 0.27$) and homogeneity of variance (Cook-Weisberg test for heteroskedasticity, $X^2 = 7.90$, 1-tail $p = 0.16$).

Compliance with the exercises was poor, particularly at the end of radiotherapy, but there were no appreciable differences between the groups (data obtained from the patients’ logs).

**Health-related QoL**

Subscales (taken from the EORTC QLC-C30) related to eating, weight loss, pain, and mouth opening, were predicted to be more sensitive to changes than others in patients with trismus. However, there was no appreciable difference in the change in mean scores from baseline to six months between groups for any of these items.

**Telephone interviews**

Telephone interviews were designed to explore the consequences and possible effects of the exercises on pain and compliance with the exercises as well as their nature, acceptability, and impact in terms of motivation and perceived improvement in mouth opening. Of the 15 patients interviewed, some had complied and some had not during the three and six-month follow-up periods, but compliance in the Therabite® group seemed better at both time points. Patients felt they had to stop or do fewer exercises towards the end of the course of radiotherapy until roughly four weeks after it had stopped because of painful mucositis. They began again when the side effects had abated.

Key feasibility and acceptability messages were: change the wording of the exercise regimen to at “least three times a day” rather than five times a day; stop doing the exercises when the side effects of radiotherapy are at their worst; contact healthcare professionals more regularly.

**Health economics assessments**

Completion rates (at baseline, and at three and six months) of the three health economics measures were: CSRI: 89%, and 100%, at three and six months, respectively; EQ-5D-3L: 90%, 78%, and 87%, respectively; and ICECAP-A: 59%, 49%, and 74%, respectively. Across the time points, overall completion rates were 95%, 85% and 61% for the CSRI, EQ-5D-3L and ICECAP-A, respectively.

Although it was not a core feasibility objective, we also made an exploratory analysis of the cost consequences (from the perspective of the NHS) of the participants who had complete cost and outcome data ($n = 30$) (Tables 2–5).

Table 2 shows the number of contacts with primary and secondary care health services six months after baseline. Differences between the groups were not significant.

---

**Table 2**
Contacts with primary and secondary care health services by 30 participants six months after baseline.

<table>
<thead>
<tr>
<th>NHS primary care:</th>
<th>Therabite (n = 16) Total; mean, median (range)</th>
<th>Wooden spatula (n = 14) Total; mean, median (range)</th>
<th>Mann Whitney p value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer nurse</td>
<td>10; 0.63, 0 (0-4)</td>
<td>6; 0.43, 0 (0-6)</td>
<td>0.313</td>
</tr>
<tr>
<td>General practitioner</td>
<td>51; 3.19, 2 (0-13)</td>
<td>32; 2.29, 2 (0-5)</td>
<td>0.697</td>
</tr>
<tr>
<td>Practice nurse</td>
<td>25; 1.56, 0 (0-14)</td>
<td>7; 0.50, 0 (0-3)</td>
<td>0.637</td>
</tr>
<tr>
<td>Community nurse</td>
<td>128; 8.00, 1 (0-56)</td>
<td>47; 3.36, 1 (0-22)</td>
<td>0.667</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>2; 0.13, 0 (0-2)</td>
<td>18; 1.29, 0 (0-9)</td>
<td>0.294</td>
</tr>
<tr>
<td>Speech and language therapist</td>
<td>43; 2.69, 2 (0-14)</td>
<td>36; 2.57, 2 (0-9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Occupational health therapist</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Dietician</td>
<td>41; 2.56, 1 (0-16)</td>
<td>51; 3.64, 2 (0-11)</td>
<td>0.637</td>
</tr>
<tr>
<td>Other healthcare professional</td>
<td>81; 5.06, 1 (0-52)</td>
<td>28; 2.00, 1 (0-10)</td>
<td>0.667</td>
</tr>
</tbody>
</table>

NHS secondary care:

| Oncology inpatient ward (bed days) | 256; 16.06, 9 (0-78) | 217; 15.50, 6 (0-74) | 0.790 |
| Medical inpatient ward (bed days) | 31; 1.94, 0 (0-14)   | 51; 3.64, 0 (0-30)   | 0.854 |
| Intensive care inpatient ward (bed days) | 0                             | 0                              | 1.000 |
| Other inpatient ward (bed days)     | 6; 0.38, 0 (0-6)      | 0                              | 0.790 |
| Physiotherapist inpatient consultation | 62; 3.88, 0 (0-55) | 3; 0.21, 0 (0-2)     | 1.000 |
| Speech and language therapist inpatient consultation | 4; 0.25, 0 (0-2) | 4; 0.29, 0 (0-2)    | 0.918 |
| Dietician inpatient consultation    | 56; 3.50, 1 (0-25)   | 38; 2.71, 1 (0-20)    | 0.822 |
| Occupational health therapist inpatient consultation | 2; 0.13, 0 (0-2)     | 0; 0.00, 0 (0-0)     | 0.790 |
| Other inpatient consultation        | 3; 0.19, 0 (0-2)     | 0; 0.00, 0 (0-0)     | 0.580 |
| Outpatient visits                   | 76; 4.35, 1 (0, 30)  | 74; 5.29, 1 (0, 58)  | 1.000 |
| Accident and emergency              | 1; 0.06, 0 (0, 1)    | 18; 1.29, 0 (0, 12)  | 0.154 |

$^a$ Significant at 5% significance level.
Table 3 shows the mean costs of all contacts with NHS primary and secondary care services over the same period. The Therabite® intervention cost £251.94/patient compared with £2.84/patient for wooden spatulas. The mean (SD) total cost/patient was £12 946 (£14 137) in the Therabite® group and £12 561 (£13 675) in the spatula group (£385 more in the Therabite® group; bootstrapped 95% CI: -£8916 to £10 014).

Table 4 shows mean EQ-5D-3L index scores, mean (SD) quality-adjusted life years (QALY) and incremental mean (SD) QALY between the groups over the six-month period. Change in mean ICECAP-A index scores between study time points and the difference in change in the mean ICECAP-A index scores between groups over the six-month study period were assessed for 19 of the 30 participants who had complete ICECAP-A data (Table 5).

Discussion

A recent systematic review has shown that exercises with devices to mobilise the jaw after treatment yield better results than no exercise in patients with radiotherapy-induced trismus after treatment for cancer of the head and neck. The Therabite® intervention was no more effective than use of wooden spatulas or active range-of-motion exercises. However, Pauli et al reported that mouth opening increased more after use of a Therabite® device (a wooden clothespeg with an attached rubber band), although compliance was comparable. An earlier study by Buchbinder et al also showed that the Therabite® was more efficient than unassisted stretching or stretching using...
Table 4
Mean (SD) EQ-5D-3L index scores, mean (SD) quality-adjusted life years (QALY) and incremental mean (SD) QALY six months after baseline.

<table>
<thead>
<tr>
<th></th>
<th>Therabite (n = 16)</th>
<th>Wooden spatula (n = 14)</th>
<th>Incremental mean QALY between groups(^a) (bootstrapped 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D-3L index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.6914 (0.1863)</td>
<td>0.6209 (0.2806)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>0.6935 (0.2523)</td>
<td>0.6824 (0.2999)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>0.3283 (0.1082)</td>
<td>0.7481 (0.1844)</td>
<td></td>
</tr>
<tr>
<td>QALY over 6 months</td>
<td>0.3283 (0.1082)</td>
<td>0.7481 (0.1844)</td>
<td>-0.0137 (-0.0978 to 0.0706)</td>
</tr>
</tbody>
</table>

\(^a\) Incremental mean QALY between groups = mean QALY for intervention group minus mean QALY for control group.

Table 5
Mean (SD) ICECAP-A capability index scores, change in mean ICECAP-A index score between study time points and difference in mean (SD) change in scores between groups six months after baseline (n = 19/30).\(^b\)

<table>
<thead>
<tr>
<th></th>
<th>Therabite(^a) (n = 8)(^b)</th>
<th>Wooden spatula (n = 11)(^b)</th>
<th>Difference in mean change scores between groups(^a) (bootstrapped 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICECAP-A capability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>index scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.8733 (0.1092)</td>
<td>0.8914 (0.1524)</td>
<td>-0.0347 (-0.1726 to 0.0828)</td>
</tr>
<tr>
<td>3 months</td>
<td>0.8095 (0.1967)</td>
<td>0.9175 (0.0927)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>0.8551 (0.1209)</td>
<td>0.9079 (0.1506)</td>
<td></td>
</tr>
<tr>
<td>Change in mean score</td>
<td>-0.0182 (0.0873)</td>
<td>0.0165 (0.2029)</td>
<td></td>
</tr>
<tr>
<td>between baseline and 6 months</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Difference in mean change scores between groups = (Mean change score for intervention) minus (Mean change score for control).

