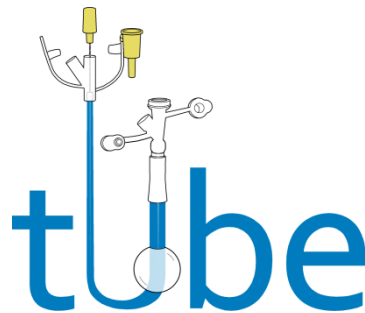


Full title of project

A feasibility randomised controlled trial of pre-treatment gastrostomy tube versus oral feeding plus as-needed nasogastric tube feeding in patients undergoing chemo-radiation for head and neck cancer.

Short title of project

TUBE trial



- ISRCTN Number: 48569216
- REC Reference: 14/NE/0045
- Sponsored by Newcastle upon Tyne Hospitals NHS Foundation Trust
- NUTH NHS Trust reference: 6680
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Chief Investigator:

Professor Vinidh Paleri

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Database Manager	Jonathan Prichard
Speech Therapist:	Dr Joanne Patterson
Qualitative Lead:	Dr Nikki Rousseau
Qualitative Researcher:	Dr David Hamilton
Biostatistics Lead:	Dr Deborah Stocken
Trial Statistician:	Mike Cole
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2. Randomisation Service web link:

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3. Study Website address:

<http://research.ncl.ac.uk/tube/>

4. Protocol Signature Page

Chief Investigator signature

Signature Date

Professor Vinidh Paleri, Chief Investigator

Senior Statistician Signature

Signature Date

Dr Deborah Stocken, Biostatistics Lead

Trial Manager

Signature Date

Dr Ann Marie Hynes, Trial Manager

Local Site Principal Investigator signature

I confirm that I have read and understood protocol version _____ dated _____.

I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature Date

Print Name

Site Name/I.D.

5. Glossary of Abbreviations

CEAC:	Cost-effectiveness acceptability curves
CI:	Chief Investigator
CRT:	Chemo-radiation therapy
CRUK:	Cancer Research UK
DMC:	Data Monitoring Committee
EVOI:	Economic value of information
EVPI:	Expected value of perfect information
EVPII:	Expected value of partial perfect information
EVSI:	Expected value of sampling information
G tube:	Gastrostomy tube
HNSCC:	Head and neck squamous cell cancer
IMRT:	Intensity Modulated Radiotherapy
MDADI:	MD Anderson Dysphagia Inventory
MDT:	Multi-disciplinary Team
NCRI:	National Cancer Research Institute
NE RDS:	North East Research Design Service
NG tube:	Nasogastric tube
NJ tube:	Nasojejunal tube
NHS:	National Health Service
NPT:	Normalization Process Theory
PI:	Principal Investigator (at site)
QALY:	Quality adjusted life years
RCT:	Randomised controlled trial
RT:	Radiation therapy
TMG:	Trial Management Group
TSC:	Trial Steering Committee

6. Responsibilities

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust will act as sponsor for this study.

Funder: National Institute for Health Research, the HTA programme are funding this study.

Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trials Unit.

Principal Investigator: The local site Principal Investigator will have overall responsibility for the conduct of the study at a particular trial site

Trial Management:

The following functions falling under the responsibility of the sponsor will be delegated to Professor Vinidh Paleri [Chief Investigator]:

- Ethics Committee Opinion (including application for research ethics committee favourable opinion, notification of protocol amendments and end of trial, site specific assessment & local approval).
- R&D Approval (including application for global checks, via NIHR CSP).
- Good Clinical Practice and Trial Conduct (including GCP arrangements, data monitoring, emergency & safety procedures).
- Administration of funding for the study.

Trial conduct at sites:

Site Investigator responsibilities:

- Study conduct and the welfare of study subjects.
- Familiarity with the study intervention(s).
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events.
- Screening and recruitment of subjects.
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event.
- Obtaining local approval and abiding by the policies of Research Governance.

- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, the Data Protection Act and any other relevant legislation and regulatory guidance.
- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- The Principal Investigator (PI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed & dated curriculum vitae as evidence for the Trial Master File.
- Ensuring Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintaining study documentation and compliance with reporting requests.
- Maintaining a site file, including copies of study approval, list of subjects and their signed informed consent forms.
- Documenting appropriate delegation of tasks to other study personnel e.g. Research Nurse, Co-Investigator(s), Trial Coordinators, Data Managers.
- Ensuring data collected is accurate, timely & complete.
- Providing updates on the progress of the trial.
- Ensuring subject confidentiality is maintained during the project and archival period.
- Ensuring archival of study documentation for a minimum of 5 years following the end of the study, unless local arrangements require a longer period.

7. Protocol Summary

Short title: A feasibility randomised controlled trial of tube feeding methods in patients undergoing chemo-radiation for head and neck cancer (TUBE trial).

Protocol version: 2.0

Protocol date: 12th November 2015

Chief Investigator: Professor. Vinidh Paleri

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust

Funder: National Institute for Health Research, HTA programme

Trial design: A mixed methods multicentre study to establish the feasibility of a RCT

Trial Intervention:

A multicentre randomised controlled feasibility trial comparing oral feeding plus pre-treatment gastrostomy versus oral plus as required nasogastric tube feeding in patients with head and neck squamous cell cancer (HNSCC).

Primary objective:

To determine whether a definitive RCT in head and neck cancer patients undergoing chemo-radiation comparing prophylactic gastrostomy tube feeding versus oral feeding plus as-needed nasogastric tube feeding is feasible.

Secondary objectives:

To inform the design of a future multicentre definitive RCT by investigating patient, friends and relatives and staff experiences of trial recruitment and participation. To estimate the expected value of information of conducting further research.

Primary outcome measure:

Feasibility defined as:

1. Assess willingness to randomise (by qualitative interviews with /health professionals) and be randomised (by review of patient screening logs).
2. Assess retention and drop-out rates.

