Biostatistics Research Group
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LiTEFORM

A Randomised Controlled Trial of the Clinical and Cost Effectiveness of Low Level Laser in the Management of Oral Mucositis in Head and Neck Cancer Irradiation.

Statistical Analysis Plan
SAP Version number: 1.0
SAP Date: 13.12.19

This statistical analysis plan is based on protocol version 4 [03/09/2019]

ISRCTN Number: ISRCTN14224600
EudraCT Number: N/A
REC Reference: 17/WM/0096

Sponsor: The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Sponsor protocol number: 8097

Funder: NIHR Health Technology Assessment Programme
Funder reference number: 15/57/160

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This statistical analysis plan (SAP) provides a framework and guidelines for the statistical analysis and reporting of the LiTEFORM trial.

The SAP applies to a clean and validated dataset. Detailed information on data collection tools, data validation, consistency and accuracy checks and data storage and archiving can be found in the current version of the Data Management Plan (version 1.0 [23/08/17]).

Any deviation from the methods outlined in this SAP will be documented in the statistical end of trial report. Example Tables, Figures and Listings are for illustrative purposes only and are subject to change.

This SAP, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Section' of the Trial Master File (TMF) held and maintained by the IHS Biostatistics Research Group. The final signed SAP will also be stored in section 16 of the main TMF (16. Statistics / 16.1 Final signed Statistical Analysis Plan).

Revision history

Version	Date	Changes made	Justification for change	Timing of change
1.0	13.12.19	NA – first draft	NA	NA

Contents

1. INTRODUCTION

1.1 Background and rational

Table 1: Summary Information

Trial Title	**A Randomised Controlled Trial of the Clinical and Cost Effectiveness of Low Level Laser in the Management of Oral Mucositis in Head and Neck Cancer Irradiation**
Acronym	LiTEFORM
Summary of Trial Design	A multicentre blinded randomised controlled trial of low level laser versus sham low level laser therapy (LLLT) in the prevention and management of oral mucositis in head and neck cancer irradiation
Summary of Participant Population	Adults (≥18 years) referred for head and neck cancer irradiation
Planned Sample Size	380 adults (190 per arm)
Planned Number of Sites	Up to 10 sites (including 7 pilot sites)
Intervention Duration	6 weeks after first LLLT
Follow Up Duration	12 weeks after first LLLT 4 months after last LLLT 14 months after last LLLT
Final Follow Up Visit	14 months post LLLT and CRT (for patients who started laser therapy after 06Jul2018 the final follow-up visit will be 4 months)
Planned Trial Period	47 months (including 9 month pilot phase)
Intervention	Low Level Laser Therapy (LLLT)
Primary Outcome:	OMWQ-HN score at week 6 following start of LLLT treatment.
Primary Objective:	To compare the clinical effectiveness and cost effectiveness of LLLT plus standard care vs standard care alone as measured by the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) in adult HNC patients receiving (C)RT.

1.2 Objectives

1.2.1 Primary objective

- To compare the clinical effectiveness and cost effectiveness of LLLT plus standard care vs standard care alone as measured by the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) in adult HNC patients receiving (C)RT.

1.2.2 Secondary objectives

- Determine the effectiveness of LLLT in preventing severe OM during RT or CRT for HNC as measured by WHO mucositis scores.
- Apply evidence derived from the trial to inform NHS guidance in the use of LLLT for managing OM.
- Investigate the short and long term benefits to patients in terms of dependence on feeding tubes, nutritional status, pain control, admission to hospital, treatment interruptions and swallowing function and quality of life.

- Investigate the long term risks of LLLT (survival, recurrence, disease progression).
- Identify barriers and facilitators to implementing LLLT in routine clinical care through a qualitative process evaluation.

See protocol version 4.0 for further objectives associated with the economic and qualitative sub studies.

2. STUDY METHODS

2.1 Trial design

LiTEFORM is a multi-centre (up to 10 regional cancer centres in England, Scotland and Wales), 2 arm parallel group, blinded randomised controlled trial (RCT). LiTEFORM aims to evaluate the effectiveness and efficiency of LLLT in reducing the severity and impact of OM in adult patients receiving (C)RT for HNC.

Patients are randomised 1:1 to receive standard care plus LLLT verses standard care plus sham LLLT. Both arms receive the current standard care which includes optimisation of good oral hygiene, hydration and use of analgesia, topical analgesics and coating gels for pain management. Treatment allocation is stratified by two factors:

1. planned treatment (radiotherapy alone or chemo-radiotherapy)
2. unilateral or bilateral radiotherapy fields.

2.2 Study setting and patient population

This trial will take place in up to 10 HNC treatment centres in England, Scotland and Wales. Patients will be approached about the trial at the time they are consented for their (C)RT.

Recruitment will take place over 24 months (9 months pilot, 15 months RCT) with trial completion at 47 months (submission of final report).

2.2.1 Inclusion criteria

- Adults aged ≥ 18 years diagnosed with HNC
- Capacity to provide informed written consent
- Histological diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx, larynx, hypopharynx or unknown squamous cell primary of head and neck origin histologically confirmed
- (C)RT patients discussed in a Head and Neck MDT meeting and deemed medically fit for an agreed treatment plan for primary or adjuvant radiotherapy ± concurrent or induction chemotherapy (cisplatin or cetuximab)
- Patients planned to receive a minimum of 60Gy to a defined clinical target volume in the oral cavity or oropharynx, or neck levels Ia/b as defined by the current RTOG criteria

2.2.2 Exclusion criteria

- Known to be pregnant or planning to become pregnant within the trial treatment period
- Photosensitive Epilepsy
- Parotid tumours
- Previous radiotherapy for HNC
- Current/ongoing OM and trismus limiting laser access for treatment