\(^b\) ICECAP-A analysis was conducted on 19 out of 30 participants who had complete ICECAP-A data (n = 8 Therabite\(^a\) group, n = 11 wooden spatula group).
Limitations of the study

Patients who felt a tightening of the jaw before radiotherapy were included in the study, but those in whom it may have developed during treatment were omitted. This could be considered in a more adaptive study design such as a stepped wedge design in which patients would be randomised as soon as the jaw tightened.

A larger group of patients and more study-specific follow up may have provided more representative data on both the quantitative and qualitative aspects of the study. Telephone interviews with a larger group of patients would have provided additional information about the problems they face. Patients’ suggestions to alter the exercise regimen to “up to five times a day”, when exercises were more likely to be done three times a day, have not been validated. A dose-effect analysis of a new protocol would be required in future studies.

The attrition rate for this study, which was set at 25% as in other head and neck cancer toxicity intervention studies, was higher than we expected. This could have been caused by the demands of the prescribed exercise regimen and the difficulty of complying in the presence of severe mucositis.

It would be useful to use a more sensitive scale such as the Gothenburg Trismus Questionnaire to measure trismus-specific symptoms in a full-scale trial, as it can be used to track changes in symptoms. Unfortunately it was not available at the start of our study.

To the best of our knowledge, this is the first study to provide a credible regimen before radiotherapy, and to include a health economics aspect within the design to enable healthcare professionals make evidence-based decisions about treatment and use of resources. The overall response rates for all the health economics measures were good. In line with a study by Clarke et al, our findings show that it is feasible to collect information about health economics in a definitive randomised trial in this group.

In conclusion, this feasibility study has shown that mouth opening had generally increased in both groups, and that exercises during and after radiotherapy can relieve trismus in these patients.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients’ permission

The study was approved by the ethics committee and all patients gave written informed consent before the study started.

Acknowledgements

We would like to thank the dedicated clinical, research, and allied health professional teams in helping to run this study. Special thanks for all patients for their participation, help, and time in assisting with this study.

References


Chapter 5
Perspectives of patients with head and neck cancer on feasibility of undertaking proactive mouth exercises throughout and beyond a course of radiotherapy: a qualitative study.
“The Christie NHS Foundation Trust Hospital acknowledges the support of the National Institute of Health Research Clinical Research Network (NIHR CRN: Trismus RfPB trial (portfolio ID 13415))

Trial registration with clinicaltrials.gov NCT01733797

Keywords
Trismus
Mouth Cancer
Radiotherapy
Proactive Exercise
Feasibility
Qualitative Research
Abstract

Background: Trismus (limited mouth opening) in patients with head and neck cancer can be caused by tumour or its treatment, and have an adverse impact on jaw function, influencing other aspects of quality of life. Exercises are routinely used after trismus has become established. However, little is known about the acceptability, from the patient’s perspective, of performing proactive mouth exercises prior to, throughout and beyond a course of radiotherapy, in order to prevent or ameliorate trismus.

Methods: Fifteen semi-structured telephone patient interviews, nested within a randomised feasibility study, were undertaken to explore patient feasibility of undertaking the study intervention, which was a proactive exercise regimen. Data were analysed using Framework Analysis.

Results: Participants found it acceptable to undertake proactive exercises throughout radiotherapy; however they strongly linked their ability to do so to their stage of radiotherapy and consequent symptoms experienced. Whether participants undertook exercises was influenced by setting a good routine, loss of function and current symptoms. Participants adapted their exercise routine, or stopped exercises entirely, when the side effects of the radiotherapy were at their worst.

Conclusions: The study’s findings have important implications for development of proactive trismus prevention regimens, both in clinical practice and in future research trials. Frequency of proactive exercises needs to be modified at different stages of the treatment pathway, with a planned break when side effects of radiotherapy are at their worst. Future trials in this area would benefit from adaptive study designs.

Keywords: Qualitative, Trismus, Radiotherapy, Proactive exercises, Feasibility
Introduction

Around 7,900 patients were diagnosed with cancer of the mouth in the UK in 2014 [1]. Standard treatment for these patients uses a variable combination of surgery, radiotherapy and chemotherapy [2,3]. These patients experience debilitating effects of treatment including xerostomia, mucositis, dysphagia and trismus [2]. Short and long term morbidity may include physical, functional and psychological problems including lack of self-esteem and even contemplation of suicide [4,5]. This in turn has been shown to interfere with eating, swallowing, speaking, and oral hygiene, greatly impacting on quality of life [6,7]. To help combat trismus, patients are typically encouraged to undertake jaw-stretching exercises. Two devices widely used in trismus management are the Therabite® Jaw Motion Rehabilitation System™ [8] and wooden spatulas, which are flat-stacked lengthways in the patients mouth.

The Trismus multi centre feasibility study (Trial registration with clinicaltrials.gov NCT01733797) randomised patients to receive either Therabite® or wooden spatulas (current standard treatment) as a proactive intervention for prevention and amelioration of trismus. The study addressed efficacy, cost effectiveness and acceptability of these interventions during radiotherapy and its design was informed by the Medical Research Council (MRC) Complex Intervention Framework [9, 10]. Patients with oral or oropharyngeal cancer followed a proactive exercise regime throughout radiotherapy, and results have been previously reported [11].

Methods:

Nested within the Trismus study was a qualitative study, which consisted of semi-structured telephone interviews designed to explore participants’ perspectives on the acceptability of undertaking mouth exercises during and after radiotherapy. The study, was approved by the North Manchester Ethics committee (12/NW/04/14) and all patients gave written consent prior to conduct of the telephone interviews. The qualitative study was designed with input from a Patient User Group. Participants’ anonymity was maintained by assigning a unique identifier to each patient dataset. The interview topic guide addressed patients’ perceptions of the benefits and challenges of undertaking exercises; how they undertook their exercise...
regimen; views on the usefulness of proactive exercise and its acceptability during a course of radiotherapy and beyond.

**Participants and Settings:**
Trial participants were recruited from three cancer centres in England, per criteria detailed in Table 1. The trial intervention protocol involved participants commencing Therabite® or spatula use approximately three weeks post-surgery and /or three weeks pre radiotherapy until six months after the start of the intervention [12]. All Trismus trial participants (N=73) were invited to participate in the nested qualitative study on a voluntary basis.

**Procedures:**
Recruitment to the qualitative study took place after the trial’s six month primary end point; this was to ensure that participants had completed the study, had relevant experience of the trial interventions and were able to discuss these in similar terms. Since participants’ locations of residence were geographically dispersed, all interviews were conducted by telephone, at a time selected by the participant. All interviews were conducted by the same researcher (RL) and transcribed verbatim. Field notes were also made during and after each interview. Consolidated Criteria for Reporting Qualitative Research (COREQ) guidance [13] was drawn upon to enhance the rigour of the qualitative study.

**Data Analysis:**
The data were analysed using Framework Analysis [14], which involves initial familiarisation with the transcripts; identifying a thematic framework which is then indexed, charted and finally mapped and interpreted in a transparent and reproducible manner. Data analysis was led by RL, with input from AC and PK.

**Results:**

**Participant characteristics:**
15 trials participants consented to interviews (see Table 2). Per the Trismus trial inclusion criteria (Table 1), all participants in the nested qualitative study had experienced subjective tightening of the prior to study entry and all had received radiotherapy.
Overview of the Interview Data:

The core theme of the timing of the intervention and its relationship with other aspects of acceptability of the exercise intervention which arose from the data are summarised in Table 3. The categories of everyday tasks, treatment side effects whilst at their worst and abating are discussed below, with the core theme of timing woven throughout. Participants talked in very similar terms about acceptability issues regardless of which device they were using.

Acceptability of the intervention on everyday tasks

Prior to radiotherapy, participants reported being able set a good exercise routine and were well motivated and supported to adhere to it from day to day. The majority of participants reported that they were able to see the benefits of regular jaw exercises. These included increases in function of the jaw allowing a feeling of ‘release’, improved mobility of the jaw itself, enabling participants to eat, communicate and brush teeth better. Due to these perceived benefits participants had in general, hope and a positive attitude towards performing the exercises to a set routine.

As long as there is an improvement I will keep doing it. It is not really a problem for me...Well we used to do the measuring so it gives you sort of hope when you are doing them and progressively you can start to open up your mouth just a little bit more, so I think that was the main thing, it gave me hope’ (051).

During this initial phase participants were generally able to cope with exercising five times a day; however some participants felt that exercising five times a day was too time consuming even at this point.

‘to find 5 times in a day, you no sooner after putting it away were having to get it out again. I actually wrote on the form explaining this was too much. I do think that if it was three times a day, it would be more appropriate’ (034).
Many participants commented on how partners had helped them set up a good routine through the study by providing support, and reminders to do the exercises.

‘...it was a difficult time mentally and psychologically but I am a very positive person and my wife is amazing’ (032).

