LiTEFORM

Full 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.
Short Title/Acronym:	LiTEFORM **Li**te **T**herapy **E**ffectiveness **F**or **OR**al **M**ucositis Trial
Protocol Version Number & Date:	**Version 2.1 dated 31st May 2017**

Statement:

This protocol has regard for the HRA guidance.

1. RESEARCH REFERENCE NUMBERS

IRAS Number:	209809
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Research Registry & References:	ISRCTN14224600

RESEARCH SPONSOR

Sponsor Name:	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Sponsor Reference:	8097

RESEARCH FUNDER(S)

Funder Name:	NIHR Health Technology Assessment Programme
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2. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the Research Governance Framework, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as applicable.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

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Trial Website	http://www.liteform.org.uk

4. TRIAL SUMMARY

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	14 months after last LLLT
Planned Trial Period	47 months
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.

5. CONTENTS

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6. GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ANCOVA	Analysis of covariance
AR	Adverse Reaction
ARSAC	Administration of Radioactive Substances Advisory Committee
CI	Chief Investigator
Conmeds	Concomitant Medications
CRF	Case Report Form
(C)RT	Chemotherapy/ Radiotherapy
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol five dimensions questionnaire
EORTIC QLQ30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ C30/H&N 35	EORTC Quality of Life Module for Head and Neck Cancer
GCP	Good Clinical Practice
Gy	Gray (unit)
HNC	Head and Neck Cancer
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LLLT	Low Level Laser Therapy
MDT	Multi Disciplinary Team meeting
NGT	Naso-Gastric Tube

Newcastle CTU	Newcastle Clinical Trials Unit
NHS	National Health Service
OM	Oral mucositis
OMWQ-HN	Oral Mucositis Weekly Questionnaire - Head and Neck Cancer
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QC	Quality Control
QOL	Quality of Life
R&D	Research & Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
RTOG	Radio Therapy Oncology Group
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
USAR	Unexpected Serious Adverse Reaction
WHO	World Health Organisation

7. BACKGROUND

Around 4000 patients per year in England and Wales [1] undergo chemotherapy or radiotherapy (C)RT for head and neck cancer (HNC). 97% of these patients will develop oral mucositis [2].

Oral mucositis (OM) is a debilitating, painful complication characterised by inflammation of the mucous membranes, erythema and ulceration [3]. The tissue inside the mouth can feel as though it has been burnt, with ulcers developing on the mouth lining, tongue and lips. These ulcers can become infected with bacteria in the mouth. The infection can spread to the blood and other organs (sepsis) which can be life threatening. Thus patients with OM are likely to find that their ability to talk, eat and drink is profoundly affected. Swallowing difficulty (dysphagia) is the major determinant of post treatment quality of life [4].

Over 90% of patients need nutritional support for severe dysphagia during and after (C)RT[5]. Weight loss has been shown to lead to poorer survival, and longer periods without food or drink increase the likelihood of long term dysphagia and dependency on tube feeding [6]. The feeding tube can be inserted through the nose or directly into the stomach. To start the feeding and control pain, patients require hospital admission for several days. Feeding tubes can lead to distress and isolation as patients often do not want to be seen in public with a feeding tube in place. Insertion of feeding tubes has a complication rate of 5-15%, and a mortality rate of around 2% [7]. Long-term tube feeding is an independent predictor of long-term quality of life [5] and increased use of painkillers (analgesics).

Mucositis is an independent risk factor for pharyngo-oesophageal stricture. This is a devastating complication which can develop after HNC radiotherapy. A ring of scarring partially or completely blocks the gullet. This can result in the inability to swallow, aspiration and dependence on a feeding tube [8,9].

OM is a predictable side effect of (C)RT treatment, but current management varies across the UK depending on the funding available. Current treatment for OM includes patient education through reinforcing the importance of good oral hygiene, hydration as well as providing nutritional advice and pain management using analgesics, mouthwashes and coating gels. It is determined by the level of side effects that the patient is experiencing and which drugs are available on local formularies.

Low Level Laser Therapy (LLLT) is another treatment that can reduce the severity of OM. LLLT involves the application of low level light (laser) at the affected tissue to reduce inflammation and improve healing. The light is absorbed into the mitochondria, increasing the activity of the cell and accelerating cell healing as well as inhibiting pain receptors. The effect of the laser depends on the wavelength and density of the light as well as the period of time applied.

The expected benefits of LLLT in the patient population are:

1. Reduced pain and associated requirement for painkillers/pain management
2. Improved nutrition throughout treatment
3. Less dependence on feeding tubes both short and possibly long term
4. Reduced admission to hospital
5. Fewer treatment interruptions. Sometimes patients may not feel well enough to attend the hospital for their CRT session. Any treatment gaps allow for tumour repopulation, which may also promote the regrowth of chemotherapy –resistant populations. [10]
6. Improved patient quality of life during the treatment period and thereafter, particularly regarding swallowing outcomes but also reducing social isolation as many people avoid public places with a nasogastric tube (NGT) in situ.

8. RATIONALE

There is emerging evidence of the efficacy of LLLT as a treatment for OM, which is the most significant cause of acute morbidity of HNC (C)RT. However, there is inadequate evidence of the effectiveness of LLLT for it to be recommended as standard of care. LLLT remains unavailable to NHS patients undergoing HNC apart from, at the time of writing, a small pilot involving one centre. There is a lack of evidence as to whether LLLT is cost effective and how it is most efficiently delivered.

There are two current trials in France and Spain which do not address these important issues. There are no reported studies of potential long term functional and quality of life benefits for the treatment.

A recent systematic review was conducted by Oberoi et al 2014[11]. This included 18 randomised control trials of LLLT as a treatment for OM. The review concluded that prophylactic (preventative) LLLT reduced severe OM in patients with cancer (RR 0.37, 95% confidence interval (CI) 0.20 to 0.67; P = 0.001). It suggested that future research should identify the optimal characteristics of LLLT and determine feasibility in a clinical setting. If its effectiveness can be evidenced, this therapy would meet the well described but as yet unmet needs of patients during (C)RT. The burden on carers and the NHS would also be reduced.

The incidence of head and neck cancer, oropharyngeal cancer in particular, is rising rapidly. In the UK, oropharyngeal cancer has more than doubled between 1995 and 2006 [12]. In Scotland, oropharyngeal cancer has the fastest rate of increased incidence of any cancer. In the U.S., it is estimated that in 2020 oropharyngeal cancer will be more common than cervical cancer. This group of patients is also younger, with fewer comorbidities, and thus likely to survive longer.

Feedback from patients and the public have included comments of 'I was in agony, I could have given up in two weeks' and 'eating was like putting acid on a fire'. OM can have a lifelong impact on the patient. Potential benefits from LLLT include an improved quality of life in an area that is consistently rated by patients as one of the most problematic and distressing for them. If shown to be effective, LLLT could be implemented into practice. The results from this trial have the potential to change the management of this group of patients in the UK and worldwide.

8.1 Risk Assessment

The laser is being used within the CE (Conformité Européenne) marked indication for reducing pain and inflammation for patients with OM.

Class 3b lasers are potentially harmful to the retina. This hazard can be reduced with the provision of laser glasses from the device manufacturer which must be worn by both the practitioner and the patient whilst the device is in operation. The eye protection can be worn over prescription glasses. The risk of unintended laser irradiation of the eye will also be reduced through the removal and covering of reflective surfaces in the treatment area. The door of the treatment area will be locked and a sign displayed to indicate the use of laser therapy.