Secondary Outcome Measures:

3. Assess compliance and refine interventions and study processes.
4. Estimate parameters to inform definitive trial design.
5. Assess value of information based on modelling exercise.
6. Assess incidence of reported adverse events.

Number of study sites: 3 (with an option to increase if necessary)

Recruitment Target: 60
Trial duration: 24 months

8. Background

Over 7000 new head and neck squamous cell cancers (HNSCC) are treated by the NHS every year. The incidence of oropharyngeal cancer in the UK has more than doubled in the ten years between 1995 and 2006¹. In Scotland, oropharyngeal cancer is the fastest rising of all cancers². In the U.S., it is estimated that in 2020 oropharyngeal cancer will be more common than cancer of the uterine cervix³. Patients with this type of HNSCC form the major group of patients who will be eligible for this research project.

Several advanced (stage III and IV) HNSCC are now treated non-surgically by radiation therapy (RT), or chemoradiation therapy (CRT). In CRT, chemotherapy is delivered concurrently with RT, potentiating tumour kill, but also toxicity. Thus, CRT profoundly affects eating and drinking by causing a range of side effects: loss of taste, dry mouth, pain, loss of appetite and impaired swallow mechanism. Over 90% of patients need nutritional support for severe dysphagia and weight loss during and after CRT, which can be delivered through a pre-treatment gastrostomy (G) tube or nasogastric (NG) tube feeds when necessary. Some clinicians advocate that patients with adequate pre-treatment swallow function and oral intake have pre-treatment G tubes and continue with oral diet during treatment until they are no longer able to take adequate amounts of oral diet to maintain nutritional status. Conversely, others offer patients with adequate pre-treatment swallow function the option of continued oral feeding, until they are unable to take adequate oral nutrition to maintain nutritional status and then proceed with (reactive) passage of an NG tube as and when necessary^{4,5}. Generic guidance suggests that G tubes should be placed in patients that need enteral tube feeding for more than 4 weeks⁶. Approximately 2500 gastrostomies are performed for HNSCC patients in the UK. The insertion costs alone are approximately £3m per annum.

G-tube placement is an invasive procedure with a small, but defined risk of acute serious complications⁷; 25 to 35% of patients retain the tube for >1 year after CRT, 10% > 2 years⁸. A G-tube has a major impact on patients' and carers' quality of life (QoL)^{9,10}, due to leakage, soiling of clothes, and interference with family life, intimate relationships and hobbies¹¹. While NG tube placement is relatively simple, the smaller diameter tube makes it prone to blockage, thus needing repeated placement. When care is not taken to ensure correct placement and /or regular checking of tube tip position, NG tube mis-placement in the lungs and subsequent feeding can lead to significant morbidity, now categorised as a "never event" by the Department of Health¹². Systematic reviews fail to demonstrate evidence for functional, nutritional, quality of life or health economic benefit of either approach^{13,14}. UK practice is correspondingly variable and problematic to quantify¹⁵. Both NG and G tube users need community support, with greater needs for NG tube users. The National Patient Safety Agency recommends that a full multidisciplinary supported risk assessment should be made and documented, before a patient with a nasogastric tube is discharged from acute care to the community. There is evidence that clinicians in some areas opt for G-tubes due to barriers to the delivery of NG tube nutritional support in the community. However, a recent British Society of Gastroenterology survey showed that only 64% of G-tube services offer an aftercare service¹⁶.

Long-term dysphagia is now recognised as the principal functional consequence of CRT for HNSCC, and patients report this as a top priority^{14, 17}. Dysphagic patients and those dependent on tube feeds (G and NG tubes) need significant long-term supportive care and suffer from impaired quality of life⁹. The effect of enteral feeding route on the swallowing outcome is not well understood. Prophylactic Gastrostomy placement allows patients to start enteral feeding immediately compared to reactive NG Tube feeding. Some patients may choose to use their gastrostomy sooner than if a reactive NG Tube is placed. Patients should always (regardless of feeding tube placed) be encouraged to take oral diet however it is likely that patients using gastrostomy tubes may exhibit a reduction in use of the swallowing musculature. This reduction in use of the swallowing musculature, combined with the mucositis caused by radiation has been hypothesised to increase the risk of fibrosis in the muscles and pharyngo-oesophageal stricture.

The most severe CRT reaction that causes dysphagia is complete closure of the gullet, devastating for the individual and with huge costs for the NHS. This risk may be higher with G-tube use, which bypasses the gullet, unlike an NG tube which maintains a degree of oesophageal patency. Reconstruction requires complex major reconstructive surgery of the upper aerodigestive tract - with direct care costs of \approx £32,000 per patient¹⁸ and a significant morbidity for the patients involved. This problem is seen even after Intensity Modulated Radiotherapy (IMRT), a new method of delivering radiation therapy, which aims to limit morbidity by sparing the dose to some structures like the salivary glands. There are national guidelines recommending that the proportion of HNSCC patients treated by IMRT be increased¹⁹. However, with respect to swallowing outcomes, IMRT has been shown to increase stricture rates by 3.3 times²⁰, up to 46% of HNSCC patients treated by IMRT may need oesophageal dilatation,²¹ an intervention that needs inpatient care, is distressing to the patient and associated with complications.

A systematic review¹⁴ has suggested that feeding route during treatment may impact on the swallow performance after CRT. Four retrospective studies²²⁻²⁵ one prospective study²⁶ and one RCT (with small patient numbers)²⁷ have identified that swallowing difficulties are more prevalent in patients receiving a prophylactic G-tube, even in the long-term. However, existing research on the association of early G-tube feeding and long term swallow impairment has been inconclusive due to small participant numbers, by the use of insensitive dysphagia measurements and by limited long-term follow-up. The sole RCT²⁷ recruited from a single Australian centre in an area of low population density. A Cochrane review¹³ identified no further eligible trials and concluded that there was insufficient evidence to determine the optimal method of enteral feeding for patients with HNSCC receiving RT or CRT.