Acceptability of the intervention when side effects are at their worst

Participants’ ability and desire to undertake exercises during the second half of the course of radiotherapy was strongly influenced by the side effects of radiotherapy such as pain, dryness, soreness, in the mouth and insertion of gastroscopy.

‘when you have had major surgery in your mouth and then treatment afterwards my mouth my throat and my tongue, what is left of my tongue is just one pure blister and to actually put something in your mouth when you can’t even swallow water is just a no go and you are just not going to do it (034).

‘... because my neck was so sore because once I had finished the radiotherapy I came home but I still had a tube up my nose so I couldn’t even swallow water and my neck was just blistered, just full of big popping blisters..’ (036).

Most participants reported being unable to cope with the exercises during the latter part of radiotherapy due to their mouths being extremely painful and because of nausea or vomiting being experienced during chemo radiotherapy.

‘...I did the stretching as far and as wide as I could physically tolerate, you know it was just so difficult not being able to open it properly so I thought this is my best chance of getting it right by doing it and pushing myself. Unfortunately I was very sick during the treatment as I had radiation treatment as well as chemo. I was really poorly with it and during that time when I found it very difficult to do the jaw exercises ...I just couldn’t bear the thing in my mouth I was just heaving’ (027).
Overall, participants reported feeling that they had significant cancer treatment-related issues to deal with at this stage of the treatment pathway. Their focus was therefore on ‘getting through the treatment’, ‘getting on with life’ and coping with the sickness and pain.

‘I think it was because, even now my mouth is so sore, you know and I just didn’t want to do it any more, you know it was just so uncomfortable. I suppose really, ...but at the end I felt so ill I just didn’t want to think about it I just wanted to get on with my life and I think that’s perhaps why I didn’t because it just took me back to a very unpleasant time’ (007).

Taken together, these issues led to a marked reduction in the acceptability of the intervention at this phase of the treatment cycle. Participants reported this as persisting beyond completion of radiotherapy and into the period immediately post-treatment, when side effects were still ongoing.

**Acceptability of the intervention when treatment side effects are abating**

Following resolution of acute toxicity, participants’ narratives demonstrated recovery from radiotherapy side effects and, in most cases, feeling able to recommence mouth-opening exercises.

‘Did exercises more than five times a day or more often as could see the benefits. Only took a break for two weeks during radiotherapy and then began the exercises again’

Many participants reported feeling motivated to re-start the exercises due to being able to see that their mouth opening had increased or had not deteriorated and attributing this to the exercises. This was important to participants, because at this stage their priorities were re-focusing activities of daily living.

‘Well it definitely helped me to increase the opening size of my mouth and it actually improved the flexibility for me to open my mouth, definitely’ (020).
‘At the start only fit 20 or so Wooden Spatula into mouth and towards the end could fit in 44/45 Wooden Spatula’ (055).

‘At the start of exercises could not even fit a fork into my mouth and towards the end 100% better’ (032).

For some participants, tangible improvement in their mouth opening gave them hope. For others, being able to contribute to their own management was valued.

**Discussion**

This nested qualitative study has shown that the acceptability of carrying out proactive exercises throughout and beyond radiotherapy, is complex and multi factorial. Factors other than the nature and delivery of intervention itself impact on its acceptability, and this must be borne in mind when developing and delivering proactive exercise regimens for trismus prevention. Our findings demonstrate that the chronology of radiotherapy toxicities during and after treatment plays a vital role in the acceptability of proactive trismus prevention regimens for this group of patients. They further demonstrate that other concerns, such as mucositis, nausea and vomiting, hospitalisation for gastrostomy insertion - all of which are prominent when side effects of treatment are at their worst – can deter even the most stoical and motivated patients from undertaking mouth exercises, and hence require proactive management. Our findings align with those of Astrup’s group who have reported that at study enrolment of patients receiving radiotherapy for head and neck cancer, the symptom burden includes difficulty swallowing, dry and sore mouth [15].

Melchers *et al* have reported on Therabite® exercise adherence in patients with radiation induced trismus and concluded from semi-structured in-depth interviews that internal motivation to exercise, perceived positive treatment effect, self-discipline and having a clear exercise goal influenced Therabite® exercise adherence positively [16]. Our data support these findings, but add an important dimension, not previously identified, regarding the timing of the intervention. Melcher’s group underpinned their assessment of acceptability with Ajzen’s theory of planned behaviour. Whilst this is an appropriate theory, in that it addresses health-related behaviour, developments in the field of implementation science have led to the generation of
several models, which bring together a number of theories of health behaviour. These include Sekhon et al’s Theoretical Framework of Acceptability (TFA) [17], the Theoretical Domains Framework (TDF) [18] and the Capability Opportunity Motivation –Behaviour model and the associated Behaviour Change Wheel (COM-B) [19]. The TFA has been selected for use in this study because of its strong focus on the acceptability of medical interventions from the patients’ and was therefore well suited to our study (see Fig 1). The authors of the TFA do not rank the constructs in any order of priority, hence our representation in a cyclical fashion. The current findings suggest that patients may, generally, be motivated to complete the exercises - consistent with 'self efficacy' within the TFA. However, the overwhelming nature of the cancer experience, including side effects of radiotherapy, plays a critical role in whether they can do so, according with the construct of 'burden' in the theoretical framework. However, our data diverge from the TFA in a number of ways, namely that this theoretical framework does not take into account the impact of the underlying medical condition on acceptability of an intervention nor does it consider whether/how the timing of an intervention, particularly within a cycle of treatment (such as radiotherapy) may impact on acceptability. These need to be considered in future intervention development in this area. The clear message from participants was the need for modification of the exercise regimen to align with their current experience of side effects of radiotherapy.

Pauli et al, in their study of an exercise intervention in patients with radiation-induced trismus, found that most participants exercised three times per day, as opposed to their per protocol five times per day (which was in the per-protocol frequency in our trial) [7]. Our participants also found exercising five times a day too time consuming, even when not experiencing treatment side effects and found exercising three times a day more suitable. Having a less onerous exercise regimen may therefore be a way forward to enhance acceptability of proactive exercise regimens, but would require future studies to assess efficacy. This finding has important implications for practice and, particularly, for trials, where the focus is on consistency in delivery of the intervention.

The findings suggest the need for advance consideration of side effects, potentially through adoption of adaptive trial designs in future trials in this area [20]. This might take the form of a scheduled break from the exercise intervention when side effects
are at their worst or of allowing trial participants to individually tailor and adapt their regimen, within agreed parameters, during the trial. Greater proactive symptom management in trial participants who report significant problems with pain, soreness and ulceration in the mouth is also clearly indicated.

To our knowledge this is the first study to assess in depth participants’ views on the acceptability of performing proactive mouth exercises with a device through a course of radiotherapy and beyond. The findings provide valuable, patient-generated insights which could enhance the acceptability of exercise interventions designed to relieve and prevent trismus in people with oral or oropharyngeal cancer. Our study included individuals who had had primary surgery or chemotherapy and radiotherapy, giving a diverse patient population and thus enhancing the transferability of findings. Group interviews may have provided richer data as participants may have bounced ideas off each other [21]. A prospective study of assessment of acceptability as an element of process evaluation may be of value in future intervention studies, to better capture and understand how patients adapt their exercise routine over time.

The findings from our study add to the growing body of evidence regarding the importance of adequate acceptability testing and process evaluations in trials, in order to enable development of interventions and trial protocols which are more likely to succeed and be subsequently adopted in clinical practice.

**Conclusions:**

This study provides a unique patient perspective of what it is like for people with oral and oropharyngeal cancer to perform mouth exercises through radiotherapy and up to six months post treatment. This study also highlights the need to identify the optimal exercise regimen, including the relative efficacy of lower frequency three times daily regimens compared with current five times daily routines. Overall, the findings point to the need for greater individualisation and patient control over their exercise regimen to improve acceptability of proactive exercises throughout and beyond a course of radiotherapy. The findings underscore the need to enable patients to have more input into designing and, if needed, modifying their exercise regimen to take account of their current circumstances. This could be achieved by the use of adaptive
study designs. Consideration should be given to including a pre-planned break (e.g. from two to six weeks), from exercises when radiotherapy side effects are at their worst.

**Conflict of Interest**
None

**Ethics statement/confirmation of patients permission**
The study was approved by the Ethics committee and all patients gave written informed consent prior to study commencement.

**Acknowledgements**
We would like to thanks all the patients who gave up their time to participate in this nested study; all the study sites and staff therein who supported this research and the members of the Patient User Group.
References


[3] "How are head and neck cancers treated? was originally published by the National Cancer Institute https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet, 10.04.2018


compare the use of Therabite® with wooden spatulas to relieve and prevent trismus in patients with cancer of the head and neck.: doi.org/10.1016/j.bjoms.2018.02.012.


[21] Novick G. Is there a bias against telephone interviews in qualitative research?