Before the treatment starts the operator will ask the patient to report if the light from the laser becomes too hot. If the heat becomes excessive, the laser will be stopped and the probe allowed to cool down.

The laser must not be used over the pregnant uterus, but will only be used in the oral cavity for this trial. Although in line with manufacturer recommendations the laser can be used with caution in pregnant women, women who are known to be pregnant at the time of their treatment, or are planning to become pregnant, will not be eligible to take part in LiTEFORM. Each participating site will follow their standard protocols for (C)RT , which ensure that women of childbearing age are not pregnant whilst undergoing their (C)RT. If a woman is reported to become pregnant during the treatment, LLLT treatment will be stopped immediately. The patient will be followed for the duration of the trial for outcomes unless she withdraws from the trial.

There is some anxiety amongst physicians that if the laser can stimulate healing of normal cells, that it may have a preserving effect on cancer cells. At present the effects of LLLT on tumour behaviour have been inadequately studied. There are a few published in vitro studies. These studies have inconsistent results, which may reflect varying dosimetry and power of the laser. Although there are no case reports of adverse outcomes following LLLT, it remains biologically plausible that LLLT may have an adverse impact on tumour behaviour resulting in poorer outcome and survival. This trial will

aim to address this question by collecting and reporting tumour recurrence and progression during the study period.

9. OBJECTIVES AND OUTCOME MEASURES

The main aim of the study trial is to establish the benefit of LLLT delivered 3 times weekly delivered by trained staff in the management of OM in HNC irradiation.

9.1 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.

9.2 Secondary Objective(s)

- 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.

Economic evaluation:

- To compare the total costs, of LLLT and sham LLLT measured at 4 and 14 months, calculated by combining data collected from the eCRF, Health Utilisation and Time and Travel Questionnaires with nationally available unit cost data [13].
- To compare quality-adjusted life years (QALYs) derived from the responses to EQ-5D-5L and EORTC QLQ30 measured at baseline, throughout the trial (week 6 and 4 and 14 months).
- To compare the cost-effectiveness measured in terms of the incremental cost per change (improvement) in OMWQ-HN score recorded between baseline and at week 6 of therapy (as detailed in the statistical primary end point).
- To evaluate incremental cost per QALY of LLLT when compared to standard care (from the

perspective of the NHS and personal and social services to participants and families over 14 months)

Qualitative Sub-study:

- To identify barriers and facilitators to recruitment by interviewing patients, interviewing health professionals, observing launch event and site initiation visits, and audio-recording recruitment consultations.
- To feedback to sites regarding barriers and facilitators that have been identified by developing a detailed action plan and site specific feedback.
- To understand practitioners' and site experiences of training in and delivering LLLT and the "fit" of LLLT within the treatment pathway.
- To identify barriers and facilitators to wider implementation of trial findings and LLLT.

9.3 Outcome Measures

9.3.1 Primary outcome measure

Primary Outcome: OMWQ-HN score at week 6 following start of LLLT treatment.

9.3.2 Secondary outcome measures:

- OMWQ-HN and WHO mucositis scores collected at baseline and weekly during weeks 1-6 of treatment.
- Long term reported health related quality of life as measured by EORTC QLQ C30 (version 3.0), EORTC QLQ C30/H&N 35 (EORTC QOL Module for Head and Neck Cancer) and the EQ-5D-5L at baseline, week 6, month 4 and month 14, and MDADI at baseline, week 6, month 4 and month 14.
- Nutritional Parameters as measured by Performance Status Scale's (PSS-HN) collected weekly at baseline, weeks 1-6, month 4 and month 14. Recording of weekly weight changes from baseline during treatment, the quantity of enteral nutrition consumed, number of days of feeding tube in situ.
- Changes in swallowing function measured by the timed water swallow test collected at baseline, week 6 of LLLT month 4 and month 14.
- Pain outcomes as measured by use of analgesics/ topical treatment and pain domain of EQ-5D-5L and OMWQ-HN at randomisation and weekly to week 6 during treatment.

- Safety, specifically adverse events attributed to LLLT and clinical complications notably number of days as inpatient hospital admissions and interruptions in CRT treatment (recorded weekly 1-6 during treatment).
- Clinical outcomes specifically patient survival, quality-adjusted survival recurrence and persistence of disease at 14 months.

Economic outcomes:

- Incremental cost per change in OMWQ-HN score recorded between baseline and at week 6 of therapy and incremental cost per QALY over 14 months
- Quality-adjusted life years based upon EQ-5D-5L [14] and EORTC-8D [15] utility scores measured at baseline, week 6 and 4 and 14 months
- Costs associated with treatment (weeks 0-6) will be collected weekly via the eCRFs (e.g. adverse events and use of analgesics)
- Health care utilisation based on responses to Health Utilisation Questionnaire administered at 4 and 14 months (assessing: visits to the GP/walk-in clinic/A&E etc.)
- Participant and family costs collected via the Time and Travel Questionnaire administered at 14 months
- Total costs of LLLT and sham LLLT measured at 4 and 14 months, from the perspective of the NHS and personal and social services to participants and families

Qualitative outcomes as identified through:

- Observations of training
- Interviews with health professionals delivering LLLT
- Interviews with other relevant members of the head and neck cancer team
- Audio-recording of recruitment discussions

10. TRIAL DESIGN

This 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 will be randomised 1:1 to receive standard care plus LLLT (n=190) verses standard care plus sham LLLT (n=190). Both arms will 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 will be stratified by two factors: 1. planned treatment (radiotherapy alone or chemo-radiotherapy 2. Unilateral or bilateral radiotherapy fields.

As part of the qualitative evaluation, a sample of patients who have consented or declined the main trial will be invited to take part in a telephone interview (n≤36). Staff at participating sites involved in trial recruitment/patient care, staff delivering LLLT, and other relevant members of the HNC team, will also be invited to take part in interviews. There will be observations of trial training and audio-recording of recruitment discussions (approximately 6-8 per site selected for analysis).

Pilot Study:

LiTEFORM includes a 9 month pilot phase (7 sites) with robust progression criteria to the full RCT (an additional up to 3 sites with a total of up to 10 sites). The pilot will look at all aspects of feasibility, safety and efficiency for LiTEFORM, with a qualitative process and economic evaluation. All 7 pilot sites will be set up as quickly as is possible during the pilot phase.

Progression Criteria:

Month 1 - Contractual start date and month funding starts from is 01 January 2017.

- Site set-up to be complete for 4 pilot centres by month 4 post funding, including the training of a minimum of 2 nurses or delegated staff to deliver LLLT in each centre to a competent level to ensure no gaps due to leave breaks etc. The second phase of an additional 3 centres - to be set up by month 6.
- First 4 pilot centres recruiting on average 1.5 patients per month for the first 4 months post funding.
- First 4 sites recruiting at full rate, on average 2 patients per month from months 5 to 9 Post funding
- Additional 3 sites recruiting on average 1.5 per month during months 3 and 4.
- Additional 3 sites recruiting on average 2 patients per month during months 5- 9.
- Completion of OMWQ- HN at week 6 in at least 80% of randomised patients
- Minumum of 100 patients recruited and randomized into LiTEFORM by completion of the pilot.

11. TRIAL SETTING

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).