These two methods have never been properly compared to establish which leads to better outcomes for patients, despite calls for better information to guide patient and clinician decisions^{13, 22, 27}. We therefore wish to conduct a RCT to compare the two feeding methods (oral feeding plus pre-treatment gastrostomy versus oral feeding plus as needed nasogastric tube). Because a similar trial in Australia²⁷ failed to recruit enough patients, we wish to first carry out a feasibility study to see whether a RCT is possible and how it should be conducted. Thus, research on this area may serve to direct resources appropriately, reduce unnecessary interventions and thus reduce morbidity, mortality and improve swallowing outcomes.

9. Objectives

Our principal aim is to determine whether a definitive RCT in head and neck cancer patients undergoing chemoradiation comparing oral feeding plus prophylactic gastrostomy tube feeding versus oral feeding plus as-needed nasogastric tube feeding is feasible. Second, we seek further clarity as to how a definitive trial should best be designed from the perspectives of patients, health professionals and NHS resources. The TUBE study feasibility trial is a necessary prelude to a full trial of these complex interventions, to assess whether an adequate proportion of eligible patients can be recruited and retained in the study as assessed, both quantitatively and qualitatively.

The three specific TUBE objectives are:

A. To explore barriers and facilitators to trial implementation and to use this information to improve recruitment and retention. To this end we will review:

- i. Willingness of health professionals (including clinical oncologists, surgeons, dieticians, speech and language therapists) to recruit patients.
- ii. Willingness of participants to be randomised, to accept and persist with allocated treatment and comply with assessments.
- iii. Qualitative assessment of patient and friends and family perspectives on trial participation, barriers to randomisation among non-participants, acceptability of assessment tools and experience of the tube-feeding and the conduct of the trial in participants. Reasons for and characteristics of patients dropping out.

B. To carry out preliminary estimation of key parameters to inform design and study processes. To this end we will:

- i. Assess parameters which inform power calculations for a definitive trial with consideration to possible primary outcomes including incidence of dysphagia, as measured by CTC, and dysphagia related quality of life, as measured by MD Anderson Dysphagia Inventory (MDADI) HNSCC-specific self report scale (variation and differences in change from baseline over time).
- ii. Trial our subsidiary QoL outcomes (the European Organization for Research and Treatment of Cancer questionnaires EORTC QLQ-C30, EORTC QLQ - H&N35), SF-36 a multi-purpose, short-form health survey and data collection tools for use of health and personal social services and patient costs.
- iii. Monitor nutritional parameters: Body mass index, weekly weight changes (during treatment), quantity of enteral nutrition and type of diet texture consumed.
4. Monitor oral health parameters: caries incidence, tooth loss, periodontal indices.

5. Derive an algorithm for switch to NG tube in the oral intake arm that is acceptable to patients and dietitians.

C: Explore cost effectiveness of the two tube feeding options. For this objective we will:

- i. Assess economic value of information based upon a modelling exercise informed by the feasibility study and the existing systematic reviews.
- ii. Provide a preliminary estimate of the costs, effects and relative cost-effectiveness of the alternative methods of nutritional support based upon the modelling exercise.

10. Trial Design

This is a mixed methods multicentre trial to establish the feasibility of a RCT of feeding methods in patients with stage III and IV head and neck cancer receiving chemoradiation therapy with curative intent. The work will be conducted over 24 months.

The components are:

1. A multicentre randomised controlled feasibility trial comparing oral feeding plus pre-treatment gastrostomy versus oral feeding plus as required nasogastric tube feeding in patients with HNSCC.
2. A qualitative process evaluation to inform future trial design by investigating patient, family and friends and staff experiences of trial participation
3. An economic modelling exercise to synthesise available evidence and provide estimates of cost-effectiveness and value of information

10.1 Setting:

For the feasibility trial we envisage recruiting three tertiary NHS centres for HNSCC, two in the north and one in the south of England. If necessary additional centres could be identified and recruited via our links with the National Cancer Research Network, Comprehensive Clinical Research Network and from respondents to our national survey.

10.2 Participants:

Patients with stage III and IV HNSCC who are suitable for primary CRT with curative intent. This can include patients who are deemed suitable to receive induction chemotherapy. Eligibility is as defined in 10.11.

10.3 Feasibility Sample size:

Target recruitment is a total of 60 patients (30 per randomised intervention).

10.4 Subjects to be recruited for Qualitative process evaluation

Data collection will focus on three inter-related phases over the life of the trial; 1) study set up; 2) patient recruitment and 3) patient follow up. This includes interviews with 15-24 health professionals, interviews with 32-36 patients, observations of 9-18 recruitment discussions and observations of 6-15 MDT meetings. Numbers have been included to give an indication of the amount of data to be collected. However, in keeping with the principles of rigorous qualitative research, we will be responsive to the study context, and anticipate that in some cases fewer interviews or observations will be conducted, and in others, additional data will be collected in response to our emerging analysis or study events. We anticipate that the total number of interviews/observations will be within the ranges indicated.

10.5 Duration of study definitions (recruitment, treatment/follow-up phase)

The feasibility study has a proposed total duration of 24 months. Appendix 2 is a flow chart showing the main phases of the study for patients who are randomised.

- **Recruitment phase:** Patient recruitment is estimated to take 9 months. All patients will be consented and randomised before the onset of their CRT.
- **Treatment phase:** Treatment is defined as CRT plus randomised intervention. CRT treatment will be as usual centre practice and will usually be completed within two months.
- **Follow-up phase:** Follow-up for patients will be at 3 and 6 months after CRT treatment is completed
- **End of trial:** is defined as the last 6-month observation of the last patient in the follow-up phase of the trial and is anticipated to be 17 months after recruitment of the first patient.

10.6 Primary Outcome measure

Feasibility defined as:

1. Assess willingness to randomise through qualitative interviews with health professionals at each site
2. Assess willingness to be randomised (by review of patient screening logs).