*Res Nurs Health* 2008 31, 4 391–398
**Table 1: Trismus trial inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provision of signed, written informed consent</td>
<td>&lt;12mm mouth opening (cannot use Therabite*)</td>
</tr>
<tr>
<td>Aged 18 years and older</td>
<td>Cognitive impairment as judged by the clinicians</td>
</tr>
<tr>
<td>Able to read and write English sufficiently to be able to complete questionnaires</td>
<td>International patients treated who will not have routine UK follow up</td>
</tr>
<tr>
<td>Stage 3/4 oral and oropharyngeal cancer patients undergoing:</td>
<td>Anatomically unable to use Therabite® (for example patients who may only be partially dentate and to use the Therabite® would place extreme stress on the existing teeth)</td>
</tr>
<tr>
<td>Primary chemoradiotherapy or post-operative radiotherapy</td>
<td>Previous surgery or RT treatment to the head and neck</td>
</tr>
<tr>
<td>or post-operative chemoradiotherapy</td>
<td>Any patient who has no tightening of the jaw</td>
</tr>
<tr>
<td>All patients will receive 60-70 Gy in 30-35 fractions over 6 to 7 weeks to the region of the pterygoid muscles.</td>
<td></td>
</tr>
<tr>
<td>All patients will have at least some trismus as indicated by subjective tightening in the jaw.</td>
<td></td>
</tr>
<tr>
<td>Intervention used</td>
<td>Gender</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Therabite® = 9</td>
<td>Males=11</td>
</tr>
<tr>
<td>Wooden spatula= 6</td>
<td>Female=4</td>
</tr>
</tbody>
</table>
Table 3: Summary of the Findings

<table>
<thead>
<tr>
<th>Categories</th>
<th>Everyday tasks</th>
<th>Treatment side effects at their worst</th>
<th>Treatment side effects abating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Categories</td>
<td>Eating</td>
<td>Feeling ill</td>
<td>Improvement in function</td>
</tr>
<tr>
<td></td>
<td>Brushing teeth</td>
<td>Soreness</td>
<td>Socialising</td>
</tr>
<tr>
<td></td>
<td>Communication</td>
<td>Nausea and vomiting</td>
<td>Back to work</td>
</tr>
<tr>
<td></td>
<td>Well motivated</td>
<td>Dryness</td>
<td>Give something back</td>
</tr>
<tr>
<td></td>
<td>Good routine</td>
<td>Mucositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Support network</td>
<td>Ulcers/blisters on tongue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercises will help</td>
<td>Hospitalisation: PEG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time consuming</td>
<td>Bigger cancer issues</td>
<td></td>
</tr>
</tbody>
</table>

Core category: Timing of the Intervention
Figure 1. Proposed model, depicting acceptability of proactive exercise, during and beyond a course of radiotherapy, from patients’ perspective, using the Theoretical Framework of Acceptability [17] as a tool to explain the findings.
Chapter 6: DISCUSSION

The chapters in the thesis have been framed around questions regarding how trismus is best defined; whether it is a common clinical problem after radiotherapy and what the standard treatment is in the UK, once trismus is established. Reviewing the literature demonstrated that treatment of established trismus gives modest improvement at best, raising questions regarding whether proactive exercises before trismus becomes established would be helpful and whether these would be acceptable to patients. Therefore with these in mind, the purpose of the work reported in this thesis was to design a robust interventional study to prevent or ameliorate trismus in a way that was both feasible and acceptable to both healthcare providers and patients.

The objectives have been addressed in a series of publications and will be discussed in this chapter with reference to the existing literature. Other points for discussion include implications of the research, recommendations, and study limitations including personal reflections.

To provide information on the first question, I carried out a UK survey (39 specialists representing 35 centres) of current standard practice for treating trismus. The survey provided evidence of lack of uniformity in the assessment and management of trismus across the UK; demonstrated that trismus is not being identified, treated or followed up in a consistent manner and showed that patients are not given the same treatment options throughout the country (Lee and Slevin 2011). It was clear from this survey that the two main devices used in the UK to treat radiotherapy induced trismus were firstly, the wooden spatulas followed by the therabite device (Chapter 2).

The first objective was addressed by the collection of demographic, surgical and HRQoL data resulting in factors that could be predicted for surgical patients regarding development of trismus. The incidence of trismus and its effects on HRQoL from pre surgery to immediately post-surgery to 6 months post radiotherapy given post operatively have been reported on in Chapter 2. A threshold of ≤ 35mm (incisor to incisor) was used as the definition for trismus in this group of patients (Dijkstra et al., 2006).

The findings from the survey (Lee et al., 2011) and observational prospective work (Lee et al., 2012) indicated that trismus was indeed an underreported problem and that the increase in trismus was evident from pre-treatment to surgery and post radiotherapy. This led to the understanding that trismus was a problem prior to radiotherapy and indeed post...
radiotherapy, which needed addressing. Since, a trend of increased trismus was shown after radiotherapy, it was hypothesised that starting proactive exercises during radiotherapy may prevent or relieve trismus. Having consulted the literature on how best to test this hypothesis, the original MRC framework for complex interventions (Campbell et al., 2000) was adopted.

With the survey, prospective observational and literature data, the study design chosen was a randomised, prospective feasibility study (Phase 2).

### 6.1 Rationale for the Study Design

A randomised feasibility study was selected as it is perceived to reduce study bias (Chambers et al., 1981) as well as clarify patient recruitment, compliance and outcome measurement. This decision was taken in line with the collective results of the survey carried out to gain insight as to which was the current standard treatment options nationally being used to treat trismus. The results of this survey showed that wooden spatulas (41%) were used slightly more often, to treat trismus, with the therabite (35%) being used less frequently. The limited literature suggested that the use of therabite may have a better out-come in increasing maximum mouth opening than using wooden spatulas to exercise the jaw (Table 1). These published studies were, however, conducted on very small number of patients and without comparators. It was deemed unethical to withhold treatment from one cohort of patients (ie have a ‘no intervention’ arm), therefore patients were randomised to receive either the wooden spatula or the therabite device, as these are treatment options that are currently being used in routine practice (Chapter 3).

Our data and others have reported that patients with oral and oropharyngeal cancers have been shown to be the biggest group to present with trismus both at pre and post treatment (Teguh et al., 2008; Steelman et al., 1998; Ichimura and Tanaka, 1993). This is also in agreement to the findings of Fingeret and Scott, where both groups have reported that stage 3 or 4 oral and oropharyngeal patients have an increased risk of developing trismus (Fingeret et al., 2009, Scott et al., 2008). For our proposed study design we selected stage 3 or 4 oral oropharyngeal patients as this cohort of patients, in our data analysis
also showed the greatest degree of presenting with trismus pre and post-surgery (Lee et al., 2012).

Other reported RCT intervention studies have used the objective measurement of 35mm or less as an inclusion criterion (Chapter 1, table 1) in order to relieve established radiation induced trismus. Therefore, the assessment of a subjective tightening of the jaw was a crucial one, since medical teams made the decision on whether to treat trismus or not dependent on functional impairment from the patient’s perspective (survey data, Chapter 2). It was not part of routine clinical practice to measure maximum mouth opening at any point in the patient treatment pathway. It was also felt that patients who did not report a subjective tightening may not see the merits of taking part in the study or indeed feel motivated to use an intervention.

From the literature, it was evident that radiotherapy was a risk factor for patients to develop trismus. Unfortunately all the studies reviewed were cross sectional in design and had no pre radiotherapy trismus status. If patients were used to using either the wooden spatulas or therabite prior to radiotherapy treatment, it was reasoned that the patients may be more compliant if they were accustomed to using the devices prior to side effects of radiotherapy preventing them from initially starting the intervention.

The rationale for using only the EORTC 30&35 questionnaires was derived from our preliminary study which showed that both the UWQoL and the EORTC 30 picked out the same significant variables at the same time points (Chapter 2). Therefore, it was decided to reduce the burden on the patients by collecting just the EORTC 30&35 questionnaires. Cann et al., reported that postoperative radiotherapy was the clinical parameter that affected health related HRQoL, but again there was no pre-treatment data to compare the variables, as this was a pilot, cross sectional study carried on a small number of patients. They and others have reported the affected HRQoL items were all associated with eating problems, for example use of feeding tube, nutritional supplements, swallowing, social eating, mouth opening and dry mouth which the combined EORTC questionnaires were able to pick out (Cann et al., 2005, Huguenin et al., 1999). Cann et al., also report that there was no significant difference in HRQoL in these patients who were reviewed either less than or greater than a year apart. Our data implied that the worse problems faced by our trismus patients were experienced prior to treatment and again at post surgery and these parameters were back to pre-cancer levels at 6 months post treatment. Therefore, the duration of our planned study was 6 months posttreatment. The reported literature also supports the findings that there is no
statistical difference between HRQoL variables between 6 months and 12 months post treatment Goldstein et al., 1999; Goldstein et al., 2007; Chundu et al., 2005; Mehanna et al., 2006; Rogers et al., 1999; Shepard et al., 2004; Wells et al., 1998), indicating that the proposed six month follow up was justified.