12. ELIGIBILITY CRITERIA

12.1 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

12.2 Exclusion Criteria

- Known to be pregnant or planning to become pregnant within the trial treatment period
- Photosensitive Epilepsy
- Primary 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

- Unable to provide written informed consent

13. TRIAL PROCEDURES

13.1 Recruitment

13.1.1 Patient Identification and Pre-Screening

Patients will be identified as potentially eligible by staff with delegated responsibility following head and neck multidisciplinary team decision making. Patients will be informed about LiTEFORM when they attend clinic to consent for their radiotherapy and/or chemotherapy. This initial clinic appointment with the oncology team will cover the standard information about the side effects of their treatment and patients will be consented at this stage to undergo (C)RT (this consent process relates to the treatment and is entirely separate to the trial consent process). LiTEFORM will not be discussed in any great detail at this time. A lot of information will be given to patients by the oncologists and they will likely receive standard MacMillan information on (C)RT side effects from their clinical nurse specialist. The patient will be told how the LiTEFORM trial relates to these side effects and all patients who are potentially eligible will be given a Patient Information Sheet to read and consider in their own time.

13.1.2 Screening and Consent

Potential participants will be screened against the inclusion and exclusion criteria using the clinic lists and patient medical notes.

All patients who were given a LiTEFORM Patient Information Sheet will be re-approached about the trial when they attend the oncology clinic for their (C)RT planning appointments.

Informed consent discussions will be undertaken by a delegated member of the research team (as per the delegation log) with the opportunity for the patient to ask any questions and discuss the trial in more detail. All patients will be given a minimum of 48 hours after receiving the Patient Information Sheet to decide whether or not they would like to take part.

After eligibility has been confirmed, full written informed consent will be provided by signing, dating and initialling the consent form, which will be witnessed by a member of the research team who has documented and delegated responsibility so to do. The original signed consent forms will be retained in the Investigator Site File (ISF), with a copy filed in the clinical notes and a copy provided to the patient.

Qualitative sub-study:

Audio-recording: Verbal consent will be obtained to audio-record the recruitment and trial consent discussion with patients, at the start of the discussion. All those present must give verbal consent, including friends and family. If anyone declines then the discussion will continue without being recorded. All those present must provide written informed consent for the audio-recording at the end of the discussion or it will be deleted immediately. Consent can be withdrawn at any point during the discussion.

All those present who gave written informed consent for the discussion to be audio-recorded will be given a follow up information sheet to explain how they can contact the research team or qualitative researcher should they change their mind about the recording.

Patient Interviews: During the trial consent discussion all patients will be asked if they can be contacted about a telephone interview. All patients will be invited to take part, including those who declined taking part in the randomised trial. Not all patients who consent to be contacted about an interview will be contacted, and they may be contacted either 1-2 weeks after the recruitment discussion, and at approximately month 4 or month 14. There will be no more than 2 interviews per patient.

Patients will be given an Interview Patient Information Sheet to take away with them for consideration and asked for written consent to be contacted, allowing their details to be passed securely to the research team. The qualitative researcher will telephone the patient and, if the patient agrees, arrange a convenient time and date to conduct the interview. Verbal consent will be obtained at the very start of the call, including to audio-record the interview. The recorder will be switched on and the research will go through the consent form questions before the interview starts.

Staff Interviews: Interviews with health professionals will take place throughout the trial duration using purposeful sampling. Most interviews will be done via telephone, although some may be done face to face (for example to co-incide with a SIV observation). Taking part will be optional. There will be no more than 2 interviews per staff member. For all telephone interviews, the same process regarding obtaining verbal consent will be followed as for the patient interviews. Written informed consent will be obtained for all face to face staff interviews.

Observations: Written informed consent will be obtained from all staff present at the launch event site initiation visits and training sessions, at the start of the visit. If an individual does not wish to take part in an observation of a group activity, the researcher will not make any notes about that person or their involvement in the group. Anyone present can ask that observations are not undertaken at

any particular time and for any individual situation where, in their judgement, this course of action is not considered appropriate.

13.2 Randomisation

Patients will be 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 will be 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 will access the web based randomisation system and enter in the required information. The system will return 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.

13.3 Blinding

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.

13.4 Un-blinding

Only delegated members of the Newcastle Clinical Trials Unit will be able to un-blind a participant and only when deemed as necessary. Un-blinding may be needed for safety reasons that may influence the future clinical care of the patient. For example accidentally shining the laser in the eye of a participant or staff members during treatment, which would require further examination by an ophthalmologist within 24 hours.

If a patient or staff members becomes convinced they know which treatment they are receiving, this will be recorded along with any reasons provided. However, unless there are safety concerns for the person they will not be un-blinded in this case.

The independent Data Monitoring Committee (DMC) will require access to un-blinded data to ensure continued safety of the trial. The code break will be provided directly to the DMC by members of the Clinical Trials Unit operating the randomisation system who are independent of the trial.

13.5 Trial Assessments & Data

- **OMWQ-HN**

The OMWQ-HN is an oral mucositis-specific questionnaire [16] consisting of 9 items that assess impact of OM on a patient's well-being and oral functions. It will be administered by the research nurse and will take approximately 5 minutes to complete (Appendix 1). The patient will be asked to complete the questionnaire whilst they are at their research visit. 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 futher 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 3 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.

- **WHO Mucositis Oral Toxicity Scale**

The World Health Organisation has developed a grading system for mucositis [17] (Appendix 2) which measures objective, subjective and functional aspects of OM based on clinical appearance and

functional status. The score is collected by the clinician and will take no more than a few minutes to complete.

- **MD Anderson Dysphagia Inventory (MDADI)**

The MDADI [18] (Appendix 3) is patient-reported swallowing outcome measure, specifically designed for the HNC population. Patients will be given the 20-item written MDADI questionnaire to complete at their research visit. The assessor will be available to help should the patient require assistance, but will not direct any answers. It will take approximately 10 minutes to complete. Each item on the MDADI follows a five-point response scale. Five scores can be calculated from the MDADI including 2 summary scores (global, total/composite) and 3 subscales (emotional, functional, physical) each calculated as a weighted 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.

- **EORTC QLQ C30 (version 3.0), EORTC QLQ C30/H&N 35 (version 3.0) and EQ-5D-5L**

The EORTC quality of life questionnaire is an integrated system for assessing the health-related quality of life (QOL) of cancer patients participating in clinical trials. There is a set of core questions (QLQC30) [19], supplemented by a HNC specific module (H&N 35) [20]. H&N 35 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 comprises five functional scales, three symptom scales, a global health status / QoL scale, and six single items. All of the scales and single-item measures range in score from 0 to 100 and high scale score represents a higher response level.

The EQ-5D-5L [21] consists of 2 pages – the EQ visual Analogue scale (EQ VAS) and EQ-5D-5L descriptive system. Responces to the EQ-5D-5L descriptive system will be converted into utility weights using an algorithm (anchored at full health (1) and dead (0)) facilitating the calculation of QALYs that are used to inform economic evaluations of health care interventions. A utility scores can range from 1 to -0.281 (for the worst health state, 55555).

Patients will be given the written EORTC QLQ-C30, H&N35 and EQ-5D-5L questionnaire (Appendix 4) to complete independently, at their research visit. The assessor will be available to help should the patient require assistance, but will not direct any answers. Patients are asked to reflect on their symptoms, functioning and quality of life over the previous week. The questionnaire takes approximately 15 minutes [22].

- **Performance Status Scale's (PSS-HN)**

The PSS-HN [23] 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. The PSS-HN will be rated by health professionals including speech and language therapists, clinical nurse specialists and research nurses. The person collecting these data will remain consistent as far as is feasible, throughout the course of the trial. It will take approximately 5 minutes to complete.

- **Weight and Body Mass Index (BMI)**

Weight and BMI will be performed as part of standard care and will be recorded by the research nurse for the trial.