- Patients who are experiencing active heavy tumour bleeding from the mouth (haemorrhage)
- Patients for whom the MDT recommend short course palliative radiotherapy
- Patients on immune suppressant drugs (except low dose steroids)
- Participation in other trials assessing different treatments for OM

2.3 Randomisation and blinding

Patients are randomised to receive standard care plus LLLT or standard care plus sham LLLT on a 1:1 basis using a method of random permuted blocks of concealed variable block size and stratified by 1: planned treatment (radiotherapy alone or chemo-radiotherapy) 2: Unilateral or bilateral radiotherapy fields. To ensure concealment of allocation, patients are centrally randomised by the Newcastle Clinical Trials Unit using a secure web-based system. It provides ease of operation with in-built validation/plausibility checks at time of data entry. The PI at site or an individual with delegate authority accesses the web based randomisation system and enter in the required information. The system returns a unique patient trial number and the randomised treatment allocation which corresponds to one of the two settings on the laser machine. A telephone and/or email randomisation service will be used should the web based system be unavailable for any reason.

The equipment manufacturer has modified the laser device to deliver the sham treatment. The protective glasses block the red colour of the light and prevent staff delivering the LLLT from knowing if the machine is delivering the sham output or active laser. Staff will operate the machine following the Standard Operating Procedure for the trial and laser safety rules, and the machine will be switched off prior to removal of all safety glasses.
LLLT will be delivered in a locked room with all reflective surfaces covered or absent. The machine will emit audible beeps when delivering both the sham and the intervention. All staff trained to deliver LLLLT will wear protective eye glasses as per the laser instructions for use (which comply with EU legal requirements).

The sham LLLT has built in additional resistors in the head of the probe to create warmth as if it was delivering the laser therapy. This reduces the risk of un-blinding of the patient and staff delivering LLLT.
The trial doctors and nurses administering the assessment tools for data collection and the researcher conducting the qualitative interviews will be unaware of which treatment each patient has received. The staff taking the WHO mucositis score will take an intraoral photograph at the time of their final score, which can be anonymised for independent fully blinded evaluation by another member of the research team. All of the Trial Management Team will be unaware of which patients have received which treatment except the staff performing the randomisation.

2.4 Definition of outcome measures

2.4.1 Primary outcome measure

Oral Mucositis Weekly Questionnaire–Head and Neck Cancer:
The primary outcome is the OMWQ-HN score at week 6 following start of LLLT treatment.

The OMWQ-HN is an oral mucositis-specific questionnaire [1] consisting of 9 items that assess impact of OM on a patient's well-being and oral functions. Question 1 describes mouth and throat soreness using a 5-point scale, with 0 indicating no soreness and 4 indication extreme soreness. If the patient scores 0 on this first question, they should stop and not proceed to any further questions. The second question is made up of five items, addressing the impact of mouth and throat soreness on patient function, with each item being scored on a 5-point scale with 0 indicating the function is not limited and 4 indicating the patient is unable to do the function. The remaining three questions assess the degree of mouth and throat pain and soreness using an 11- point scale, with 0 indicating no pain or soreness and 10 indicating the worst pain or soreness

imaginable. Responses to the OMWQ-HN will be summed to give a total overall score between 0 and 54 (a higher score indicating poorer wellbeing and oral function).
The OMWQ-HN was collected at baseline, weekly during weeks 1 to 6 of treatment, and at 4 month follow-up.

2.4.2 Secondary outcome measures

Note: Data for any 14 month outcomes (marked with asterisk) were only collected for participants who commenced laser therapy prior to 6th July 2018.

WHO Mucositis Oral Toxicity Scale:
The World Health Organisation has developed a grading system for mucositis [2] which measures objective, subjective and functional aspects of OM based on clinical appearance and functional status. The WHO scale is scored on a five point scale, with 0 indicating none, 1 indicating mild, 2 indicating moderate, 3 indicating severe, and 4 indicating life-threatening OM.

The WHO scale was collected by the clinician at baseline, weekly during weeks 1 to 6 of treatment, and at 4 month follow-up.

M.D. Anderson Dysphagia Inventory (MDADI):
The MDADI [3] is patient-reported swallowing outcome measure, specifically designed for the HNC population. The MDADI contains 20 items. Each item on the MDADI follows a five-point response scale ranging from 1 (strongly agree) to 5 (strongly disagree). The MDADI is comprised of four subscales: global (1 item); emotional (6 items); functional (5 items); and physical (8 items). Five scores can be calculated from the MDADI including 2 summary scores (global, total/composite) and 3 subscales (emotional, functional, physical) each calculated as an average with a range of 20 (worst impairment) to 100 (no impairment). The 19-item total (or composite) score will be used to summarize overall impairment on the basis of physical, functional, and emotional domains.

The MDADI was collected at baseline, week 6 of treatment, and at 4 month and 14 month follow-up*.

EORTC-QLQ-C30 (version 3.0) and EORTC-QLQ-H&N35 (version 3.0):
The EORTC quality of life questionnaire is an integrated system for assessing the health-related quality of life (QOL) of cancer patients. There is a set of 30 core questions (QLQ-C30) [4], supplemented by a HNC specific module (H&N 35) [5]. H&N35 is a diagnosis-specific module designed to be used in conjunction with the QLQ-C30 and is intended for use among a wide range of HNC patients, varying in disease stage and treatment modality. The QLQ-C30 contains 30 items which comprise five functional scales, three symptom scales, a global health status scale, and six symptom items. With the exception of the global health status questions, possible question responses range from 1 (not at all) to 4 (very much); for the global health status these range from 1 (very poor) to 7 (excellent). Each of these may be transformed into a score in the range 0-100. Higher scores on the global health status / QoL scale represent better quality of life, higher scores on the QLQ-C30 summary score represent higher levels of functioning and lower symptomology, and higher scores on the H&N35 symptom scales/items represent greater symptomology/more problems.