6.2 Adaptive changes made to the Protocol

During the course of the study it was necessary to make some changes to the protocol in order to improve recruitment. It was hoped that by modifying the inclusion criteria by including patients with tonsillar cancer and opening more sites would achieve this end. Furthermore, the proposed reference groups were changed to individual telephone interviews, as it was hoped that this would provide greater access to patients to guage their perspective. These adaptive changes to the protocol are discussed and justified below:

1. The original thought behind including surgical patients with free flap was based on the results from Chapter 2 and the publication by Scott et al., 2011 where oral orophyngeal patients who had undergone free flap surgery were more likely to be stage III and IV tumours, which correlated with greater prevalence of trismus post surgery. A review of the recent literature has shed some light on the incidence of trismus from different head and neck cancer sites. Pauli et al., 2016 had reported that patients with tumours of the tonsil are more prone to develop trismus. Their results show that 24 out of 75 (32%) tonsillar head and neck cancer patients developed trismus in the study cohort. In light of this publication the proposed inclusion criteria (RfPB documents appendix) were amended to capture these patients, as most tonsillar surgical cancer patients would not receive free flap during surgery and thus would have been excluded from the study.

2. It was originally proposed that the number of patients required could be recruited from two centres from the North West of England. It was evident that the predicted recruitment targets were not being met. The reasons for this may have been due to several factors including the following: Patients at pre-radiotherapy treatment may not have started to experience any tightening of the jaw and thus would be ineligible to take part in the study, even though these patients may have
met the objective definition of trismus. Our previous publication and others (Scott et al., 2011, Lee et al., 2012) have shown that the prevalence of trismus increases post surgery and again post radiotherapy treatment. It is not known at which point during radiotherapy patients may start to experience tightening of the jaw. As the inclusion criteria asked the patients if they had experienced any tightening of the jaw pre radiotherapy our pool of eligible patients would be unavoidably reduced. The actual recruitment rates were lower than the predicted recruitment rates (see protocol). In order to compensate for lower than predicted recruitment rates a change in the protocol was proposed to open up other interested centres within England. These changes did help with study recruitment rates.

3. Due to the initial slow recruitment it had not been possible to select 8 to 10 patients at a similar time point to set up the focus groups at the allocated time points. The work of Polit and Hungler 1991 and Polit and Beck 2018 chapter 12 were consulted in order to ascertain a robust method to gain an insight of the individual patient lived experience of what it was like to undertake the exercises through radiotherapy and beyond. Therefore, it was of paramount importance to have an alternative format to ascertain ‘patient acceptability to intervention’, focus group interviews were changed to individual telephone interviews. The question of whether there is a bias against telephone interviews has been extensively reported on by Novick (2008) and the author reports that there is no evidence in the data to support this assumption and reported that telephone interviewees are more likely to render sensitive information more freely (Novick 2008). Both focus group and telephone interview methods use the COREQ 32 item checklist to enhance the transparency of reporting of the findings (Tong et al., 2007), Chapter 5 in thesis. Table 2 below highlights the main differences between the reference groups I ran, prior to conception of the thesis and the individual telephone interviews I conducted as part of the qualitative aspects of this body of work. As can be seen there are merits and disadvantages to both these methods but one to one interviews were chosen due to accessibility to study patients and reducing travel burden on them once we introduced more sites.
Table 2. Interview Styles: Group Interviews verses Individual telephone Interviews

<table>
<thead>
<tr>
<th>Results of Discussion with my Reference Group, in preliminary work, prior to thesis.</th>
<th>Results of my Experience of Individual Telephone Interviews as part of thesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>May encourage patients to express themselves freely if others feel the same as them….</td>
<td>No influence from other patients, would get patient view</td>
</tr>
<tr>
<td>Patient views not similar, therefore may not want to go against the group.</td>
<td>Patients may be able to explore specific topics relevant to themselves instead of generic topics.</td>
</tr>
<tr>
<td>Some patients have expressed a view that they don’t want to be approached for the group discussion but happy to ask them individually</td>
<td>Patients maybe keener to participate because they would not be conscience of meeting other patients due to their appearance or problems with speech due to cancer/treatment.</td>
</tr>
<tr>
<td>Talk about issues relevant to the group as opposed to the individual</td>
<td>Unable to jump on scheduled visits to reduce patient time and travel</td>
</tr>
<tr>
<td>May not be able to get a sample of 7-8 patients at similar time points, practice issue.</td>
<td>Greater pool of potential patients willing to consent for individual discussion, as no visits needed.</td>
</tr>
</tbody>
</table>

R.Lee observations from reference group discussions and individual telephone interviews.

The telephone interview method reduced the burden on patients having to travel to the hospital from various geographical sites especially during a period when they may have still been feeling the side efforts of the radiotherapy. Fifteen patients were interviewed over the telephone thus making this choice of collecting qualitative data by individual telephones justifiable. There was no travel budget to help with travel costs which may have deterred some patients from attending the focus groups. It is also recognised that this group of head and neck cancer patients are more likely to be from lower socioeconomic groups making paying for extra visits more demanding (Al-Dakkak, 2010, Conway et al., 2010). Due to the strong association made by Walkers group between socioeconomic deprivation in patients with head and neck cancer and travel time to cancer treatments centres, makes the choice of conducting telephone interviews the most appropriate method to collect qualitative information from this group of cancer patients but also in future larger scale studies (Walker et al., 2017).

6.3 Critique of the Methods used

The proposed study design was a, longitudinal, feasibility study and the limited literature suggested that the use of therabite may have a better outcome in increasing maximum mouth opening than using wooden spatulas to exercise the jaw (Table 1). These published studies were conducted on very small numbers of patients. A randomised
A ‘stepped wedge’ research design may be more appropriate in future trials, in which the whole group will eventually receive the intervention, but with randomisation built into the phasing of the study (Brown and Liford, 2006; Hemming et al., 2015). This may have helped to increase the recruitment rate as patients may well have experienced tightening of the jaw during radiotherapy treatment and therefore been eligible for study entry at that point. However, although patients are seen every week during radiotherapy, it was not possible to assess patients for tightening of the jaw, due to resourcing constraints within the study. Consideration of this type of adaptive study design would be warranted when conducting a future definitive phase III trial, with a view to better personalising the study design to fit in with patients’ needs. For example when subjective tightening becomes evident, may be at different stages of radiotherapy for different patients. This would need to be properly scoped prior to using the stepped wedge design as a model as there may be specific time points during radiotherapy that subjective tightening of the jaw becomes more apparent.

The criteria of selecting only oral or oropharyngeal patients with subjective tightening at post surgery and post induction chemotherapy was taken on the premise that both these treatment regimens had not increased the patients maximum mouth opening prior to radiotherapy. This is also shown by the results presented in Chapter 2, in which the trismus incidence rates increased for these post operative surgical patients after radiotherapy. Patients treated by induction chemotherapy were not assessed in this preliminary work, as I only collected data from maxillofacial clinics prior to and after surgery and again post radiotherapy for this body of work. This was rectified in the present study which included patients treated with surgery, as well as induction chemotherapy followed by radiotherapy, as these two pathways represent treatment regimes for oral, oropharyngeal cancers (Parliament et al., 2005). However, our data and others have reported that patients with oral and oropharyngeal cancers have been shown to be the biggest group to present with trismus both at pre and post treatment (Teguh et al., 2008; Steelman et al., 1998; Ichimura and Tanaka, 1993). For our proposed study design we selected patients with stage 3 or 4 oral or oropharyngeal
cancer as these cohort of patients show the greatest degree of presenting with trismus pre and post surgery (Scott et al., 2008) and as a consequence presented a greater homogeneous patient group therefore making the study more robust and minimising bias. Therefore, making this selection of patients in terms of stage (stage III and IV), tumour site (oral and oropharyngeal) and definitive treatment (surgery or chemotherapy prior to radiotherapy) is justifiable and ethical.

3. The duration of our planned study was 6 months posttreatment, as the reported literature supports the findings that there is no statistically significant difference between HRQoL variables between 6 months and 12 months post treatment for head and neck patients receiving radiotherapy (Goldstein et al., 1999; Goldstein et al., 2007; Chundu et al., 2005; Mehanna et al., 2006; Rogers et al., 1999; Shepard et al., 2004; Wells et al., 1998). However, to have a 12 month follow up period would have given us follow up data on whether patients kept up with the exercises and if reduced mouth opening was still a problem for these patients; this is considered further in recommendations.