- **Timed water swallow test (WST)**

The WST [24] provides an indication of overall swallowing performance. It will be conducted unless deemed not appropriate or unsafe by the managing clinician. It will not be performed in patients who must remain nil by mouth, who will automatically score 0 for the test. If there are overt signs of significant aspiration (explosive coughing, prolonged coughing) or the patient is becoming distressed, the assessment will be stopped and the remaining amount in the cup measured and recorded. Measures of swallow capacity (mls/time) and swallow volume (mls/number of swallows) are derived from the data. Non-completion of the test will be recorded.

The WST will be conducted by speech and language therapists or a research nurse trained by a speech and language therapist, with reliability checks on 10 volunteers. The person conducting the WST at each centre will remain consistent throughout the course of the trial, as far as is feasible. It takes approximately up to 3 minutes to complete in this patient population.

- **Qualitative Interviews:**

Interviews with patients and health professionals will be conducted by an experienced qualitative researcher with skills in interviewing vulnerable populations around sensitive topics. A topic guide will be developed from discussions with the wider team, including the patient panel, from normalisation process theory (NPT)[30] and from literature around trial participation. The topic guide will be used in the interviews but interviewees will be encouraged to speak freely about any other issues relating to the pilot feasibility trial. The guide will be revised as new issues emerge in each interview. Each interview is expected to last between 20 and 40 minutes.

13.6 Trial Assessments

Baseline Assessments:

The following assessments must be conducted/administered at the (C)RT planning visit(s) - after the point of consent) but before day 1 of LLLT treatment.

- OMWQ-HN
- MDADI
- EORTC QLQ C30 (version 3.0), EORTC QLQ C30/H&N 35 and EQ-5D-5L
- WHO Mucositis Toxicity Scale
- Performance Status Scale's (PSS-HN)
- Timed water swallow test
- Recording of weight (weight/BMI)
- Use of analgesics and topical treatment

Assessment on Weeks 1-5 of LLLT treatment (inclusive)

Weekly assessments at weeks 1-5 of treatment, conducted/administered once each week. These will be conducted on the same weekday each week as day 1 of LLLT for the following 5 weeks (+/- 2 days to allow for local hospital variation of their weekly clinic review), before LLLT is given that day:

- OMWQ-HN
- Performance Status Scale's (PSS-HN)
- Recording of weight (weight/BMI)
- WHO Mucositis Toxicity Scale

Week 6 Assessment of LLLT Treatment (+/- 1 week)

Primary outcome assessments at week 6, conducted/administered once in week 6, on the same weekday as day 1 of LLLT (+/- 2 days to allow for local hospital variation of their weekly clinic review), before LLLT is given that day:

- OMWQ-HN -1, +2weeks for completion
- MDADI -1, +2weeks for completion
- WHO Mucositis Toxicity Scale
- Performance Status Scale's (PSS-HN)
- EORTC QLQ C30 (version 3.0), EORTC QLQ C30/HNC 35 and EQ-5D-5L -1, +2weeks for completion

- Timed Water Swallow test
- Recording of weight (weight/BMI)

The following information will also be recorded/collected at day 1 of LLLT, and weekly during weeks 1-6 of treatment:

- Use of analgesics and topical treatment
- Hospital admissions and interruptions in treatment (from week 2 of treatment)
- Quantity of enteral nutrition consumed, number of days of feeding tube in situ.
- Adverse events will be collected and concomitant medications checked and recorded on the eCRF
- Resource use associated with treatment will be collected via the CRF (e.g. staff involved and time associated with the delivery of the intervention, equipment costs etc.)

Week 12 (+/- 1 weeks) Head and Neck Follow-up visit (at the standard care visit)

- Adverse events will be collected and concomitant medications checked and recorded on the eCRF

Month 4 (+/- 2 weeks) Head and Neck Follow-up visit (at the standard care visit)

- OMWQ-HN
- MDADI
- WHO Mucositis Toxicity Scale
- EORTC QLQ C30 (version 3.0), EORTC QLQ C30/H&N 35 and EQ-5D-5L
- Performance Status Scale's (PSS-HN)
- Recording of weight (weight/BMI)
- Timed water swallow test
- Health Care Utilisation Questionnaire (including use of primary, secondary and social health care services and time away from usual activities)

Month 14 (+/- 2 weeks) Head and Neck Follow-up assessment (at the standard care visit)

- MDADI
- EORTC QLQ C30 (version 3.0), EORTC QLQ C30/H&N 35 and EQ-5D-5L
- Performance Status Scale's (PSS-HN)
- Timed water swallow test
- Recording of weight (weight/BMI)
- Health Care Utilisation Questionnaire

- Time and travel questionnaire

The following data will also be recorded at month 14:

- Recurrence, disease progression, death
- Feeding tube use (stopping)

Qualitative Sub-study:

- Patient interviews: 1-2 weeks after the recruitment discussion, and at approximately 4 months or 14 months (maximum of 2 interviews per patient).
- Staff interviews: staff may be contacted at any point during the LiteFORM trial
- Audio-recordings: each recruitment/consent discussion with patients for the LiTEFORM trial
- Observations: launch meeting, site initiation visits and all trial training sessions

13.7 Schedule of Events

Procedures	**Patient Visits to Clinic**						
	Pre-Screening	**Screening & Planning visit (+1 week)**	**Weeks 1 to 5 of CRT Treatment *(or as per standard care pathway)***	**Week 6 of CRT (+/- 1 week)**	**12 week follow up visit (+/- 1 week)**	**4 months (+/- 2 weeks)**	**14 months (+/- 2 weeks)**
Patient Information Sheet	√						
Informed consent		√					
Eligibility Confirmed		√					
Demographics/ Medical History		√					
Randomisation		√					
MDADI		√*		√		√	√
EORTC QLQ C30		√*		√		√	√
EORTC QLQ C30/H&N 35 (HN Cancer Module)		√*		√		√	√
EQ-5D-5L		√*		√		√	√
OMWQ-HN		√*	√ (**Weekly** on day 1 of LLLT, +/- 2 days)	√		√	
Performance Status Scale's		√*	√ (**Weekly** on day 1 of LLLT, +/- 2 days)	√		√	√

Recording of Weight/BMI		**√***	√ (**Weekly** on day 1 of LLLT, +/- 2 days)	√		√	√
Recording of Analgesics/Topical Treatments		**√***	√ (**Weekly** on day 1 of LLLT, +/- 2 days)	√			
WHO Mucositis Toxicity Scale		**√***	√ (**Weekly** on day 1 of LLLT, +/- 2 days)	√		√	
Recording of Hospitalisation			√ (**From week 2: weekly** on day 1 of LLLT, +/- 2 days)	√			
Timed Water Swallow test		**√***		√		√	√
(C)RT			**√ (as per standard care)**	**√ (as per standard care)**			
LLLT/LLLT sham			**√ (3 sessions per week** from day 1 CRT – minimum 24 hrs between sessions)	**√ 3 sessions per week** from day 1 CRT – minimum 24 hrs between sessions)			
Collection of Clinical outcomes			√ **(weekly)**	√			√
Health Care Utilisation Questionnaire						√	√
Time and Travel Questionnaire							√
Adverse event assessments and Conmeds			√ (corresponding with **LLLT sessions**)	√ (corresponding with **LLLT sessions**)	√		

***Must be done after consent and prior to the first laser therapy session.**

13.8 Withdrawals and Drop Outs

Participants have the right to withdraw from treatment or follow-up in the trial at any time without having to give a reason. Site teams should try to ascertain the reason for withdrawal and document this reason within the eCRFs and participant's medical notes.