Based on published scoring guides [6, 7], 13 out of the 15 'scores' computable from the QLQ-C30 (i.e., excluding the `global health status/QoL' score and the `financial difficulties' symptom score) may be summarised as a `QLQ-C30 summary score.' representing a measure of cancer-specific health-related quality of life. The symptom scales/items that form part of the summary score will be reverse scored first to ensure that higher scores on the summary score reflect better outcomes. The H&N35 contains 35 items which comprise seven symptom scales and 11 symptom items.

The QLQ-C30 and H&N35 were collected at baseline, week 6 of treatment, and at 4 month and 14 month follow-up*.

Performance Status Scale for Head and Neck Cancer patients (PSS-HN):
The PSS-HN [8] is a 3-item scale designed to evaluate functional performance of H&N cancer patients, specifically Normalcy of Diet, Eating in Public, and Understandability of Speech. Each item is scored on an ordinal scale ranging from 0 to 100, with higher scores representing better functional performance. The Normalcy of Diet item has 11 ordinal categories which range from 0 to 100 in increments of 10, and both the Understandability of Speech and Eating in Public items have five ordinal categories: 0, 25, 50, 75, 100. For the Eating in Public item, participants who were inpatient at the time of the questionnaire were coded into a separate category.

The PSS-HN was collected at baseline, weekly during weeks 1 to 6 of treatment, and at 4 month and 14 month follow-up*.

Oral intake and tube dependency:
Data on participants' oral intake (measured as a percentage relative to their normal (i.e., pre-illness) levels of intake), level of dependency on feeding tube, whether enteral feeding was initiated, type of feeding tube used, and number of days the feeding tube was used in the past week were collected weekly during weeks 1 – 6 of treatment, and at 4 month and 14 month follow-up*.

Weight and Body Mass Index (BMI):
Weight data were collected at baseline, weekly during weeks 1 to 6 of treatment, and at 4 month and 14 month follow-up*.

Timed water swallow test (WST):
The WST [9] provides an indication of overall swallowing performance. Participants were tasked to drink 100 mL of water where they were timed (in seconds) and the number of swallows taken was recorded. The test was not performed in participants who must remain nil by mouth, who automatically scored 0 for the test. If there were overt signs of significant aspiration (explosive coughing, prolonged coughing) or the patient became distressed, the assessment was stopped and the remaining amount in the cup was measured and recorded.

The WST was collected at baseline, week 6 of treatment, and at 4 month and 14 month follow-up*.

Pain Outcomes:
The outcomes used to measure pain are: the use of analgesics/ topical treatment, the pain/discomfort domain of the EQ-5D-5L, and the OMWQ-HN (see primary outcome measure section for OMWQ-HN). There are also pain specific subscales in both the QLQ-C30 and the H&N35.

Analgesics, topical treatment, and visits to oral hygienist (other than for laser treatment):
Analgesics: whether participants had used painkillers in the last week, and the type of pain killers.
Topical treatment: whether participants had used mouth wash in the last week, and the type of mouth wash used.
Visits to oral hygienist: whether participants had visited an oral hygienist in the past week (for reasons other than laser treatment), the number of visits are also collected.

Data on the use of analgesics/topical treatment were collected at baseline and weekly from weeks 1 to 6 of treatment.

EQ-5D-5L: The EQ-5D-5L is a measure of patients' self-reported health-related quality of life [10]. The scale consists of five dimensions (mobility, self-care, usual activities, pain/discomfort/ and anxiety/depression) which are each rated along an ordinal scale of 1 (no problems) to 5 (extreme problems/unable to carry out activities in that domain). The EQ-5D-5L was also accompanied by a visual analogue scale to rate self-reported health on a scale from 0 to 100 (higher scores indicating better self-reported health). Data on the EQ-5D-5L were collected at baseline, week 6 of treatment, and at 4 month and 14 month follow up*.

Disease outcomes:
Disease outcomes were collected at 14 month follow-up* to assess disease recurrence and persistence.

2.4.3 Exploratory outcomes

Intraoral photographs
An intraoral photograph was taken at the time of the completion of the WHO mucositis score at the 4 month visit. This was anonymised for independent fully blinded evaluation (using the WHO mucositis score) by another member of the research team.

2.5 Study assessments
See protocol version 4.0 Section 13.6 for a detailed list of all study assessments and section 13.7 for a schedule of events.

2.6 Sample size and power

Original Sample Size
The original sample size calculation for this trial required a total of 380 patients. This comprised of a minimum of 100 patients recruited during the pilot phase of the trial with the remaining patients being recruited during the main trial phase.

This primary outcome measure is the OMWQ-HN score at 6 weeks following start of irradiation. According to Epstein 2007, a group difference of 4 points reflects a meaningful treatment effect and at 6 weeks and the standard deviation of the OMWQ-HN is 10.7. The trial was powered with small and acceptable errors of 5% α and 10%.β A total of 152 patients with primary outcome data are required in each treatment group to be able to detect this size of clinically relevant difference with 90% power. The sample size was inflated to 190 patients recruited in each trial arm assuming a maximum of 20% drop-out or missing data.

Closure of the trial prior to reaching the original target sample size
Due to the lack of patient recruitment the HTA requested that plans be drawn up to manage the closure of the trial prior to reaching the original recruitment target of 380 participants. The trial closed to recruitment on 31st March 2019, the last patient recruited was randomised on 1st April 2019 at which point there were 87 randomised participants. All participants were followed up to their 4 months visit; 14 month visit data could only be collected for participants who started laser therapy prior to 6th July 2018. The last patient visit was the 27th October 2019.