4. In a recent randomised control study, Loorents et al., 2016, reported on prophylactic training for the prevention of radiotherapy-induced trismus and concluded that they did not feel the need to burden head and neck cancer patients with an intense prophylactic training program during radiotherapy and 12 months beyond. The authors’ selection criteria included patients with greater than or equal to 35mm at study commencement and no restriction on tumour site or stage (Loorents et al., 2016). This conclusion may have been drawn because the patients would have entered into the study with an objective definition of no trismus which equates to 35mm or above, and, may not have presented the patients with any deterioration in function nor associated deterioration in HRQoL as these factors were not recorded. These factors may have been a contributing influence for these patients having little or no motivation to strive towards an improvement nor for maintaining their mouth opening. This is in opposition to our inclusion criteria of a subjective tightening of the jaw since diagnosis of cancer. Patients felt and reported a reduced function in mobilising the jaw as a tightening and hence had the motivation to overcome this by a self-administered intervention. These patient views are in concordance with the loss of function due
to tightening of the jaw that were expressed by the patients in the semi structured interviews.

5. It may have been prudent to use a patient reported screening tool so that patients waiting to be seen in clinic could have indicated if they experienced any problems with jaw opening and to discuss this with the treating teams. This may have helped recruitment rates by alerting the medical teams that jaw opening was a problem and that the trismus study could be discussed with the patient. In a busy clinic environment this may have reduced time in the consultation and helped to identify more patients for the study.

6. I should have carried out a more detailed scoping of the anticipated recruitment rate which was predicted by the clinical consultants to be one patient per week from each of the two centres but was actually, on average one patient maybe every two weeks. This may have given a more accurate rate of actual recruitment, which, over the initial recruitment target of 18 months, was not sufficient to recruit the required number of patients, within the study timelines. In addition, an assessment should have been made at the time of scoping to ascertain the number of stage III and IV oral/oropharyngeal patients indicating a tightening of the jaw prior to radiotherapy, in order to plan more accurately the proposed recruitment rate.

7. As the main researcher, I should have maintained greater regular contact with the patients to understand the reasons for dropout rates from the patients’ perspectives to aid in planning any future Phase III trial. Regular contact with the study patients may have improved if the whole MDT was made aware of the project and if the project had received the necessary support from the speech and language therapists, physiotherapists, rehabilitation restorative dental consultants, all of whom treat hypo-mobility of the jaw.

8. Restorative head and neck dentists have put together guidelines which include trismus management from the MDT viewpoint and have recommended that exercises should start before radiotherapy inorder to provide access to a wider mouth opening for dental procedures to go ahead without impedance. Restorative and rehabilitative dental treatments are done after the mouth has sufficiently healed, which varies from patient to patient (Butterworth et al., 2016).

9. Patients were excluded from the study if their mouth opening was 12mm or below, which was set as the minimum threshold for the insertion of the therabite.
In future large scale studies provision for these patients would need to be made to allow them to exercise with the wooden spatulas initially, and when able to meet the inclusion criteria to be randomised into the study. This would fall into the realm of adaptive or flexible study designs which would make it possible to individualise studies to fit the individual patient needs and at a time that is most beneficial to the patient (Bhatt and Mehta 2016, Thorlund et al., 2018). Pitfalls of adaptive or flexible trial designs will require great care in avoiding unnecessary operational bias by proactively addressing these, specifically in the change in the participant pool (Bothwell et al., 2018). Specifically, this would mean that some patients with a mouth opening of less than 12mm would have already been exposed to some type of exercises prior to randomisation which will change the participant pool and potentially add operational bias.

10. A greater understanding of the work load of research staff and the knowledge of possible competing studies such as the Head and Neck 5000 (Ness et al 2014), which was in progress at the same time, may have helped to reduce the number of HRQoL questionnaires patients had to complete in order to reduce or avoid duplication by greater sharing of study data. This would have to be addressed in future large scale studies.

11. Presentation at more conferences in order to disseminate the findings of the research and to patient-led conferences in head and neck would have helped in providing information to patients and healthcare professionals in order for them to make more informed decisions on how to treat trismus. However, the results of this feasibility study have been written up in layman terms and posted on head and neck charity web-sites such as mouth cancer foundation (http://mouthcancerfoundation.org/news/relief-head-and-neck-cancer-patients-mouth-exercises), and the Christie NHS Trust patient section on head and neck cancer. Contact has also been made with the ‘saving faces’ (http://savingfaces.co.uk/) and ‘the swallows’ charity (theswallows.org.uk/) for inclusion into relevant patient sections of these web-sites.
I have tried to minimise researcher bias and confirmation bias by making myself aware of these in both the quantitative and qualitative aspects of this body of work (Pannucci and Wilkins 2010).
Chapter 7: CONCLUSIONS

Trismus is a common problem in patients with head and neck cancer. Therefore, the overwhelming motivation for this thesis was to provide some ‘hope’ to these trismus patients in order to improve their overall HRQoL, as this group have the lowest HRQoL levels and highest rates of suicide of all cancer patients.

In this thesis a number of studies were performed with the overall aim of ameliorating trismus by developing a novel proactive exercise regime used before, during and beyond a course of radiotherapy. Chapter two has shown that trismus is a common problem in head and neck cancer patients and that, females and those who do not drink alcohol are at particularly high risk for developing trismus. To prevent and treat trismus, patients would benefit from a multidisciplinary management strategy at an early stage in the treatment process. Chapter three describes a protocol regimen for proactive exercises during and after a course of radiotherapy. This intervention was shown in chapter four to ameliorate trismus for stage 3 and 4 oral, oropharyngeal cancers, but we found no statistically significant difference between use of therabite and wooden spatulas (control) in efficacy, compliance, quality of life or hospital/community health services utilisation. What can be said is that the cost of therabite versus wooden spatulas is higher due to the cost of the therabite itself (Chapter 4). These results are in line with the feasibility aspects of this study and as such no statistical claims can be made due to the small sample size and inadequate power calculations. Recommendations for a larger definitive phase III study are made in this thesis, along with how this body of work can inform choice of outcomes for a future definitive study. The nested qualitative study in chapter five provided a unique patient perspective of what it is like for people with oral and oropharyngeal cancer to perform mouth exercises through radiotherapy and up to six months post treatment. This highlighted the need to identify the optimal exercise regime, including the relative efficacy of lower frequency of three times a day from the current five times daily routine. Patients genuinely have the desire to perform mouth exercises but factors such as side effects of the radiotherapy can cause even the most stoical individuals to reduce or temporarily suspend exercises. Overall, the findings point to the need for greater individualisation and patient control over their exercise regimen to improve acceptability of proactive exercises throughout and beyond a course of radiotherapy. The findings
underscore the need to enable patients to have more input into designing and, if needed, modifying their exercise regimen to take account of their current circumstances. This could be achieved by the use of adaptive study designs which has been discussed in chapter seven. Consideration should be given to including a pre-planned reduction or break (e.g. from two to five weeks) from exercises when radiotherapy side effects are at their worst. This might give a template of (for example):

(i) 5 weeks of exercises

(ii) Up to 5 weeks reduced exercises, then

(iii) 25 weeks on when mucositis settles.

### 7.1 Contribution to Research

The vast majority of trismus publications, including systematic reviews, on post radiotherapy therapy for trismus have recommended that interventions should be commenced as soon as possible post radiotherapy. This body of research has shown for the first time, using qualitative and quantitative methods, that proactive exercises to prevent and relieve trismus during radiotherapy are feasible and acceptable to both healthcare providers and patients. This body of work has also contributed to the development and refinement of the intervention and associated outcome measures in order to make a future full scale trial more likely to succeed. This greater understanding of acceptability of proactive exercise intervention will help healthcare professionals to provide guidance on preventing and relieving trismus in this vulnerable group of head and neck cancer patients.

An off-shoot of this work, which is not mine, apart from the identification of trismus patients included in the feasibility study, has enabled radiotherapy researchers at The Christie NHS Foundation Trust to evaluate whether reducing the radiotherapy dose to the masseter muscles and pterygoid muscles could reduce the risk of developing trismus. The authors concluded that limiting the dose to these two structures to $\leq 40$ Gy for tumours not invading the masticatory muscles may improve treatment-related sequelae. (Hague et al.,
Another study analysed data from multi centres concluded, that limiting the dose to the ipsilateral masseter could reduce the severity of trismus (Beasley et al., 2018).

### 7.2 Recommendations

I would like to recommend a definitive phase III, RCT informed by the body of work contained in this thesis and the suggestions listed below:

1. **Foremost, to involve patients from the feasibility study in all aspects of the design of any future definitive study.** As this study came from the concerns of a group of patients it seems fitting to acknowledge their major role in future trial design. Including co-investigator status on grant applications, on published work and patient focussed literature. Recent advances in engaging patients in healthcare has taken the principles of patient participation into newer methodologies such as ‘action research’ (AR) and ‘participatory research’ (PR). These methods look at ways to involve research participants in the process of decision making in an effort to increase acceptability of research to patients by working together as stakeholders within the entire research process (Cordeiro and Soares, 2018). The NIHR has been advocating the involvement of patients and the public in this way, to work together with research teams to provide a different perspective on the research studies (https://www.nihr.ac.uk/patients-and-public).