The Principal Investigator may discontinue an individual's participation inthe trial at any time if the Investigator considers it necessary for any reason including:

- Symptomatic deterioration
- Participant withdrawal of consent
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw
- An adverse event that requires discontinuation of the trial intervention or renders the participant unable to continue in the trial
- Termination of the clinical trial by the sponsor
- Reported pregnancy

All patients who withdraw from treatment will be invited to continue follow up according to the trial protocol. Patients who withdraw consent for further follow up will be included in the analyses up to the date of withdrawal.

Separate consent will be obtained for interview participation, therefore participants are free to refuse to participate in the interview when contacted and those who choose to participate have the right to withdraw from or stop the interview at any time without having to give a reason.

Drop out:

A maximum participant dropout rate of 20% has been used when calculating the target sample size. It is estimated to be 10-15% based on data from previous trials and will be monitored by the independent DMC.

13.9 Storage and Analysis of Samples

No patient samples will be taken or used during this trial.

13.10 End of Trial

The last patient last contact will be at the 14 month follow up head and neck visit. The trial will be considered as closed at the time of database lock (expected around July 2020). The data will then be analysed, the trial report completed and results made available to the funder.

14. TRIAL INTERVENTIONS

14.1 Name and Description of Interventions

The LX2 Laser is indicated for use for OM and will be supplied by the manufacturer along with photo medicine approved glasses which must be worn by the practitioner, all observers and the patient whilst the laser is in operation.

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 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.

Low Level Laser Therapies are available to the public for health and cosmetic treatments. LLLT equipment is CE marked and commercially available. Agreement has been obtained from the supplier to provide the specially modified sham treatment equipment to all sites for the purposes of this trial. The equipment will be serviced annually. Low level lasers are classed as 3b lasers, meaning they do not cut or burn but may injure the eye.

14.2 Schedule & Modifications

The LLLT will be a red laser, wavelength 660nm, power output 75mW beam area 1.5cm2, irradiance 50mW/cm2, exposure time 60 seconds, fluence 3J/cm2 per spot.

14.3 Concomitant Medications & Therapies

Laser therapy is contra-indicated for use over any known primary or secondary lesions. In line with manufacturer safety advice, the laser can be used on patients on low dose steroids but not on patients who are taking other immune suppressant drugs.

The laser can be safely used on patients with a pacemaker. The laser will only be used in the oral cavity for this trial.

Recent studies have shown no known adverse effects of LLLT in the parameters used for oral mucositis [25] and no issues with safety or tolerance and no survival difference at 18 months [26]. It the event that patients experience persistant or severe reactions to the laser therapy, the laser therapy must be discontinued immediately.

14.4 Assessment of Compliance

LLLT will be delivered by trained staff who will record the details of each session in the patient medical notes, including any sessions not attended. Operators of the laser will be required to complete a checklist of the intervention process, including number of doses administered and site of dose. Each staff member will also be required to document that the patient glasses and staff safety glasses were worn for the duration of the treatment and any occurrences of un-blinding. Compliance for the LLLT sessions will be monitored by the Trial Management Group using the online database using for data capture as well as reviewing source data at site visits.

Completion of trial assessments will be reported to the independent Data Monitoring Committee for discussion at the DMC meetings. The distribution of response times for questionnaires will be reported and agreed with the external DMC.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

15. SAFETY REPORTING

15.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention under trial.
Adverse Reaction (AR)	An untoward or unintended response in a participant to which is related to the intervention under trial i.e. that a causal relationship between the trial intervention and an AE is at least a reasonable possibility and the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due any dose of the trial intervention, based upon the information provided.
Unexpected Serious Adverse Reaction (USAR)	A serious adverse reaction, the nature and severity of which is not consistent with the known information about the intervention under trial.

15.2 Recording and Reporting AEs, SAEs and SARs

AEs: All 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 Principal Investigator is responsible for managing AEs at site according to the protocol. Seriousness and relation of the AE to the LLLT treatment should be assessed by the site PI. The Newcastle CTU will maintain a detailed central record of all AEs that occur. There is no requirement to inform sponsor of individual AEs.

SAEs and SARs: All SAEs that occur from day 1 of laser therapy up to and including the 14 month follow up visit (+/- 2 weeks) must be reported to the CI, Newcastle CTU and Sponsor immediately but no later than 24 hours of the site learning of its occurrence. Death should be reported as an SAE if it occurs within this period. If a death occurs after the 14 month visit it does not require reporting as an SAE but must still be recorded in the patient medical notes and eCRFs.

All SARs that occur from day 1 of laser therapy up to and including the end of study, as defined in section 13.10 must also be reported. SARs should be reported using the same process as for SAEs.

The initial SAE report will be made by the site PI completing the agreed SAE form which is sent via SOHO66 (secure fax to email system) to the Senior Trial Manager, Trial Manager, CI and nominated sponsor contact. The initial report can if necessary be made to the Clinical Trials Unit by telephone or e-mail and followed up formally using the SAE form. In the case of incomplete information at the time of initial reporting, or follow up information, a new SAE form must be completed and sent via secure system as soon as possible.

Contact details for reporting SAEs:
Trial Manager, Newcastle Clinical Trials Unit
Jenn Bingham, Jenn.Bingham@newcastle.ac.uk 0191 208 2520

Please send the completed and signed SAE form(s) using the SOHO66 secure network

FAO LITEFORM TRIAL MANAGER to: **TBC**

All SAEs must be assessed for expectedness using the list of expected adverse events in LiTEFORM Protocol **section 15.2.1** and receive full review by the PI at site and discussed with the CI. It is encouraged that the CI consults with the Chair of the TSC and DMC.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the PI
- Whether the event is considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Newcastle CTU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Expected AE/ARs:

Most adverse events that occur in this trial, whether they are serious or not, will be related to the (C)RT that the patient is receiving as part of their standard care and not related to delivery of the LLLT.

The following are AEs that could be reasonably expected to occur in this population of patients who are undergoing (C)RT for HNC. It is expected that patients receiving primary or adjuvant radiotherapy ± chemotherapy for head and neck cancers may require admission for symptom control of the following:

- Mucositis
- Dysphagia
- Pain
- Nausea and vomiting
- Weight loss
- Poor oral intake
- Infection
- Fatigue
- admission for hydration and/or feeding via NGT or Radiologically Inserted Gastrostomy (RIG) if the patient has one in situ

Patients may also experience tinnitus (chemotherapy related) and anaemia, although may not require admission for these symptoms.

15.2.1 Expected AEs after receiving LLLT:

- nausea
- dizziness
- increase in OM symptoms within 24 hours of receiving laser therapy
- decrease in OM symptoms within 24 hours of receiving laser therapy
- tingling sensation in the mouth
- feeling of warmth in the mouth

It the unlikely event that a patient experiences persistant or severe reactions to the laser therapy, the laser therapy must be discontinued immediately.

All occurrences of **expected** SAEs/AEs will be included in the first annual progress report but will not require completion of the SAE form or expedited reporting to REC. They must be recorded by the site on the eCRFs and in the patient notes. Treatment related AE and All SAEs will be reviewed by the DMC throughout the trial.

Coding:

AE's and SAEs must be coded using CTC version 4.0. SAEs will be recorded and reported according to category, severity (mild, mod, severe) and related-ness (definitely, probable, possible, unlikely, unrelated) to intervention.

15.3 Recording and Reporting USARs

All USARs occurring from day 1 of laser therapy up until the end of study must be reported to the NHS REC. The sponsor will perform this reporting.

The assessment of expectedness will be performed by the CI against the known information for the trial as per the trial protocol.