3. STATISTICAL CONSIDERATIONS

3.1 Timing of analyses

Participant follow-up visits
Following the decision that the trial would close, the HTA agreed that follow-up could end once the last participant to enter the trial had reached their 4 month follow-up visit. Fourteen month visit data was only collected for participants who started laser therapy prior to 6th July 2018

3.2 Analysis populations

The serious breach
A randomisation schedule was prepared which generated unique coordinates for allocations in a 2-dimensional grid (a 2 digit number of the form (x,y)) – the allocation in the grid at (x,y) corresponded to a treatment allocation (laser or sham). THOR had two grids which had different laser/sham settings:

- grid 1 "Internal SW2 - SW6 in 1 & 2 positions"
- grid 2 "Internal SW2 - SW6 in A & B".

THOR communicated that the laser machines had been programmed to match grid 1.
As a result of routine laser system testing it became apparent that the randomisation schedule did not match grid 1 (i.e. the allocation recorded in the randomisation log did not always match the laser therapy received). After unblinded testing it was found that the laser machines at all sites had been programmed to match grid 2 and *not* grid 1. At this point 20 participants had commenced laser therapy (involving 5 sites in total). Seven of these 20 participants had received treatment that was opposite to what they would have received in line with grid 1. The seven participants affected continued with the treatment they had started receiving [11]. The randomisation schedule was updated so that subsequent treatment allocations would match grid 2, in line with the machines' settings. The allocations for the first 20 participants were left unchanged in the randomisation log. The treatment received by the 7 affected participants was documented and stored securely by the NCTU Quality Assurance manager and an extra column was added, by the data manager, to the downloaded randomisation log with the treatment received.

Although the wrong allocation was assigned to seven participants the unique coordinates were generated randomly from the randomisation schedule, hence the allocation procedure was still random and unbiased.

The analyses will follow the intention-to-treat (ITT) principle with the ITT analysis set being modified to allow those participants who received the incorrect treatment at randomisation to be included in the treatment group corresponding to the treatment they received [11].

Modified Intention-to-treat (mITT) analysis set: This population contains all patients randomised into the study (regardless of their adherence with the entry criteria, regardless of subsequent withdrawal from treatment or deviation from the protocol). However, it is a modified ITT analysis set because it will include participants in the treatment group corresponding to the treatment they randomly received (where the randomised (x,y) coordinates for seven participants were used to generate an allocation from the wrong grid).

Statistical analyses will be conducted on complete cases from the mITT analysis set. Participants will be included in analyses if they attended the visit of interest and have evaluable data for the outcome measure of interest. Evaluable data here is non-missing for all outcome measures listed in Section 2.4 except the three questionnaires MDADI, QLQ-C30 and H&N 35, where simple imputation for missing questionnaire items in accordance with the questionnaire's scoring manual will be used.

Safety population: For the analysis of safety data all randomised patients who received at least one session of laser therapy will be included.

4. STUDY POPULATION

4.1 Participant flow through trial

Patient flow through the trial will be presented using a CONSORT diagram. Information will be provided on numbers and reasons (where appropriate) for: screened patients not being eligible; eligible patients not being randomised; patients found to be ineligible after randomisation; patients deviating from allocated treatment; patients not evaluable for the primary endpoints and withdrawal from follow-up.

Figure 1: CONSORT flow diagram

4.1.1 Screening, eligibility and recruitment

Screening and recruitment will be summarised. Reasons for ineligibility and reasons for eligible patients not being recruited will also be summarised (where available).

The following table and graphs will be included:

Table 2: Number of patients recruited by site per month

Figure 2: Total number of patients recruited by site

Figure 3: Cumulative target and observed recruitment per month

4.1.2 Withdrawals and follow-up

4.1.2.1 Withdrawals

Withdrawals from the trial will be presented in a line listing, noting when the participant withdrew, if routine data was still collected and the reason for withdrawal.

Example Table 3: Line listing of withdrawals from laser therapy

Trial ID	Treatment group	Days from randomisation to withdrawal	Reason for withdrawal	Completion status

Example Table 4: Line listing of complete withdrawals from study

Trial ID	Treatment group	Days from randomisation to withdrawal	Reason for withdrawal	Completion status

4.1.2.2 Participant follow-up

Participants were scheduled to return for their study assessments at the following time points:

Baseline (after consent but before day 1 of laser therapy)
Weeks 1 to 5
Week 6
4 months after end of week 6 laser therapy (± 2 weeks)
14 months after end of week 6 laser therapy (± 2 weeks)

Example Table 5: Participant follow-up by visit and treatment group

		Sham	Laser	Total
Randomisation		n (100%)	n (100%)	n (100%)
Baseline		n (% of randomised)	n (% of randomised)	n (% of randomised)
Week 6		n (% of randomised)	n (% of randomised)	n (% of randomised)
4 months	Compliance with visit window	n (% of randomised)	n (% of randomised)	n (% of randomised)
14 months	Compliance with visit window	n (% of randomised)	n (% of randomised)	n (% of randomised)

4.1.3 Adherence to protocol – laser therapy

Patients are scheduled to receive three laser sessions per week, during weeks one to six of their radiotherapy. Patients will receive LLLT plus standard care or sham LLLT plus standard care 3 times weekly by

a non-contact method for a period of 6 weeks (from day 1 of (C)RT dose). LLLT will be administered ideally within 2 hours, but always before (C)RT session, with a minimum of 24 hours between each of the 3 laser therapy sessions. Each session will last approximately 20-30 minutes, with LLLT at 6 pre-determined anatomical sites in the oral cavity.