2. **In order to improve recruitment into a larger study, it may be possible to better identify which patients have problems with mouth opening in a future study by introducing the use of the Patient’s Concern Inventory (PCI), which has been championed by Rogers et al. and is to be investigated in a cluster RCT in two centres, Liverpool and Leeds (Rogers et al., 2018).** Guidance documents could also be written to help guide MDT members on how to refer patients to a future study.
3. Another recommendation to put forward in a larger definitive trial is also to open up more centres to increase recruitment and to follow up patients more frequently. The number of patients required and confidence intervals have been provided in Chapter 3 for 80% power. The recommendations made in this body of work can be used to increase the number of recruited patients and hence increase the confidence of the findings from a definitive study.

4. The use of the Gothenburg trismus questionnaire would also be a great tool to assess trismus related problems such as eating limitations, muscular tension and facial pain scores which can be compared over time in a larger study; unfortunately it only became available half way through the current feasibility study (Johnston et al., 2012, Pauli et al., 2014, Pauli et al., 2016, Lee et al., 2018b).

5. A recent publication outlining preliminary data on a RCT on swallowing therapy and progressive resistance training in head and neck cancer patients undergoing radiotherapy has shown that exercise for swallowing according to protocol is tolerable and feasible. This consisted of performing a swallowing and mouth-opening exercise under supervision by healthcare professionals which may also improve adherence to the exercise regimen (Hajdu et al., 2017, Krekeler et al., 2018). In light of these recent publications, it may be possible in a future definitive study to combine interventions for trismus and swallowing exercises. This may have the added benefit of ameliorating trismus as well as swallowing difficulties which can also be monitored more closely by healthcare professionals by involving the whole MDT, especially the speech and language therapists and physiotherapists (Marrafon et al., 2018).

6. Other recommendations such as limiting the radiation dose to the masseter muscles and pterygoid muscles to ≤40 Gy for tumours not invading the masticatory muscles may also improve treatment-related sequelae such as trismus (Hague et al., 2018).
7. A larger study may also provide an opportunity to collect samples for genotyping, since TGFβ genotype may likely be an important predictor of post radiotherapy fibrosis and hence trismus (Mancini and Sonis 2014). An association has been reported by Rubab et al., 2013, for trismus with human papilloma virus (HPV) in chewable tobacco users. They conclude that the frequency of HPV in oral cavity was high in patients with trismus. It may be possible for a larger study to incorporate a test for p16 in our patient population (Oguejiofor et al., 2013; Faquin 2018). This may also provide general information on HPV, oral/orophygeal cancers and possibly trismus as the fraction of oropharyngeal cancer related to HPV has been increasing worldwide over the past two decades (de Martel et al., 2017).

8. The patients views expressed in the qualitative aspects of this thesis combined with the quantatitave measurement of number of times a day patients exercised show promise that reducing the exercise regime from five times a day to three times a day would increase the acceptability of using either intervention through radiotherapy and beyond; this would need to be tested for effectiveness. But, the widespread adoption of the regimen would require more extensive testing in a future definitive study.

9. This future research study could also plan to look at process evaluations of the interventions which have since been built into the up-dated MRC framework (Moore et al., 2015) in order to assess whether the same processes were being followed in all the study centres. This would ensure that the intervention was used consistently in the same way and would make the data more robust. It would be useful to also include in the patient information sheet as part of the process evaluations and the reasons for ‘drop outs’ if patients were willing to disclose this information. Careful ethical consideration would have to be given in this context as the consent form clearly states that consent can be withdrawn at any time without giving a reason (appendix).

10. It would also be of benefit to interview patients prior, during and after intervention to assess the acceptability of intervention during these time lines
to better understand the issues faced by patients when they occur, and to provide support and advice when required.

11. Future adaptive or flexible trials may benefit from adaptive platform trials technology which have been shown to be more flexible in enabling change in the intervention within the study design if the intervention appears be ineffective and therefore making these types of studies designs more cost effective to run. (Stern and Mehta 2018).

The preliminary work has been performed to plan for a Phase III randomised controlled trial which falls within the scope of the MRC framework of conducting and evaluating complex interventions (Moore et al., 2015). It is hoped that the information in this thesis will inform choice of outcomes and increasing patient recruitment for a future RCT.

7.3 Overall Conclusion

It may be prudent to undertake a smaller feasibility study to look specifically at improving recruitment rates and also reducing dropout rates prior to conducting a definitive phase III RCT. This thesis has highlighted these issues and suggests looking more closely at the informed consent process explaining the rationale more clearly to improve patient engagement. There needs to be greater interaction with the study participants by the research team during the study to reduce drop out as well as greater monitoring of the side effects of the radiotherapy to reduce pain and mucositis as it is reported. Trotter’s group reported a dropout rate as high as 66% in one study due to under management of pain and there are reports of up to 47% patients experiencing dropout due to mucositis in head and neck trials (Trotter et al., 2012, Gussgard et al., 2014). Together these specific patient reported problems point to a need for further feasibility testing.

Head and neck cancer patients are regarded as the ‘Cinderella’ of cancers and as such do not get the same public sympathy as other high profile cancer groups. The findings of this body of research offer the scope for providing head and neck cancer patients
experiencing subjective tightening of the jaw with a proactive exercise regimen that could help to maintain jaw function or ameliorate trismus induced by radiotherapy and hence, improve the HRQoL for this vulnerable group of patients.
REFERENCES


Melchers, I.J., Van Weert, E., Beurskens, C.H.G., Reintsema, H., Slagter, A.P.,
due to head and neck oncology: a qualitative study into the use of the Therabite®. *Int J Oral Maxillofac Surg* 38(9):947-54


Novick G (2008). Is there a bias against telephone interviews in qualitative research? *Research in Nursing and Health*; 31, 4-16.


APPENDICES
Research out-puts


3. *ESTRO*: Turin, Italy Poster: *April 2016*


5. *10th International QOL conference*: Liverpool:
   Oral Presentation November 2016
Dear Dr Slevin

Full title of study: A randomised pilot study of TheraBite® use versus wooden spatula in the amelioration of trismus in head and neck cancer patients

REC reference number: 12/NW/0414
Protocol number: 09_DOG08_43
EudraCT number:

Thank you for your letter dated 12 June 2012. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 01 June 2012. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering Letter</td>
<td></td>
<td>12 June 2012</td>
</tr>
<tr>
<td>Participant Consent Form: General</td>
<td>3</td>
<td>12 June 2012</td>
</tr>
<tr>
<td>Participant Consent Form: Focus Groups</td>
<td>2</td>
<td>12 June 2012</td>
</tr>
<tr>
<td>Participant Information Sheet: General</td>
<td>3</td>
<td>12 June 2012</td>
</tr>
<tr>
<td>Participant Information Sheet: Focus Groups</td>
<td>2</td>
<td>12 June 2012</td>
</tr>
</tbody>
</table>

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor’s responsibility to ensure that the documentation is made available to R&D offices at all participating sites.
Yours sincerely

Ms Cynthia Carter
Committee Co-ordinator
This letter has been signed electronically. If you require a wet ink version please request one from the Committee Co-ordinator by email and it will be sent in the post.

Copy to:  Christine Cooper, Research Assistant, The University of Manchester
christine.cooper@manchester.ac.uk

Alex Molassiotis, Professor of Cancer & Supportive Care, The University of Manchester
alex.molassiotis@manchester.ac.uk

Rana Lee, Head & Neck Researcher, The Christie Hospital NHS Foundation Trust
rana.lee@christie.nhs.uk

Angela Ball, R&D Manager, The Christie Hospital NHS Foundation Trust
angela.ball@christie.nhs.uk
PATIENT INFORMATION SHEET

A randomised pilot study of the Therabite use versus wooden spatula in the amelioration of trismus in head and neck cancer patients.

You are invited to take part in a research study that will investigate maximum mouth opening and the quality of life of patients with mouth cancer at each stage of treatment and post treatment. These questionnaires will assess the symptoms that you may have experienced as a result of your illness or treatment, and how you have been feeling during the past weeks. Please feel free to discuss this information with friends and family and take time to decide if you wish to take part or if you need more information to help you decide.

Thank you for your time taken to reading this information.

What is the study for?
The information obtained from this study will give us the opportunity to evaluate the change in maximum mouth opening using exercises using an instrument called a Therabite or Wooden spatula throughout your treatment and relate this to your overall quality of life and wellbeing, which will be used to assess this treatment. With this information we can assess which type of instrument gives the most benefit to you.

Why have I been chosen?
We would like patients who will be undergoing treatment for mouth cancer which may lead to a change in how wide they can open their mouth, to take part. You will be asked to complete these exercises and questionnaires, which have been specifically developed to assess the quality of life of patients with mouth cancer.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. You can withdraw at any time, you simply need to contact us. A decision to withdraw will not affect the standard of care you receive.