USARs must be reported no later than 15 calendar days after the sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a USAR they must contact the CI, sponsor representative sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- Patient trial number and date of birth

- Name of intervention
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

This information must be provided by email. The site is expected to fully cooperate with the sponsor in order that a full and detailed report can be submitted to the NHS REC within the required timelines.

PIs will be informed of all USARs by the sponsor.

15.4 Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for laser therapy or at the week 12 follow-up
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events.
- Ensuring that all SAEs and SARs, including USARs, are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness to SARs.
- Immediate review of all USARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

Sponsor

- Assessment of expectedness of any USARs
- Expedited reporting of USARs to the REC within required timelines
- Notification of all investigator sites of any USAR that occurs

TSC/DMC

- Reported to DMC/ TSC Review of safety data collected to date to identify any trends

15.5 Notification of Deaths

All deaths from day 1 of laser therapy up to and including week 12 follow up will be reported as SAEs irrespective of the cause of death and reported to the sponsor, CTU and CI. All deaths will be reported to the DMC.

15.6 Pregnancy Reporting

If a female participant becomes pregnant within 12 weeks of receiving laser therapy the details of the pregnancy needs to be reported to the Chief Investigator, Trial Manager and Sponsor within 24 hours of the site learning of its occurrence on the pregnancy reporting form.

15.7 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, Newcastle CTU must be notified immediately and details of the USM given. Newcastle CTU must inform the NHS REC within 3 days of the USM taking place in accordance with the sponsor's/NCTU's standard operating procedures.

16. STATISTICAL CONSIDERATIONS

Definitions of outcome measures, scoring procedures and derivations of overall and domain scores for the primary outcome OMWQ-HN score and secondary measures of WHO mucositis score, EORTC QLQ C30 (version 3.0) EORTC H&N 35, EQ-5D 5L (version 1.0) are presented in Appendix 4.

Adverse events are coded according to MEDRA coding with severity coded according to WHO CTC 4.0 grading system.

Survival is defined as date of randomisation to date of death from any cause, survivors censored at their date of last follow-up visit.

Time to recurrence is defined as date of randomisation to date of clinical recurrence for patients with confirmed date of clinical recurrence or patients with confirmed disease related death - survivors who are recurrence-free and patients who have died from other causes are censored at their date of last follow-up visit.

Primary analyses are carried out on an intention to treat, retaining all randomised patients in the analysis according to their randomised treatment allocation, and a complete case basis. Sensitivity analyses may be performed on a per protocol basis, according to treatment received, and on an imputed dataset, should missing data deem this necessary. Treatment related adverse events will be reported in all patients starting treatment.
A full analysis plan will be in place prior to any comparative analyses, and will be reviewed by the oversight committees.

16.1 Statistical Analysis Plan

The primary analysis of the primary outcome is a comparison of the OMWQ-HN score at 6 weeks following start of RT (+/- 2 weeks) in the two randomised arms. Mean baseline and 6-week scores will be presented (with 95% CI) as well as the mean difference from baseline score. Transformation may be appropriate for non-normally distributed data. The null hypothesis to be tested is H0: mean 6-week score in patients randomised to LLLT = mean 6-week score in patients randomised to sham LLLT. Randomisation is stratified by known clinical confounders of cancer treatment: 1. planned treatment (radiotherapy alone or chemo-radiotherapy 2. Unilateral or bilateral radiotherapy fields.

The size and significance of any treatment effect will be estimated in a multivariable linear regression model adjusting treatment by the stratification factor. Secondary analyses of the primary outcome will adjust the size and significance of any treatment effect by other important baseline clinical covariates (importance assessed through univariate modelling) using multivariable regression and ANCOVA. Underlying assumptions of the regression models and non-linear continuous covariates will be investigated, reported and addressed. A two-sided 5% level of significance will be used.

A sensitivity analysis may be carried out on an imputed dataset, based on multiple imputation methods, to deal with missing data and will be described in the Statistical Analysis Plan, which will be

finalised prior to any analysis of unblinded data.

Comparison of secondary outcome measures has not been powered. As such, descriptive statistics such as means (sd, 95% CI), medians (inter-quartile ranges, range) will be presented by randomised treatment arm for continuous secondary outcome measures, specifically scores, feeding tube days, inpatient admission days, water swallow times. ITT proportions (95% CI) will be calculated and presented for categorical measures.

Time to event summary statistics will be estimated using the method of Kaplan and Meier, and 3, 6 and 12-month estimates (with 95% CI) reported. Differences between 'survival' distributions will be estimated using the hazard ratio (95%CI), unadjusted and adjusted by stratification factors.

Quality adjusted survival analyses will be carried out to simultaneously assess quality and survival functions. A Quality function, based on the EQ5D global score, will be estimated at each survival event time using interpolation, and the survival distribution down-weighted by any negative quality function. The area under each of the survival and quality adjusted survival curves will be presented as (with 95%CI).

Long term data will be presented graphically including proportions of positive and negative changes from baseline. Standardised area under the curve analysis will be used to describe longitudinal quality of life scores. Exploratory, descriptive hierarchical modelling, not based on significance testing, may be used to explore repeated measures nested within patients accounting for important baseline clinical confounders and stratification factors.

Hypothesis testing is not planned for the analyses of secondary outcome measures.

16.2 Planned Subgroup Analyses

The size of the treatment effect will be estimated and presented descriptively within each stratification subgroup. The treatment effects will not be statistically tested within each subgroup, but rather a test of heterogeneity may be conducted across subgroups.

Sensitivity analysis may be conducted of the primary outcome measure in the per protocol compliant subgroup.

16.3 Planned Interim Analyses

An independent Data Monitoring Committee (DMC) will be established, whose remit is to review the trial's progress and saftey. Interim analyses will be conducted and presented by the trial statisticians,

in confidence, to the DMC in accordance with the DMC Charter. In the light of interim data and accumulating worldwide evidence, the DMC will recommend to the Trial Steering Committee (TSC) if, in their view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated. Appropriate proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard errors in the interim analysis of a major endpoint may be needed to justify halting or modifying the trial prematurely, for the superiority hypothesis. The final decision lies with the TSC.

16.4 Sample Size Calculations

A total of 380 patients will be recruited from ten head and neck cancer treatment centres across England and Wales. A minimum of 100 patients will be recruited during the pilot phase of the trial with the remaining patients being recruited within the main trial phase.

The primary outcome measure is OMWQ-HN score at 6 weeks following start of irradiation. According to Epstein 2007, a group difference of 4 points would reflect a meaningful treatment effect. Epstein also reported variability in the QMWQ-HN as a standard deviation of 10.7. As a definitive trial, LITEFORM is powered with small and acceptable errors of 5% α and 10% β. With these parameters, 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 trial team estimate there will be patient drop out, hence the sample size is inflated to 190 patients recruited in each trial arm assuming a maximum of 20% drop-out or missing data. This sample size was calculated using the *power two means* option in Stata (version 13.1) and validated using Julious 2009. The underlying assumptions of the sample size will be monitored by the external Data Monitoring Committee.