LLLT will be delivered to the patient by nurses, allied healthcare professionals or delegated staff at a convenient time before the (C)RT treatment session (within an hour of the CRT dose). All patients will also receive the standard care offered for OM by each centre. Standard care varies across NHS Trusts but typically consists of oral hygiene instruction, topical analgesics and coating gels.

It is possible that a (C)RT session may be missed due to reasons such as an infection or the patient being unable to attend that visit. The LLLT will be delivered at the next session that the patient is able to attend for their (C)RT treatment as long as a minimum of 24 hours has passed, however data will still be collected wherever possible, particularly if the patient is an in-patient in the hospital.

Laser therapy received and (C)RT treatment interruptions will be summarised as indicated in the following tables.

Example Table 6A: (Chemo-)Radiotherapy treatment and interruptions (n=xx)

Radiotherapy alone			
	Laser (n =)	**Sham (n =)**	**Total (n =)**
Aim of radiotherapy, n (%)			
Primary radical radiotherapy			
Adjuvant radiotherapy			
High dose palliative radiotherapy			
Missed radiotherapy, n (%)			
Number of missed fractions Median (IQR) …Range			
Reason for missing radiotherapy	x reasons (n participants)	x reasons (n participants)	x reasons (n participants)
Adverse Event			
Patient Choice			
Clinical Decision			
Technical or staffing issue			
Other			
Chemo-radiotherapy			
	Laser (n =)	**Sham (n =)**	**Total (n =)**
Aim of radiotherapy, n (%)			
Primary radical radiotherapy			

Adjuvant radiotherapy			
High dose palliative radiotherapy			
Missed radiotherapy, n (%)			
Number of missed fractions Median (IQR) …Range			
Reason for missing radiotherapy	x reasons (n participants)	x reasons (n participants)	x reasons (n participants)
Adverse Event			
Patient Choice			
Clinical Decision			
Technical or staffing issue			
Other			
Type of chemotherapy /biological therapy, n (%)			
Cetuximab			
Cisplatin +/- 5 FU			
Carboplatin			
Other			
Amount per dose Median (IQR) …Range			
Missed chemotherapy doses, n (%) Number of missed doses Median (IQR) …Range			

Example Table 6B: laser therapy sessions by week

	Sham (n = xx)						**Laser (n = xx)**						**Overall (n =)**					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Number of patients continuing with laser treatment																		
													n =	**n =**	**n =**	**n =**	**n =**	**n =**
Number of laser sessions received																		
0													X (%)					
1																		
2																		
3																		
Missing																		

4.2 Baseline characteristics

Demographic, clinical and baseline characteristics and trial stratification factors: type of planned treatment (radiotherapy alone/chemo-radiotherapy) and type of radiotherapy field (unilateral/bilateral) at randomisation will be summarised across treatment groups descriptively. We will report the number and percentage in each group for all categorical variables (e.g. gender) and mean, SD or median, IQR and range, as appropriate, for all continuous variables. No significance testing will be carried out due to the randomised nature of the study.

Example Table 7: Baseline characteristics

	Sham (n=xx)	**Laser (n=xx)**	**Overall (n=xx)**
Age (years), mean (SD) **Height (cm), mean (SD)** **Weight (kg), mean (SD)**			
Gender Female Male			
Type of planned treatment Radiotherapy alone Chemo-radiotherapy			
Type of radiotherapy field Unilateral Bilateral			
Site of disease Nasopharynx Oropharynx-HPV positive Oropharynx-HPV negative Oropharynx-HPV undetermined Larynx Oral Unknown Primary Missing			
TNM Classification **Primary Tumour** TX T0 Tis T1 T2 T3 T4 Missing			
Regional Lymph Nodes NX NO N1 N2 N3 Missing			

Distant Metastasis MX MO M1 Missing			
Patient to receive chemotherapy in addition to radiotherapy? No Yes Missing			
How will the chemotherapy be administered? Concurrent Induction Induction and Concurrent NA Missing			
Patient to have IMRT No Yes			
Patient has had surgery to primary tumour No Yes Missing			
Adult Co-morbidity evaluation (ace-27) None Grade 1 - Mild Decompensation Grade 2 - Moderate Decompensation Grade 3 – Severe Decompensation Unknown Missing			
WHO Mucositis Scale 0 (none) I (mild) II (moderate) III (severe) IV (life-threatening) Missing			

Data are n; %, mean (SD) or median (IQR); range, unless otherwise stated

5. ANALYSIS METHODS

5.1 Primary outcome

Definition of the primary outcome:
The primary outcome is the OMWQ-HN score at week 6 following start of LLLT treatment.

Primary outcome measure
The primary outcome measure is the OMWQ-HN score. The OMWQ-HN was collected at baseline, weekly during weeks 1 to 6 of treatment, and at 4 month follow-up.

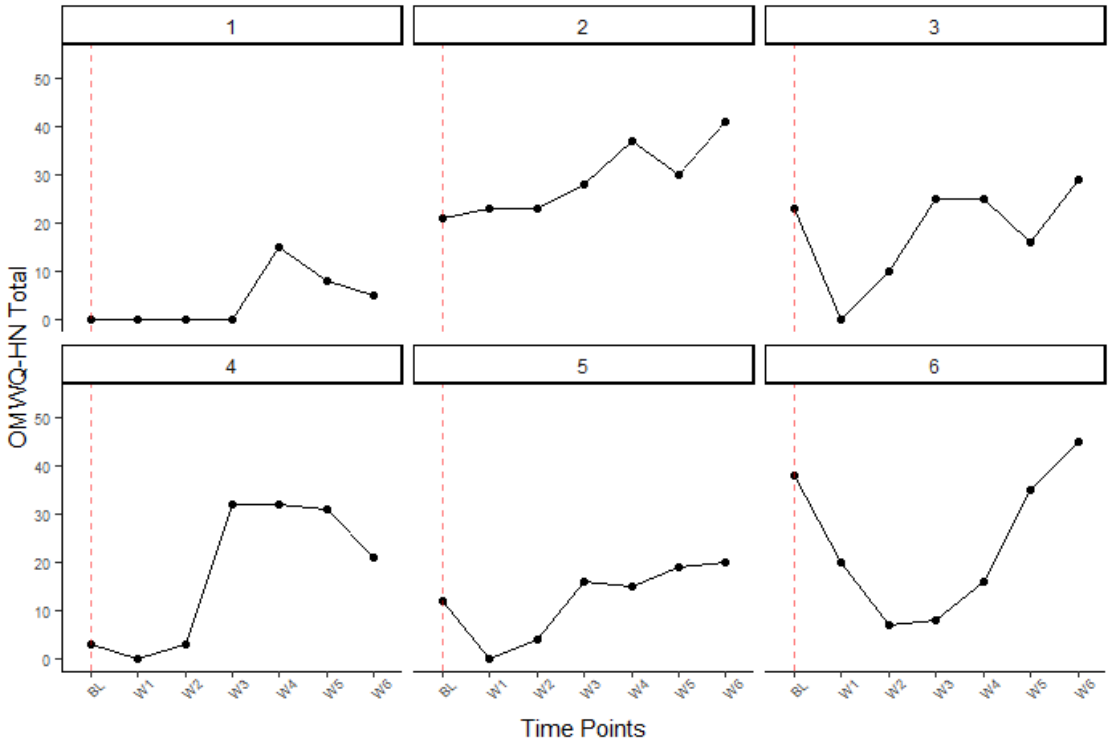
Responses to the OMWQ-HN will be summed to give a total overall score between 0 and 54 (a higher score indicating poorer wellbeing and oral function). The total score will not be computed for participants who had missing data on ≥ 1 item, with the exception of participants who scored `0' (=no soreness) on question 1 (who would not then proceed to the remaining questions and would be given a total score of 0).

Example Table 8: Completeness of primary outcome data by visit and treatment group

	Laser				Sham				Total			
	n	Fully missing	Partial missing	Complete	n	Fully missing	Partial missing	Complete	n	Fully missing	Partial missing	Complete
Baseline												
Week 1												
Week 2												
Week 3												
Week 4												
Week 5												
Week 6												
4 month												

The OMWQ-HN will be explored graphically using individual participant plots over time and at 6 weeks using histograms or dotplots and/or boxplots by treatment group. The OMWQ-HN will be summarised numerically as mean, standard deviation, median, interquartile range, and range at each time point for each of the treatment groups.

Example Figure 4: Individual participant plots of OMWQ-HN by visit [baseline to week 6]



Example Table 9: Summary statistics for OMWQ-HN over time

Laser								
	Baseline (n =)	Week 1 (n =)	Week 2 (n =)	Week 3 (n =)	Week 4 (n =)	Week 5 (n =)	Week 6 (n =)	4 Month (n =)
Min Median (IQR) Mean (SD) Max								
Sham								
	Baseline (n =)	Week 1 (n =)	Week 2 (n =)	Week 3 (n =)	Week 4 (n =)	Week 5 (n =)	Week 6 (n =)	4 Month (n =)
Min Median (IQR) Mean (SD) Max								
Higher scores on the OMWQ-HN indicate poorer wellbeing and oral function.								

5.1.1 Primary analysis of primary outcome

The difference between treatment group means at week 6 will be reported with 95% confidence interval.

Example Table 10: Mean difference in OMWQ-HN at 6 weeks between treatment groups

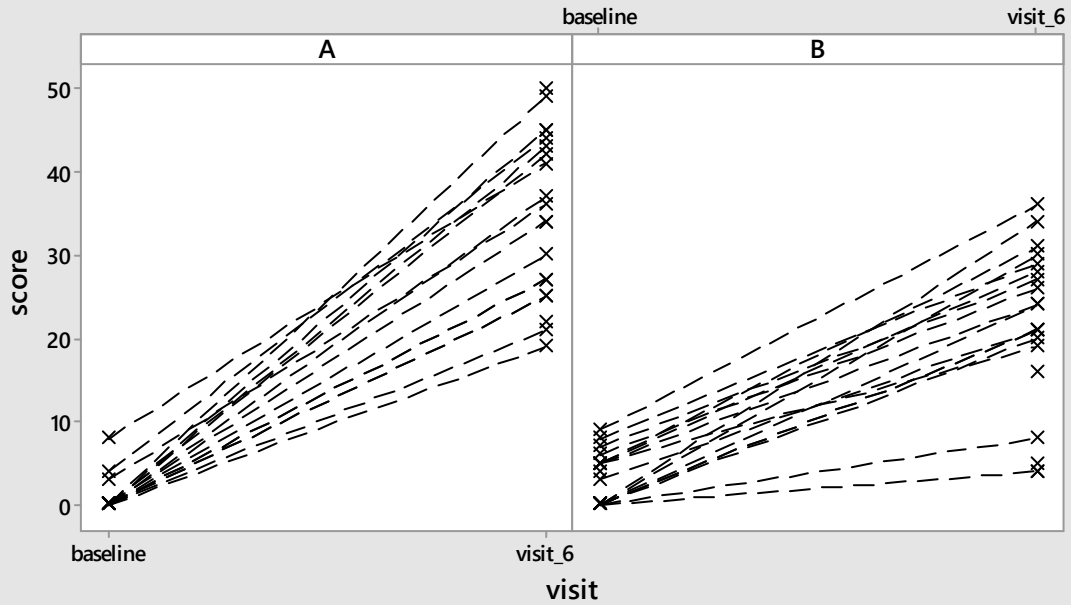
OMWQ-HN at week 6 Mean(sd)		Difference in means (95% CI) (Sham minus Laser)
Sham (n=)	Laser (n=)	
		Mean diff (95% CI)