What will happen if I take part?
If you agree to take part in this study, you will be allocated to one of two groups. The reason for this is that we do not know which instrument to use which will provide the best improvement in maximum mouth opening so we need to make comparisons. Patients will be put into groups by a computer which will randomly chose which group you will go into and then the two groups will be compared.

One group will be the wooden spatula group and the other will be the Therabite group. Patients from both groups will be asked if a maximum mouth opening measurement can be taken along your treatment pathway. You will be trained on the use of either instrument to exercise your jaw and asked to keep a log of how wide you can open your mouth at the end of each exercise. You will also be given an electronic instrument containing quality of life questionnaires: this will take approximately 20 minutes to complete. We will ask you to complete these questionnaires before any treatment, then again 3 months after the introduction of the exercises and then 3 months after that. You will be in the study for approximately 6 months from when you begin the exercises. These assessments will be performed at your routine scheduled hospital visits.

What are the possible benefits of taking part?
We hope that both wooden spatulas and the Therabite will help you to maintain your mouth opening or increase it but this cannot be guaranteed. The information we get from this study may help us decide which instrument to choose when treating future mouth cancer patients.

What happens when the research study stops?
If your doctors think that you are getting some benefit from the exercises then you may choose to continue with them, but this will only be decided with talking to you. You will be monitored in the usual way by the medical team.

Will my data be confidential?
The information you and other patients with mouth cancer provide, will be kept confidential. Only the researchers involved in the study will have access to your mouth opening readings and questionnaire data. All the hard copies of the data (mouth opening readings, patient logs) will be kept securely in a locked cabinet. All electronic data collected from the questionnaires will be encrypted and password protected and the touch screen computer looked after.

What will happen to the results of the research study?
Your contribution will help us to find out which form of instrument is best to use in patients with mouth cancer. This information will help us to evaluate the maximum mouth opening whilst using the jaw exercises and see how these can improve your quality of life. Once, this study is finished we maybe able to use one instrument over the other in jaw exercises which may then be used as a standard method for improving other patients mouth opening. The electronic questionnaires may be used to assess quality of life of patients in clinics.

We will publish the results in a respected medical journal and or medical conferences, but this will not be for several years since we are looking at the long term benefits. A committee of independent experts will review the results before this happens. You will not be identified in any report or publication. The results will help us to decide if exercising the jaw before any treatment will improve the maximum mouth opening and overall quality of life for mouth cancer patients in the future.

What happens if something goes wrong?
There is no evidence to show that using the devices will harm you in any way. Your legal rights will not be affected by your agreeing to take part in this study. If you have any concerns about any aspect of this study, you can speak to any of the contacts listed below, who will do their best to answer your questions.

What if I agree and then change my mind?
If you change your mind about taking part in the study you are free to withdraw at any time. You do not have to give a reason. We would however like to ask your permission for the research team to use the data that they have collected. This will ensure that the quality of the research is not impaired. If you do not want us to collect this information please tell your doctor or researcher.

Who is organising and funding the research?
The funding for this study has come from the National Institute for Cancer Research will is part of the Government. The research will be co-ordinated by the Christie Hospital NHS Trust in Manchester and the Aintree University Hospitals NHS Foundation Trust in Liverpool. Your doctor will not receive any payment for entering patients into this study.

Who has reviewed the study?
The South Manchester Local Research Ethics Committee has reviewed the study.

Contact for further information
Dr Nick Slevin, Consultant in Clinical Oncology, Christie Hospital NHS Trust, 0161 4463418
Mr Brian Musgrove, Consultant in Maxillofacial Surgeon, MRI/Christie Hospital, 0161 2768639
Rana Lee, Researcher, Christie Hospital NHS Trust, 0161 4468590
You will be given a copy of the information sheet and a signed consent form to keep.
CONSENT FORM

Title of Project: A randomised pilot study of the Therabite use versus wooden spatula in the amelioration of trismus in head and neck cancer patients.

Name of Researchers: Dr Nick Slevin/ Mr Brian Musgrove/ Rana Lee

Please initial box

1. I confirm that I have read and understand the information sheet dated ................. (version ..1..) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. If I choose to withdraw from the study I consent to my doctor providing authorised Researchers with basic clinical information which would routinely be collected and written in my clinical notes.

5. I agree to take part in the above study.

________________________ ________________ ____________________
Name of Patient Date Signature

_________________________ ________________ ____________________
Name of Person taking consent Date Signature (if different from researcher)

__________________________ ________________ ____________________
Researcher Date Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes
Re: A randomised pilot study of the Therabite use versus wooden spatula in the amelioration of trismus in head and neck cancer patients.

Your patient (name) has agreed to take part in the above fore mentioned study. Your patient has been diagnosed with stage 3/4 oral or oropharyngeal cancer and has met the criteria to be enrolled in this study.

The study itself is a randomised trial looking at exercises with either wooden spatula’s or with a Therabite prior to radiotherapy therapy inorder to maintain or increase maximum mouth opening for this group of patients. The patients will be asked to complete quality of life questionnaires prior to treatment and 3 months and 6 months following the intervention. Patients will also record their maximum mouth opening in a patient log. Please see enclosed Patient Information Sheet.

If you have any questions about the study or the involvement of your patient to the study, please do not hesitate to contact the Principle Investigator at the Christie Hospital NHS Trust, tel. 0161 4463418 or by email at: nick.slevin@christie.nhs.uk

Yours truly,

Dr Nick Slevin
Consultant Clinical Oncologist
Health Related Quality of Life Questionnaires used in Chapter 5.

Health related Quality of Life (HRQoL) assessments were preformed at baseline, 3 and 6 months post intervention. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C 30) and Head and Neck (H&N) module (EORTC QLQ H&N 35). Data was collected using QoLproforma sheets.

Gothenburg Trismus Questionnaire (GTQ) was used part way through the study.

An end of study questionnaire was developed to ascertain patient acceptability of answering trismus/study specific issues.

Health Economics Assessments:

The following assessments were used:

EQ-5D-3L (baseline, 3, 6 months) - This is a validated generic, health-related, preference-based measure comprising five domains: mobility; self-care; usual activities; pain and discomfort; anxiety and depression.

ICECAP-A (baseline, 3, 6 months) This is a more encompassing quality of life measure. There are 5 domains: attachment, security, role, enjoyment and independence.

CSRI - A Client Service Receipt Inventory. Patients’ contacts with primary and secondary care services were collected retrospectively at 3 and 6 months by interview. This included their contacts with services such as speech and language therapy, dietary and nutritional advice and/or artificial feeding and orthodontic interventions including surgery.
Trismus Trial results:

Relief for head and neck cancer patients with mouth exercises

**Background:**
Around 6,800 patients were diagnosed with cancer of the mouth in the UK in 2011. Standard treatment varies but may involve surgery, chemotherapy and radiotherapy.
Patients can develop a reduction in mouth opening called trismus from their disease or as a result of treatment. Trismus affects the jaw muscles and makes mouth opening difficult. This can result in problems with eating, swallowing, speaking, oral health, dental integrity, nutrition and can affect breathing.
Radiotherapy would be expected to worsen trismus. To potentially combat trismus, patients could undertake jaw stretching exercises before the mouth opening starts to get worse. This means starting exercises *before* radiotherapy. This is the first study of its kind to show that exercises can help and that it is safe to do the exercises before and whilst on radiotherapy treatment and to continue the exercises after radiotherapy treatment has finished.

**Trial design:**
The aim of this study was to examine whether prophylactic jaw exercises using the Therabite® (TB) (a hand operated device which fits inside a patient’s mouth) or wooden spatulas (WS) (lollipop sticks stacked in a patient’s mouth) will relieve or prevent tightening of the jaw following radiotherapy. All patients had some sense of jaw tightening prior to study entry. Measurements of jaw opening were taken before and after radiotherapy.
The study was designed to look at factors such as compliance with the daily exercise regime, quality of life and health economics were questions the feasibility study was designed to address.
37 patients were randomised to receive the Therabite device and 34 the Wooden Spatulas for jaw exercises.

**Findings:** The study has shown that mouth openings had increased on average in both groups following the exercise intervention. There was no difference between the wooden spatulas or the Therabite. They both helped with improved mouth opening although the wooden spatulas are cheaper.

**Conclusions:** Starting exercises before during and after radiotherapy treatment can improve mouth opening in many mouth cancers. The exercise recommended regime is stretching 5 times, with 30 seconds hold, 3 times a day. But you need to discuss this with your medical team, to be shown how do the exercises safely.

**Lessons learnt:** from speaking to patients over the telephone include some of the following comments: They wanted to have more of a say in the exercise regimen for example reduce to 3 times a day.
Allowing patients to take a variable break (up to 5 weeks) from the exercises when side effects of radiotherapy are at their worst. Then start exercises again to help further to improve or maintain mouth opening.

More regular contact with the patients for encouragement and support from the medical teams.

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