17. Qualitative Sub-Study

The qualitative process evaluation will will employ a combination of qualitative research techniques, including formal (audio-recorded) face-to-face and telephone interviews, non-participating observation of launch meetings, site initiation visits and training sessions, and audio-recorded recruitment/consent discussions. Non-participant observation involves the production of contemporaneous field notes from which analytic themes will be identified. Interviews and recruitment/consent discussions will be audio-recorded with the respondent's consent, transcribed and edited to ensure anonymity of respondent. The anonymisedranscripts will be then subjected to formal analysis. Because of the large number of interviews, field-notes, and recordings of discussions

we will use QSR NVivo data collation and management software to assist in analysis. The analysis will be theoretically-informed by Normalization Process Theory. All analysis will be conducted according to the standard procedures of rigorous qualitative analysis [27]. We will use procedures from first-generation grounded theory (coding, constant comparison, memoing) [28] from analytic induction (deviant case analysis) [29] and constructionist grounded theory (mapping) [30]. Data collection and analysis occur concurrently, so that issues raised in earlier rounds of fieldwork can be explored in subsequent iterations. This will involve independent coding and cross checking and a proportion of data to be analysed collectively in 'data clinics' where the research team share and exchange interpretations of key issues emerging from the data.

18. Health Economics

Economic evaluation

A 'within trial' economic evaluation will be conducted to determine the cost-effectiveness of LLLT + usual care versus Sham LLLT + usual care over a 14 month time period. The economic analysis will take the perspective of the NHS, and social services [31]. We will also take a wider perspective by including costs borne by the participants (including, time lost from usual activities, travel time and monetary costs of accessing care). Costs will be based upon the costs of the randomised interventions received and on the use of subsequent care and services. Use of resources associated with treatment (weeks 0-6) will be collected weekly via our Clinical Record Form. This will include duration of treatment and associated staff costs (including grade of staff), additional treatment prescribed as per usual care (e.g. analgesics), appointments missed during this period and any adverse events and associated treatment during this period. Hospital inpatient stays and additional outpatient visits will also be recorded weekly during treatment. All health service utilisation as at end of LLLT will be collected retrospectively at 4 and 14 months via a health care utilisation questionnaire (e.g. use of primary and secondary care services, time off from usual activities (e.g. paid work - where applicable) and private health care payments). Data on travel and monetary costs of accessing care on patients (e.g. out of pocket expenses) will be collected via the time and travel questionnaire administered at 14 months post randomisation.

All costs associated with the delivery of the intervention will be included as part of the micro costing exercise based on information detailed in the eCRF. These will be apportioned to patients using standard methodology [32]. Data on resource use, use of services and time away from usual activities as a consequence of the intervention (obtained from the eCRF, Health Utilisation and Time and Travel

Questionnaires) will be combined with trial specific estimates and nationally available data [31] to produce a cost for each trial participant. When appropriate, discounting will be applied to costs and outcomes at UK recommended rates [33]. From these trial participant costs, a mean cost per intervention to the NHS, to the patient and to the NHS and patient combined will be estimated.

Cost-effectiveness analysis & Cost utility analysis

Two types of economic evaluation, cost effectiveness and cost utility will be carried out:

(1) Cost-effectiveness analysis, based on the incremental cost per change in OMWQ-HN score recorded between baseline and at week 6 of therapy. Mean costs for each randomised arm will be calculated as mean cost per change in OMWQ-HN score. In the cost-effectiveness analysis these will be presented as point estimates of mean incremental costs and effects (improvement in condition specific outcomes (as measured by the OMWQ-HN)) and the incremental cost per change in OMWQ-HN score.

(2) Cost-utility analysis, based on incremental cost per QALY gained. QALYs will be based upon responses to the responses to the EQ-5D 5L and EORTIC QLQ30 converted generic and disease specific utility scores using available algorithms [34]. The EQ-5D 5L and EORTIC QLQ30 will be completed at scheduled time points (baseline, week 6 and 4 and 14 months). QALYs, based upon EQ-5D 5L and EORTC-8D utility scores will be estimated using the area under the curve approach for each trial participant. Both mean cost and QALYs will be presented for each randomised group and incremental mean costs and QALY calculated along with the incremental cost per QALY gained.

For both the cost-effectiveness and cost-utility analyses the results will be presented as point estimates of mean incremental costs and effects as well as in stochastic analysis plots of cost and effects and cost-effectiveness acceptability curves. Deterministic sensitivity analyses will also be performed to explore key uncertainties e.g. valuations of time away from usual activities; sub-groups, etc. Where appropriate these analyses will be combined with a stochastic analysis with the results presented in the same ways as described above. Missing data will be handled within the secondary analysis using appropriate statistical methodologies e.g. multiple imputation methods. The impact of other methods of handing missing data will be explored using sensitivity analysis.

19. DATA HANDLING

19.1 Data Collection Tools and Source Document Identification

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening.

Trial data for an individual patient will be collected by each PI or their delegated person and recorded in the electronic case report form (eCRF) for the trial. Patient identification on the eCRF will be through a unique trial identifier number. A record linking the patient's name to the unique trial identifier number will be held only in a locked room at the trial site, and is the responsibility of the PI. As such, patients cannot be identified from eCRFs. The CI or delegated person will monitor completeness and quality of data recording in eCRFs and will correspond regularly with site PIs (or their delegated team member) with the aim of capturing any missing data where possible, and ensuring continuous high quality of data.

Patients will complete the paper assessment tools as required. The tools will also only be identified using the unique patient identifier number. Data will be entered at sites onto a secure online system, with the paper originals remaining at site.

Audio-recordings of recruitment/consent discussions will contain patient identifiable information. The original recordings will be encrypted and password protected and sent to Newcastle University where selected recordings will be transcribed using purposeful sampling.

19.2 Data Handling and Record Keeping

Overall responsibility for data collection lies with the CI. Data collected on paper assessment tools will be entered onto a secure validated clinical data management system at sites. A unique trial number is allocate at randomisation and will be used to identify participants on all paper data collection forms throughout the duration of the trial. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site. The quality and retention of study data will be the responsibility of the CI. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

Audio-recordings, with consent, will be transcribed verbatim and edited to ensure anonymity of respondent. Contemporaneous field notes from non-participant observation in clinical settings will be edited to ensure anonymity of participants. Qualitative data will be managed using NVivo software.

19.3 Access to Data

Staff involved in the conduct of the trial, including the PIs, Trial Management Group and NHS staff involved in screening and intervention will have access to the site files.

Clinical information shall not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the DMC or the REC. Secure anonymised electronic data may however be released to the trial statistician for analysis. The PI and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

19.4 Archiving

All trial data will be stored for 5 years and in accordance with GCP and the sponsor and Newcastle CTU SOPs.

20. MONITORING, AUDIT & INSPECTION

Monitoring of trial conduct and data collected will be performed by a combination of central review, site monitoring visits and external Data Monitoring Committee to ensure the trial is conducted in accordance with GCP. Trial site monitoring will be undertaken by Newcastle CTU. The main areas of focus will include consent, serious adverse events, data completeness and accuracy relating to the primary and secondary outcomes, and essential documents in Investigator Site Files.

Site monitoring will include:

- All original consent forms will be reviewed as part of the trial file. The presence of the consent form in the ISF and patient notes will be confirmed for 100% participants. Original consent forms will be compared against the trial participant identification list.
- All reported serious adverse events will be verified against treatment notes/medical records (source data verification).
- The presence of essential documents in the ISF and trial files will be checked.

- Source data verification of primary endpoint data and eligibility data for a number of participants (this number will be determined by the NCTU risk assessment which will be documented in the monitoring plan) entered in the trial.

Central monitoring will include:

- Confirmation of the presence of essential documentation and relevant approvals

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The trial may be subject to inspection and audit by the Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

Aggregated data will be analysed by the Trial Statisticians and reported to an external independent DMC at least annually, in open and closed sessions according to the DMC Charter, as agreed with the DMC members at the start of the trial.