(a higher score indicates poorer wellbeing and oral function)

5.1.2 Secondary analysis of primary outcome

The difference between treatment group means at week 6 will be estimated using analysis of covariance (ANCOVA), adjusting for baseline OMWQ-HN. This will be on a complete case basis for those participants with a score at both baseline and 6 week visit. If the assumptions of the ANCOVA model are satisfied an adjusted mean difference between treatment groups at week 6 with 95% CI will be reported. This analysis is equivalent to analysing the change from baseline adjusted for baseline. The baseline and week 6 OMWQ-HN data will be presented graphically:

Example Figure 5: Spaghetti plot, OMWQ-HN score: change from baseline to week 6



This is example data - it is not genuine OMWQ-HN data

5.2 Secondary outcomes

For all secondary outcomes the data completeness will be described as outlined for the primary outcome in Example Table 8.

WHO Mucositis Oral Toxicity Scale:
Data will be summarised descriptively as the frequency and percentage of each grade at each time point for each of the treatment groups. Due the achieved number of participants in the study it may be necessary to collapse categories in order to present more meaningful summaries. The difference between treatment groups in the percentage of participants with grade III or IV (severe or life-threatening) at week 6 will be reported with 95% confidence interval. This categorisation was proposed in the protocol and has been reported in a previous study [12]. A 95% confidence interval for the difference at 4 months will also be reported if appropriate.

M.D. Anderson Dysphagia Inventory (MDADI):
One emotional subscale item ("I do not feel self-conscious when I eat") and one functional subscale item ("I feel free to go out to eat with my friends, neighbours, and relatives") will be reverse scored in accordance with the scoring guideline [3]. Each subscale (global, emotional, functional, and physical) will be calculated as an average of its items, and then multiplied by 20 in order to rescale the scores to be from 20 (worst impairment) to 100 (no impairment). A subscale score will only be calculated if at least half of its items are non-missing.

The 19-item total/composite score will also be used to summarize overall impairment based on the weighted average of the raw (i.e., before rescaling) physical, functional, and emotional subscale scores [13]. The total/composite score will then be multiplied by 20 to rescale the range to be from 20 (worst impairment) to 100 (no impairment). All three subscale scores must be non-missing for the total/composite score to be calculated.

Data on the global, emotional, functional, physical, and total/composite scores will be summarised descriptively as mean, standard deviation, median, interquartile range and range at each time point for each of the treatment groups. The difference between treatment group mean total/composite score and mean global score at week 6 adjusted for the baseline of the score will be reported with 95% confidence intervals (only if the assumptions of the ANCOVA model are satisfied). This will be on a complete case basis for those participants with a score at both baseline and 6 week visit. A 95% confidence interval for the difference at 4 months will be reported if appropriate

EORTC-QLQ-C30 (version 3.0) and EORTC-QLQ-H&N35 (version 3.0):
Procedures for scoring the scales and items of the QLQ-C30 and H&N35 will be in accordance with the published scoring manual [6]. Therefore, a scale's score will only be calculated if at least half of its items are non-missing. The QLQ-C30 summary score will be computed as the mean of 13 scores from the QLQ-C30 (excluding the global health/QoL and financial difficulties scores) [7]. The symptom scales/items that form part of the summary score will be reverse scored first to ensure that higher scores on the summary score reflect better outcomes.

Data on the 21 outcome measures will be summarised descriptively as mean, standard deviation, median, interquartile range and range at each time point for each of the treatment groups. The difference between treatment group means for each of the 21 outcome measures at week 6 adjusted for the baseline of the outcome measure will be reported with 95% confidence intervals (only if the assumptions of the ANCOVA model are satisfied). This will be on a complete case basis (after pro-rating) for those participants with a score at both baseline and 6 week visit. A 95% confidence interval for the difference at 4 months will also be reported if appropriate

Performance Status Scale for Head and Neck Cancer patients (PSS-HN):
Data will be summarised descriptively, by subscale, as the frequency and percentage of each score category at each time point for each of the treatment groups. Given there were only 87 patients randomised in total and the frequency tables will have either 22 cells (11 categories by 2 treatment groups) or 10 cells (5 categories by 2 treatment groups) it may be necessary to summarise the data as the frequency and percentage of participants scoring ≤50 for the subscale [14, 15]. As these subscales are made up of ordinal categories, the median and range will also be presented.

Oral intake and tube dependency:
Data on the oral intake, feeding tube dependency, whether enteral feeding was initiated, and type of feeding tube will be summarised descriptively as the frequency and percentage at each time point for each of the treatment groups. Data on the number of days the feeding tube was used in the past week will be described using appropriate summary statistics.

Weight and Body Mass Index (BMI):
BMI scores at each time point will be calculated using height data collected at baseline and weight collected at each time point. Data on weight and BMI will be summarised descriptively as mean, standard deviation, median, interquartile range, observed range at each time point for each of the treatment groups.

Timed water swallow test (WST):
Measures of swallow capacity (mL/time taken), swallow volume (mL/number of swallows), and swallow speed (time taken/number of swallows) will be derived from the data.

Data on swallow capacity, volume, and speed will be summarised descriptively as mean, standard deviation, median, interquartile range, observed range at each time point for each of the treatment groups.

Pain outcomes
OMWQ-HN will be summarised numerically as mean, standard deviation, median, interquartile range, and range at each time point (baseline to week 6) for each of the treatment groups [as above].

EQ-5D-5L pain/discomfort domain will be summarised as median, interquartile range, and range [16].at baseline and week 6 only for each of the treatment groups

Analgesics, topical treatment, and visits to oral hygienist (other than for laser treatment)
The number of visits to an oral hygienist over the past seven days will be summarised descriptively as median, interquartile range, and range at each time point for each treatment group. The remaining data will be summarised descriptively as the frequency and percentage at each time point for each of the treatment groups. Data on analgesics will be categorised as no analgesia, simple analgesia (e.g., ibuprofen, paracetamol), opioids (e.g., morphine, oxycodone), and others. Data on mouthwash will be categorised as simple (e.g. FluoriGard, saline, sodium bicarbonate), analgesic (e.g., Difflam), antiseptic (e.g. chlorhexidine), mucosa protecting mouthwash (e.g. Mugard, Gelclair, Caphasol), and others.

Disease outcomes:
Data on disease outcomes collected at 14 months will be summarised descriptively as the frequency and percentage for each of the treatment groups.

5.3 Planned subgroup analyses

In order to inform future studies the OMWQ-HN score at week 6 will be summarised descriptively within each stratification subgroup:

1. planned treatment (radiotherapy alone or chemo-radiotherapy)
2. unilateral or bilateral radiotherapy fields.

5.4 Additional / Exploratory Analyses

Intraoral photographs

WHO Mucositis Oral Toxicity Scale assessments based on photographs taken at the 4 month visit will be summarised descriptively as the frequency and percentage for two collapsed categories 0-I (none to mild) and II-IV (moderate to life-threatening) based on the reasoning that it would not be possible to discriminate between the grades further from a photograph [agreed at the TMG on 24.10.19]. The two WHO assessments (based on looking in the participant's mouth and based on the assessment of the photographs) will be cross-tabulated.

5.5 Missing data

Statistical analyses will be conducted on complete cases from the mITT analysis set. Participants will be included in analyses if they attended the visit of interest and had evaluable data for the outcome measure of interest. Evaluable data here is non-missing for all outcome measures listed in Section 2.4 except the three questionnaires MDADI, QLQ-C30 and H&N 35, where simple imputation for missing questionnaire items in accordance with the questionnaire's scoring manual will be used.

6. SAFETY

6.1 Adverse events

All adverse events (AEs) that occur from day 1 of laser therapy up to and including the 12 week follow up visit (+/- 1 week) must be recorded on the eCRFs and in the patient medical notes.

The severity of symptoms are graded using the Common Terminology Criteria for Adverse Events (CTC) 4.0. The CTC grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

Adverse events will be coded using the MedDRA dictionary and presented by preferred term, grouped by system organ class.

Treatment emergent adverse events, i.e. those that occur or worsen on or after first dose of study IMP, will be summarised by grade according to the worst grade experienced since day 1 of laser therapy. Data will also be presented separately for related (possibly, probably, definitely) and unrelated (unrelated, unlikely) events. The occurrence of non-serious adverse events will be tabulated, as required for EudraCT reporting. All data will be presented in the safety population by randomised treatment group.

Example Table 11: All adverse events by type: worst severity reported

	Laser (n =)	Sham (n =)
System Organ Class 1, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
System Organ Class 2, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		

Example Table 12: Non-serious adverse events by type: worst severity reported (unrelated and unlikely causality)

	Laser (n =)	Sham (n =)
System Organ Class 1, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
System Organ Class 2, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		

Example Table 13: Non-serious adverse events by type: worst severity reported (possible, probable, and definite causality)

	Laser (n =)	Sham (n =)
System Organ Class 1, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
System Organ Class 2, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		

Example Table 14: Non-serious adverse events by type: worst severity reported (not assessable)

	Laser (n =)	Sham (n =)
System Organ Class 1, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		
System Organ Class 2, n (%)		
Preferred Term		
Mild		
Moderate		
Severe		
Life-threatening consequences		
Death		
Total number affected		

6.2 Serious adverse events

Example Table 15: Line listing of serious adverse events

SAE number	Patient ID	Treatment group	Laser start date	Laser end date	SAE onset date	Description	Severity[A]	Action[B]	Causality[C]	Expected	Resolution date

A: Mild/Moderate/Severe/Life-threatening consequences/Death
B: None/ Treatment adjusted or interrupted/Treatment discontinued/Concomitant medication/Non-drug therapy given/Hospitalisation
C: Unrelated/Unlikely/Possible/Probable/Definitely/Not assessable

7. STATISTICAL SOFTWARE

Data will be downloaded directly from MACRO into the STATA statistical software package. Statistical analyses will be carried out by the Trial Statisticians. All programs will be stored in the School Statistics folder on the IHS server. A paper master copy of all analysis reports will be stored securely in the statistical section of the trial master file held in a locked fire-proof cupboard with restricted access.

8. STORAGE AND ARCHIVING

Trial data are entered by individual site staff into a MACRO database held and maintained by the Newcastle Clinical Trials Unit, Newcastle University. Access to the database is limited to authorised personnel with specific access levels. All systems are backed-up on regular basis in accordance with current SOPs.

The Database Manager will release study data to the Trial Statisticians at time points agreed by the TMG in accordance with current SOPs. Any snapshots of the database taken are kept on the NCTU server, which is backed up daily.

At the end of the study, permissions for the database will be removed for data entry personnel and the status of the MACRO database will be changed to "Closed to Follow-up", ensuring that no further data can be entered or changed. The data used for the final analysis will be archived according to current SOPs. The Chief Investigator will receive a CD containing data from MACRO in CSV (comma-separated values) format, including a full download of all participants' data (with audit trail) in PDF and HTML formats. An additional CD/DVD with all the study data will be archived with the TMF.

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