Defined as:

- i. the number of patients consenting to be randomised as a proportion of all patients approached about the trial, with reasons for non-consent
 - ii. qualitative assessment of barriers and facilitators to recruitment
3. Assess retention and drop-out rates. Defined as:
 - i. the number of patients who start randomised treatment as a proportion of the number randomised, with reasons for non-compliance
 - ii. the number of patients who complete randomised treatment as a proportion of the number randomised, with reasons for non-compliance (including death)
 - iii. the completeness of primary outcome measurement (MDADI at 6 months).
 - iv. qualitative assessment of barriers and facilitators to data collection and participant retention.

10.7 Secondary Outcome Measures:

1. Compliance with interventions and study processes defined as the number of patients who complete patient reported outcomes at each time point, including baseline, with reasons for non-compliance (including death).

Outcome measures for a definitive trial will be rehearsed in this feasibility trial with assessment before randomisation, the end of CRT and at 3 and 6 months after CRT treatment. In the majority of cases who are not receiving induction chemotherapy, data collection will take place at approximately 4-8, 20 and 32 weeks after baseline (assuming that CRT treatment will be completed in most cases between weeks 4-8 post randomisation). Cases who receive induction chemotherapy will usually receive this within the first 6 weeks of screening and

baseline/randomisation with CRT following on at around week 6. In these cases the research data collection will therefore take place at approximately 10-14, 26 and 38 weeks after baseline.

Data will be requested of all randomised patients and will be collected by research nurses/clinical team members in clinic:

- a) The MD Anderson Dysphagia Inventory (MDADI).
- b) Quality of Life outcomes: The European Organization for Research and Treatment of Cancer questionnaire EORTC QLQ-C30 (version 3.0) and the EORTC QLQ - H&N35 is the head and neck module.
- c) Short Form 36 (SF-36)
- d) Nutritional parameters will include:
 - i. Body mass index
 - ii. Weekly weight changes and the quantity of enteral nutrition consumed during treatment.
 - iii. Type of diet texture consumed (Performance Status Scales: Normalcy of Diet)
- e) Oral health assessment (full dental chart with panoramic radiographs) at randomisation and at 6 months for all dentate patients. This will allow identification of caries and periodontal bone levels. Periodontal and oral hygiene assessment and plaque scores will also form part of this assessment. WHO CPITN scores will routinely be recorded as will plaque scores.
- f) Other clinical outcomes to be recorded:
 - i. Number of pharyngeal/oesophageal dilatations per patient
 - ii. Tumour status at follow up (decisions made as per local practice): clinically disease free, Alive with disease, Died of disease, Died of other causes
 - iii. Tube dislodgements
 - iv. Migration from NG group to G tube

2. Estimate parameters to inform the design of a definitive trial.

Assess parameters which inform design for a definitive trial with consideration to possible primary outcomes including incidence of dysphagia, as measured by CTC, and dysphagia related quality of life, as measured by MD Anderson Dysphagia Inventory (MDADI) HNSCC-specific self report scale (variation and differences in change from baseline over time), as described in the previous section.

3. Assess value of information based on modelling exercise:

Health Economics Costs (see section 18).

Use of health and personal social services and costs to patients and their families.

4. Assessment and reporting of incidence of adverse events reported.

10.8 Definition of end of study:

The end of study will be the last 6-month follow up observation on the last patient in the follow-up phase of the trial.

10.9 Subject population:

Patients with stage III and IV HNSCC who are suitable for primary CRT with curative intent. This can include patients having induction chemotherapy prior to CRT. All patients would have been investigated and diagnosed as above by the respective cancer MDT.

10.11 Inclusion and Exclusion Criteria

Inclusion criteria:

1. Grade 1 pre-treatment dysphagia, as defined by Common Terminology Criteria for Adverse Events v4.0 (defined as: asymptomatic / symptomatic / able to eat regular diet).
2. Consent to be randomised.

Exclusion criteria

Patients who:

1. decline to participate.
2. are unable to give informed consent.
3. cannot receive a gastrostomy for medical reasons.
4. do not receive treatment with curative intent.
5. have malnutrition requiring immediate initiation of enteral feeding.

Clinical experience suggests that patients with primary sites in the oropharynx, hypopharynx larynx, nasopharynx and unknown primaries are those who will fulfil the inclusion criteria (~35% to 40% of all HNSCC patients).

11. Screening, Recruitment and Consent

11.1 Identification and screening of participants

All potentially eligible patients will be identified from the Head and Neck cancer MDT meetings, subject to satisfying the inclusion and exclusion criteria for the trial. This information will be captured on site screening records and ultimately transferred into an electronic screening form on the electronic data capture system for the trial. Criteria for trial participation can often be ascertained by reference to records; where further information is necessary, the PI will gather this by taking a careful history from the participants. An eligibility screening form will be completed by the investigator to document participants' fulfilment of the entry criteria for all patients considered for the study and subsequently included or excluded.

The screening records for each patient will be updated following recruitment discussions and randomisation to document recruitment outcome details of all subjects invited to participate in the study. The log will record information relating to inclusion and exclusion criteria and whether or not patients wish to be part of the randomised feasibility trial and/or the qualitative interviews. Regular review and completion of the screening logs by sites will ensure that potential participants are only approached once. Please see the TUBE Enrolment Flow chart (APPENDIX 1).

The screening assessments (as per routine clinical practice) would usually occur about 2 weeks prior to collection of baseline data and randomisation.

11.2 Recruitment procedures

All sites where patients are recruited are full research sites. Eligible patients will be seen at routine appointments for CRT planning and invited by the PI or a delegated member of the clinical team (often a research nurse) to participate in the trial. The PI or delegated individual will explain the trial to the patient, give them the Patient Information Sheet and answer any questions they may have.

There will be two versions of the patient information sheet – to account for whether patients allocated to the Pre-CRT gastrostomy arm are to have the gastrostomy inserted under x-ray guidance or endoscopically. Sites must determine which version is appropriate for their patients depending on their chosen method of insertion.

Due to the small subject population, the information sheets and consent forms for the study will be available only in English. Interpreters will be provided if necessary for patients who have difficulty understanding English.

The patients will be encouraged to take the information leaflet home and discuss it with family and friends. Following receipt of information about the study, participants will be given reasonable time (minimum of 24 hours) to decide whether or not they would like to participate. A research nurse will follow up all invited patients with a telephone call and arrange to discuss the study further with them and/or take consent at their next hospital

appointment (this could be at a mould making appointment, kidney function test appointment or MRI planning appointment for example).

If a participant refuses to join the trial, the reason for refusal would be sought. If the participant initially joins and subsequently withdraws, the reason for withdrawal would also be sought. The rights of patients to refuse to participate or withdraw without giving reasons will be respected.

11.3 Consent procedures for the randomised trial

Informed consent discussions for the randomised feasibility trial will be undertaken by appropriate site staff involved in the study (as per delegation log), including medical staff and research nurses, with opportunity for participants to ask any further questions.

The delegated site staff taking consent will ensure that the patient has understood the information and he/she would be asked to sign and date the consent form agreeing to participate in the trial. The consent form will be witnessed and dated by a member of the research team with documented, delegated responsibility to do so.

The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. Copies of consent forms will also be faxed to Newcastle Clinical Trials Unit for purposes of centralised monitoring of the consent process. The participant will specifically consent to their GP being informed of their participation in the study. At the time of consent the participant will also be asked to fill in the baseline study questionnaires, which will also be sent to/kept in the site trial office.

The right to refuse to participate without giving reasons will be respected.

At this stage, all patients will also be asked to indicate whether they would be happy to be approached for subsequent interview by the qualitative researcher. Both patients who do and do not consent to participate in the randomised trial will be invited to participate in the qualitative interviews.

Outcomes of the consent process will be updated on screening logs.

12. Study Intervention Details

Study participants will be randomised to one of two treatment arms:

- Pre-CRT gastrostomy arm

Or

- No pre-CRT gastrostomy arm

In both arms, patients will be given information about the treatment, and the intervention involved. This will be delivered by the PI at the centre and reinforced by the research nurse.

12.1 Pre-CRT gastrostomy arm:

G-tube insertion will take place before CRT commences, ideally in weeks two and three after most patients are randomised. Where patients are receiving induction chemotherapy G-tube insertion may take place on either the week before cycle 2 of induction or the week pre CRT. G-tubes are inserted into the stomach through an abdominal incision, by either endoscopic or radiologic guidance, both being functionally equivalent. Given the pragmatic nature of this study and equivalent success rates with either technique²⁹, the choice of method of insertion will be left to the treating clinician/centre. Patients will continue with oral feeding throughout CRT unless or until they are unable to maintain an adequate oral intake to meet their nutritional requirements *(see guidance in 12.3) or are unable to swallow. At this stage the use of liquid nutrition through the G tube will commence.

12.2 No pre-CRT gastrostomy arm:

This group of patients will continue oral feeding throughout CRT, unless or until they are unable to maintain an adequate oral intake*(see guidance in 15.3) or inability to swallow, when an NG tube will be placed according to local hospital policy and liquid nutrition via an NGT will commence. Confirmation of correct placement must be made based on national NPSA and local guidelines. The decision to place a nasogastric tube will be based on clinical assessment, patient request and published guidelines⁶.

12.3 Guidance on when to initiate enteral feeding in both treatment arms:

*National guidelines state that tube feeding should commence when a patient is at risk of malnutrition and has an inadequate oral intake. In practice this is quite difficult to determine without collecting detailed food/oral supplements intake data to determine when oral intake is inadequate. Such an exercise is also beyond the scope of this study.

As a guideline for this protocol we have set a figure of <75% of requirements as a measure of inadequacy and this would equate to about 1-2 lbs (0.5kg) of weight loss per week. This guideline applies to both treatment groups. The <75% threshold will not be ascertained by exact measurement but based on a dietetic assessment of 24 hour recall by patients.

This <75% guideline is more conservative and would lead to less weight loss in this patient population than the ESPEN guidelines which stipulate 60% and predict continued poor oral intake for >10days. The qualitative part of this study will further investigate patient views on the appropriate time to initiate enteral feeding.

12.4 Tube removal in both treatment arms:

Tube removal will be determined by Dietetic assessment. Once a patient is able to take >75% of estimated nutritional requirements by mouth and patient is weight stable then gastrostomy or NGT can be removed.

13. Randomisation and Blinding

13.1 Randomisation

Randomisation will be administered centrally by the Newcastle Clinical Trials Unit internet-accessed secure web-based system which provides ease of operation, accessibility 24 hours a day, with in-built validation/plausibility checks at time of data entry.

A block-stratified block method (based on permuted random blocks of variable length) will be used to allocate participants to the two groups in a 1:1 ratio. Randomisation will be stratified by centre to allow for any differences in care or case mix that could alter outcomes. The use of induction chemotherapy will not be a stratification factor in this feasibility trial but will be recorded at the time of randomisation to inform possible stratification factors in a definitive trial. An individual not otherwise involved with the study will produce the final randomisation schedule for use by this system.

The PI at site or an individual with delegate authority will access the web based randomisation system. Patient screening ID, initials and details of stratifying variables will be entered into the web-based system, which will return a unique patient trial number (TNO) and the randomised treatment allocation. Participants will be informed of their randomised treatment group at the point of randomisation.

Randomisation service website: <http://apps.ncl.ac.uk/random/>

Queries about the randomisation system can also be addressed to:
nctu-enquiries@newcastle.ac.uk

13.2 Blinding

Due to the nature of the tube feeding interventions it will not be practical to blind research nurses to the treatment allocated to patients for the follow up assessments. The baseline data capture assessments will however be completed by research nurses before randomisation in order to reduce bias.

14. Trial Data

14.1 Patient Assessments and Data Collection

Research nurses in each unit will co-ordinate assessments and data collection, once written consent has been taken. The first research visits will, wherever possible, be co-ordinated with patients' pre-treatment planning appointments and will take place in the treating hospital. Some of the assessments will already have been collected as part of routine clinical information (i.e. height / weight, oral health assessment) and permission will be sought as part of the consent process to access this clinical information to avoid duplication. Wherever possible, patients will be encouraged to complete the questionnaires at the research visit where the research nurse will be available to give assistance as appropriate and to increase the rate of returns.

The research nurse will identify the time point for the follow up research visits. These visits will be combined with follow up cancer surveillance appointments at their head and neck cancer unit, wherever possible.

See Appendix 2- TUBE Flow chart for randomised patients

The patient visits for the feasibility RCT and associated data to be collected are as follows:

Initial screening visit:

Patients will be provided with information about the trial at this appointment. An eligibility screening form will be completed.

Consent, Baseline visit(s) and Randomisation.

The consent and baseline visit will take place at least 24 hours after the patient has been provided with the trial information. If necessary this visit can be split over two appointments (to be completed 0-14 days before randomisation and thus before trial intervention).

Patient eligibility will be re-confirmed. Informed consent will be taken then baseline assessments and baseline questionnaires will be completed.

The baseline data include:

Site of disease

Patient demographics

TNM Classification

Record of whether induction chemo is planned

Record of whether or not IMRT is planned

Whether the patient has been given any pre-treatment swallowing exercises and if so, if the patient complied with them (record as yes/no)

The MD Anderson Dysphagia Inventory (MDADI).

EORTC QLQ-C30 (version 3.0)

EORTC QLQ - H&N35

Short Form 36 (SF-36)

Body mass index and usual weight

Performance Status Scale; Normalcy of Diet

Data from oral health assessment performed as standard NHS care (includes information from panoramic radiograph, dental chart, periodontal and oral hygiene assessment plaque scores, oral opening measurement and oral dryness).

After baseline data and consent is collected randomisation will be performed. Patients will be informed of their randomisation allocation and given the opportunity to ask further questions.

Intervention visit:

Interventions to be performed as follows (timing dependent on treatment arm):

Pre-CRT gastrostomy arm: G-tubes are inserted after the consent, baseline visit and randomisation but before any treatment (CRT/ IMRT) can take place. G-tubes can be inserted during induction chemotherapy if necessary.

No pre -CRT gastrostomy arm: NG tube to be inserted after the consent, baseline visit and randomisation at a point when patient and/or clinician feel this is most appropriate (see guidance in section 12.3). NG tube placement can thus be flexible i.e., during or after CRT treatment as required.

Given the inclusion criteria, it is not anticipated that any patients will need NG tube placement before the CRT treatment starts.

At the intervention visit the following details must be recorded (irrespective of treatment arm):

- Date of intervention visit.
- Pre intervention oral/dietary intake (before intervention). Expressed as a percentage of normal intake.
- Performance Status Scale; Normalcy of Diet
- Pre intervention weight (and note of any weight change since baseline).
- Adverse events

Weekly Data collection:

This additional information must be extracted from NHS patient records and recorded by research nurses/clinical teams and captured in the study eCRFs during CRT treatment:

- Dates of induction chemotherapy start and finish plus number of cycles received (if applicable).
- Dates of CRT start and finish plus number of cycles received.
- Details of RT technique (IMRT, unilateral vs bilateral, conformed vs parallel opposed fields)
- RT dose
- Mean dose to pharyngeal constrictor muscles
- Chemotherapy regimen details
- Weekly weight (during CRT the patient must be weighed weekly to document weight changes and calculate BMI).
- Performance Status Scale; Normalcy of Diet
- Any site infections and date of occurrence.
- Any x-rays (associated with tube placements) and date of occurrence.
- Any pH problems requiring NG tube placement and date of occurrence.
- Any tube changes (e.g. NG Tube to NJ Tube or NGT to another NGT) and date of occurrence.
- Degree of reliance on feeding tube use (either NG Tube, NJ Tube or G Tube) and date.
- Feed related hospital admissions (dates from/to).
- Access to dietetic services and dates.
- Once taking enteral feed – quantity prescribed and quantity consumed
- District nurse visits and dates.
- Tumour status: clinically disease free, Alive with disease, Died of disease, Died of other causes (decisions made as per local practice).
- Adverse events to be recorded in AE CRF (including details of any visits to accident and emergency (and dates) as well as any hospital admissions, (and dates) and whether nutrition related or not).

Follow up visit at CRT completion:

The following information should be collected:

MDADI

EORTC QLQ-C30 (version 3.0).

EORTC QLQ - H&N35.

Short Form 36 (SF-36).

Body mass index, weight.

Performance Status Scale; Normalcy of Diet

Update records with: Number of tube dislodgements, number of site infections, number of NG/NJ Tube placements, number of x-rays required for NG Tubes and any pH problems requiring tube replacement in the no pre CRT Gastrotomy arm.

Migration from NG-tube to G tube or replacement of NGT/G-tube.

Tube status – in or out, removal date (including a record of whether the patient met >75% nutritional requirements by oral intake at removal).

Tube used/not used.

Adverse events to be recorded in AE CRF (including details of any visits to accident and emergency (and dates) as well as any hospital admissions, (and dates) and whether nutrition related or not).

Tumour status: clinically disease free, Alive with disease, Died of disease, Died of other causes (decisions made as per local practice).

Follow up visit at three months post CRT completion:

The following information should be collected:

The MD Anderson Dysphagia Inventory (MDADI).

EORTC QLQ-C30 (version 3.0).

EORTC QLQ - H&N35.

Short Form 36 (SF-36).

Body mass index, weight.

Performance Status Scale; Normalcy of Diet

Use of health and personal social services and costs to patients and their families/friends (excluding use of weekly/biweekly services in cancer clinic).