21. ETHICAL AND REGULATORY CONSIDERATIONS

21.1 Research Ethics Committee Review and Reports

The CI/Newcastle CTU will obtain a favourable ethical opinion from an NHS REC prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

Newcastle CTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The Sponsor/ Newcastle CTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or USARs that occur during the trial.

An annual progress report will be submitted each year to the REC by the Newcastle CTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The Newcastle CTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

21.2 Peer Review

The trial has undergone peer review as arranged by the NIHR HTA as part of the funding process. The protocol has been reviewed and authorised by the sponsor, funder, Chief Investigator, co-applicants, Senior Trial Manager and Senior Statistician.

21.3 Public and Patient Involvement

A patient and public involvement (PPI) group has been involved in the design and planning of the trial from the start. Patients agreed that OM is the worst part of receiving C(RT) and that anything which might ease this and prevent eating and drinking problems is a top priority.

Two panels of HNC patients were chaired by a patient representative who has been involved in the trial management meetings and will continue in this role throughout the trial setup and duration.

The patients discussed and agreed that randomised sham and treatment groups were acceptable if supported by comprehensive patient information. They also discussed and came to some agreement about the various assessments which would be acceptable for patients to complete whilst undergoing their treatment.

This important link between the patients and the TMG will continue which will enable patients to be involved in the design of patient information sheets.

21.4 Regulatory Compliance

The trial will be conducted in accordance with the Research Governance Framework. Before any site can enrol patients into the trial, that site must have received NHS permission from the site management organisation/Higher Education Institution or NHS Research & Development department.

21.5 Protocol Compliance

It is the responsibility of the CI to ensure that the clinical trial is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI will retain overall responsibility.

Protocol deviations, non-compliances or breaches are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events should be documented in the Case Report Form (CRF) or by the completion of a File Note, in order for Corrective and Preventive Actions (CAPA) to be taken.

Deviations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach

21.6 Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The sponsor will notify the NHS REC within the required timelines in accordance with the sponsor SOP.

21.7 Data Protection and Patient Confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis.

Personal data will be regarded as strictly confidential. All trial files will be securely stored and access restricted to staff involved in the trial. Research staff at sites will enter data from paper forms onto a secure web-based electronic database run and maintained by Newcastle University. Data will be entered using participant unique trial numbers only. Access to this database will be password protected and limited to staff at research sites or Newcastle University who are involved in the trial.

To preserve anonymity, any data leaving the sites will identify participants by their initials and a unique trial identification code only.

Essential data will be retained for a period of at least 5 years following close of trial in line with sponsor policy.

The CI will be the data custodian.

21.8 Indemnity

The sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial. This indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g. General Practitioners or Dentists will provide their own professional indemnity.

This is a non-commercial trial and there are no arrangements for non-negligent compensation.

21.9 Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and trial procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group/Trial Steering Committee.

Substantial amendments will be submitted to the REC and will not be implemented until this approval is in place. It is the responsibility of Newcastle CTU to submit substantial amendments.

Non-substantial amendments may be made at any time with a record of the amendment held in the Trial Master File. Any non-substantial amendment that requires an update to the trial documentation will be submitted to the NHS REC for acknowledgement of the revised version of the document.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by Newcastle CTU.

21.10 Post-Trial Care

If (C)RT is no longer clinically indicated, this will be the reason to discontinue the LLLT treatment for the patient at site.

21.11 Access to the Final Trial Dataset

The data will be the property of the Chief Investigator and Co-Investigator(s).

22. DISSEMINATION POLICY

The findings from this trial will be disseminated to the relevant stakeholders, including medical professionals involved in the Clinical Commissioning Groups, specialised service providers, cancer research institutes, Clinical Review Groups and patient organisations.

Findings will also be published in peer reviewed journals, including open access publications, as well as conferences. The domain name www.liteform.org.uk will be used to retain stakeholder engagement as well as publicising the results.

Findings from the qualitative sub study will be fed into the trial, as well as published in selected qualitative papers at the end of the trial.

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24. APPENDICES

APPENDIX 1: **OMWQ-HN**

Oral Mucositis Weekly Questionnaire – Head and Neck Cancer

1) How much MOUTH AND THROAT SORENESS did you experience in the past week?

0 1 2 3 4

No soreness extreme soreness

2) How much did MOUTH AND THROAT SORENESS limit you in each of the following activities during the past week

	0 not limited				**4 unable to do**
1) Sleeping	0	1	2	3	4
2) Swallowing	0	1	2	3	4
3) Drinking	0	1	2	3	4
4) Eating	0	1	2	3	4
5) Talking	0	1	2	3	4

3) How would you rate your OVERALL MOUTH AND THROAT SORENESS during the past week?

no pain/ soreness worst pain/soreness imaginable/ possible

0 1 2 3 4 5 6 7 8 9 10

4) What number best describes the MOUTH PAIN that you have experienced in the past week?

no pain/ soreness worst pain/soreness imaginable/ possible

0 1 2 3 4 5 6 7 8 9 10

5) What number best describes the THROAT PAIN that you have experienced in the past week?

no pain/ soreness worst pain/soreness Imaginable/ possible

0 1 2 3 4 5 6 7 8 9 10

APPENDIX 2: **WHO Mucositis Oral Toxicity Scale**

Reference:
WHO: http://www.who.int/en/
WHO Handbook 1979, pp.15-22.
Sonis et al. Cancer 2004; 100(9 Suppl):1995-2025.

The World Health Organization has developed a grading system for mucositis based on clinical appearance and functional status.

The WHO scale is dependent on both objective and subjective variables, and measures anatomical, symptomatic as well as functional components of oral mucositis.

WHO Oral Mucositis Grading Scale

Grade	Description
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

APPENDIX 3: MD Anderson Dysphagia Inventory (MDADI)

MD Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing. The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you. Please read each statement and circle the response which best reflects your experience in the past week

1. **My swallowing ability limits my day to day activities**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

2. **I am embarrassed by my eating habits**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

3. **People have difficulty cooking for me**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

4. **Swallowing is more difficult at the end of the day**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

5. **I do not feel self-conscious when I eat**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

6. **I am upset by my swallowing problem**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

7. **Swallowing takes great effort**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

8. **I do not go out because of my swallowing problem**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

9. **My swallowing difficulty has caused me to lose income**

Strongly agree *agree* *no opinion* *disagree* *strongly disagree*

10. It takes me longer to eat because of my swallowing problem

Strongly agree agree no opinion disagree strongly disagree

11. People ask me 'why can't you eat that?'

Strongly agree agree no opinion disagree strongly disagree

12. Other people are irritated by my eating problem

Strongly agree agree no opinion disagree strongly disagree

13. I cough when I try to drink liquids

Strongly agree agree no opinion disagree strongly disagree

14. My swallowing problems limit my personal and social life

Strongly agree agree no opinion disagree strongly disagree

15. I feel free to go out to eat with my friends, neighbours, relatives

Strongly agree agree no opinion disagree strongly disagree

16. I limit my food intake because of my swallowing difficulty

Strongly agree agree no opinion disagree strongly disagree

17. I cannot maintain my weight because of my swallowing problem

Strongly agree agree no opinion disagree strongly disagree

18. I have low self esteem because of my swallowing problem

Strongly agree agree no opinion disagree strongly disagree

19. I feel that I am swallowing a huge amount of food

Strongly agree agree no opinion disagree strongly disagree

20. I feel excluded because of my eating habits

Strongly agree agree no opinion disagree strongly disagree

APPENDIX 4: EORTC Questionnaire H&N35 (version 1.0)and EORTC QLQ-C30 (version 3.0)

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 tha best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent