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

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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.

Strengths and limitations of the study

- Adequately powered, multicentre, randomised controlled trial aiming to establish whether it is feasible and acceptable to perform proactive exercises throughout and beyond a course of radiotherapy.
- Health economics input to assess the level of post-treatment clinical management/healthcare use required by patients with mouth cancer.
- Study also includes a nested qualitative component to gain insight from patients' perspective.
- A small-scale study of patient acceptability of the intervention during radiotherapy would have been beneficial prior to study commencement.

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

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of less than 5 mm on average.[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.[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.[10] Finally, a systematic review carried out by McNeely *et al* 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.[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 Sevice (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.[12] The use of the therabite may prevent deterioration by maintaining or improving range of movement.

Inclusion/Exclusion criteria

Inclusion

- Provision of signed, written informed consent.
- Aged 18 years and older.
- Able to read and write English sufficiently to be able to complete the validated questionnaires.
- Stage 3/4 oral and oropharyngeal cancer patients undergoing:

primary chemoradiotherapy or postoperative radiotherapy or postoperative chemoradiotherapy.

- All patients will receive 60–70 Gy in 30–35 fractions over 6 to 7 weeks to the region of the masticatory muscles.

Exclusion

- <12 mm mouth opening (cannot use therabite).
- 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).
- Cognitive impairment as judged by the clinicians.
- 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.
- 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.
- International patients treated at The Christie or Aintree Hospital who may not have routine follow-up at these sites.

Intervention

The Therabite Jaw Motion Rehabilitations System (Platon Medical) will be used.[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:

- Five sessions per day.
- Five openings/closing per session.
- 30 s stretch for each opening.

This regime has been selected after consultation with Platon medical who manufacture the equipment and has worldwide experience of using the device. The

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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 weeks postsurgery. 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,[8] 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

Postsurgical 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 patients have visited. Structured interview will take place at the 3 months and 6 months postintervention, 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

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during the intervention, any problems with the therabite 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.[21] 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 postintervention, 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,[22] 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 therabite device. Other factors such as anxiety, ill-fitting therabite pads and the lack of goal setting during treatment also had a negative effect.[16] 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.[9]

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 o't 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.

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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 sample 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[17–20] 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[22] 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.[23 24]

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

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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

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treatment also had a negative effect.[16] 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 all reasons has been around 25% including death and recurrence within the 6 months follow-up.

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

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