Number of pharyngeal/oesophageal dilatations per patient.

Tumour status: clinically disease free, Alive with disease, Died of disease, Died of other causes. (decisions made as per local practice)

Update records with: Number of tube dislodgements, number of site infections, number of NG/NJ Tube placements, number of x-rays required for NG Tubes and any pH problems requiring tube replacement in the no pre CRT Gastrotomy arm.

Migration from NG-tube to G tube or replacement of NGT/G-tube.

Tube status – in or out, removal date (including a record of whether the patient met >75% nutritional requirements by oral intake at removal).

Tube used/not used.

Update records with and weekly weight changes since end of CRT and quantity of enteral nutrition consumed.

Access to rehabilitation services including frequency of dietetic and speech and language therapy follow up.

Adverse events to be recorded in AE CRF (including details of any visits to accident and emergency (and dates) as well as any hospital admissions, (and dates) and whether nutrition related or not).

Follow up visit at six months post CRT completion:

The following information should be collected:

The MD Anderson Dysphagia Inventory (MDADI).

EORTC QLQ-C30 (version 3.0).

EORTC QLQ - H&N35.

Short Form 36 (SF-36).

Body mass index, weight.

Performance Status Scale; Normalcy of Diet

Data from oral health assessment performed as standard NHS care (includes information from panoramic radiograph, dental chart, periodontal and oral hygiene assessment plaque scores, oral opening measurement and oral dryness).

Use of health and personal social services and costs to patients and their families/friends.

Number of pharyngeal/oesophageal dilatations per patient.

Tumour status: Disease free, Alive with disease, Died of disease, Died of other causes. (decisions made as per local practice)

Update records with: Number of tube dislodgements, number of site infections, number of NG/NJ Tube placements, number of x-rays required for NG/NJ Tubes and any pH problems requiring tube replacement in the non pre-CRT gastrostomy group.

Migration from NG tube to G tube or replacement of NGT/G tube

.

Tube status – in or out, removal date (including a record of whether the patient met >75% nutritional requirements by oral intake at removal)

Tube used/not used

Update records with weight changes and quantity of enteral nutrition consumed.

Access to rehabilitation services including frequency of dietetic and speech and language therapy follow up.

Adverse events to be recorded in AE CRF (including details of any visits to accident and emergency (and dates) as well as any hospital admissions, (and dates) and whether nutrition related or not).

Follow up visit at twelve months post CRT completion:

The following information should be collected:

The MD Anderson Dysphagia Inventory (MDADI).

EORTC QLQ-C30 (version 3.0).

EORTC QLQ - H&N35.

Short Form 36 (SF-36).

Body mass index, weight.

Performance Status Scale; Normalcy of Diet

Number of pharyngeal/oesophageal dilatations per patient.

Tumour status: Disease free, Alive with disease, Died of disease, Died of other causes. (decisions made as per local practice).

Update records with: Number of tube dislodgements, number of site infections, number of NG/NJ Tube placements, number of x-rays required for NG/NJ Tubes and any pH problems requiring tube replacement in the non pre-CRT gastrotomy group.

Migration from NG tube to G tube or replacement of NGT/G tube

Tube status – in or out, removal date (including a record of whether the patient met >75% nutritional requirements by oral intake at removal)

Tube used/not used

Update records with weekly weight changes and quantity of enteral nutrition consumed.

Access to rehabilitation services including frequency of dietetic and speech and language therapy SLT follow up.

Adverse events to be recorded in AE CRF (including details of any visits to accident and emergency (and dates) as well as any hospital admissions, (and dates) and whether nutrition related or not).

14.2 Additional interviews and observations for Qualitative process evaluation

The qualitative sub-study involves interviews with: patients; their family/friends; staff involved in recruitment for the TUBE trial, and staff involved in clinical care for this patient group and/or delivery of the TUBE interventions. It also involves observation/audio-recording of recruitment discussions for TUBE.

Interviews with patients, friends and family members 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.

Qualitative Study Consent Details: Interviews

During the recruitment discussion where written consent is taken for participation in the TUBE trial, patients and any friends/family present will be asked whether they are willing to be contacted about an interview for the qualitative sub-study. Written consent to contact will be taken. Contact details for patients and friends/family consenting to contact for the qualitative sub-study will be made available to the qualitative researcher who will access the data on the study database.

There will be a separate information sheet for patients and any family/friends who agree to be contacted about the qualitative interviews; this will be given to those consenting to contact at the recruitment discussion. Written consent will be obtained prior to the start of face-to-face interviews; the qualitative researcher will keep a record of verbal consent for qualitative study interviews conducted by telephone.

Patient and family/friend interviews:

Those patients and carers who express interest in the qualitative interview element of the study (including both patients who consent to randomisation and those who decline randomisation) will be contacted by telephone by the qualitative researcher to further discuss their participation. Patients and family/friends from Sunderland and Newcastle will be offered a choice of location and method (telephone; face to face) of interview. Patients and family/friends outside the North East will be offered telephone interviews (efforts will be made to enable a face to face interview for patients outside the North East who have a preference for this approach however telephone interviews have proved very acceptable in other recent feasibility studies including those with patients undergoing treatment for cancer). Health care decision making is distributed³⁴ and is likely to involve other significant individuals³⁵. Patients who wish to involve a family member in their interview will be able to do so. We will conduct in-depth interviews with 10 patients who consent to participate in the RCT (5 in the G-tube and 5 in the oral feeding group) and with 6 to 10 patients who decline to participate in the RCT. Where possible, the 8-10 patients for the follow up interviews will include those interviewed at recruitment (and consenting to participate in the trial); additional participants will be recruited based on purposive criteria (including length of time of oral and/or supplementary feeding).

Interviews will take place with patients at two time points; 1-2 weeks after the initial recruitment discussions (to understand barriers and facilitators to recruitment), and during patient follow-up (to understand patients' experiences of trial participation).

Summary of interview data collection

- 1-2 weeks after recruitment discussion
 - Trial participants (n=10): experiences of recruitment; views on supplementary feeding; reasons for participation; feelings about randomised allocation.
 - Family and friends of participants (n=6-10): experiences of recruitment; views on supplementary feeding; reasons for participation; feelings about randomised allocation.
 - Trial decliners (n=6-10): experiences of recruitment; views on supplementary feeding; reasons for declining.
 - Family and friends of decliners (n=6-10): experiences of recruitment; views on supplementary feeding
- 6 months follow up
 - Trial participants (n=8-10): experiences and views of TUBE trial (outcome measurement etc); experiences of supplementary feeding.

- Family and friends of participants (n=6-10); experiences of supplementary feeding; views of TUBE trial.

Patient consent for observation/audio-recording of recruitment discussions.

Observation/audio-recording of recruitment discussions has been key to improving recruitment processes in other randomised trials³¹. However it does pose challenges because consent to audio-record needs to be obtained in advance of consent to participate in the TUBE trial. In designing our consent process for this part of the study we have been mindful of the need to avoid overburdening participants with information, and of the need to consider consent for family or friends who may attend the recruitment discussion.

This part of the study is open to all patients eligible for TUBE; including those declining participation in TUBE and including those declining participation in the interview sub-study.

We have designed a three stage consent process for this part of the study; balancing the need for informed consent with the need not to disrupt the process of consent for the TUBE trial.

The main study information sheet, given to patients in advance of the recruitment discussion, includes a brief outline of the purpose and design of the observation/audio recording of recruitment discussions.

1. At the start of the recruitment discussion, verbal consent to record the conversation will be obtained; it will be explained that more information about this will be given during the discussion and that there will be an opportunity at the end of the discussion to rescind consent. All present must give verbal consent; if anyone declines to give verbal consent then audio-recording must not take place.
2. Written consent for audio recording will be taken as part of the consent process for TUBE. There are separate consent forms for those declining participation in TUBE and for family/friends present. All present must give written consent for audio recording; if anyone present declines consent then the recording must be deleted immediately (while those declining are still present).
3. Those patients and family/friends giving written consent to keep the audio recording are given a follow up information sheet. Prominently on the front page of this information sheet is information that patients and family/friends have a further opportunity to change their minds on audio recording by getting in touch either with the recruitment nurse or the qualitative study team.

Health professionals interviews and observations:

Interviews with health professionals will be conducted by a qualitative researcher. Written informed consent will be obtained to audio-record face-to-face interviews and recruitment discussions. Where telephone interviews are conducted, verbal consent will be obtained at the start of the interview process.

Pre-pilot interviews will occur before patient recruitment commences at study sites. The aim of these interviews is to understand and map existing processes of care in relation to supplementary tube feeding in patients undergoing CRT for head and neck cancer. Each of

the three study sites will be visited for a period of 2 days; during this time key individuals from professions involved in treatment planning for HNSCC (dietitians, nurses; speech therapists; ENT surgeons (n=3-4 per site)) will be interviewed. Additional face to face or telephone interviews will be conducted if necessary with individuals not available during the main site visits.

During the period of patient recruitment data collection will again consist of visits to the study sites to interview individuals involved in patient recruitment (n=2-3 per visit). In addition, study recruitment discussions will, with consent of both patient and health professional, be observed and audio taped (4-6 recruitment discussions at each site (n=12-18 in total)). An initial visit to each site will take place shortly after (3-6 weeks) the site commences patient recruitment. The timing of subsequent visits to sites will be purposive and informed by factors such as emerging variation in recruitment rates between sites; changes in key personnel etc.

14.3 Table of Events (randomised trial and qualitative study):

Visit/Interview Type	Pre-start Activities	Initial screening visit	Consent, Randomisation and Baseline visit(s).		Trial Intervention visit	Data capture during CRT	Data capture at end of CRT	Follow-up	Follow-up
Timing	Before patient recruitment commences at sites	At least 24 hours before randomisation	Consent and baseline data collection (to occur before randomisation)	Randomisation (0-14 days after baseline and consent)	Timing dependent on treatment arm	Weekly	Last CRT clinic appointment	3 months after CRT +/- 1 week	6 months after CRT +/- 1 week
Study Discussed / PIS given		X							
Informed Consent			X						
Randomisation (after eligibility checked)				X					
Extraction of clinic and clinical note data††		X	X			X	X	X	X
MDADI			X				X	X	X
EORTC QLQ-C30 (v 3.0), EORTC QLQ - H&N35, SF-36			X				X	X	X
Economic evaluation costing tool								X	X
Trial Intervention: Pre-treatment gastrostomy or later NG tube insertion					X				

Visit/Interview Type	Pre-start Activities	Initial screening visit	Consent, Randomisation and Baseline visit(s).		Trial Intervention visit	Data capture during CRT	Data capture at end of CRT	Follow-up	Follow-up
Routine NHS oral health assessment ††			X††						X††
Nutritional assessment: weight, BMI, enteral nutrition			X		X	X	X	X	X
Performance Status Scale; Normalcy of Diet			X		X	X	X	X	X
Adverse events					X	X	X	X	X
Observation recruitment discussions**			X*						
Qualitative interviews (Health professionals)	X*			X*					
Qualitative interviews (patients)			X†						X‡

*To be conducted on a sample of health professionals and recruitment discussions meetings at each site.

† To be conducted on a sample of recruited patients (5 in the Pre-CRT gastrostomy arm (G-tube group) and 5 in the No pre -CRT gastrostomy arm) and also 6-10 patients who refuse consent for the trial but are happy to give further information about their non-participation.

‡ To be conducted on a sample of patients recruited to the trial.

†† The following data must be collated by the research team from clinical notes and routine patient appointments (including dental appointments): Whether the patient was given any pre-treatment swallowing exercises and if so, if the patient complied with them (record as yes/no), dates of induction chemotherapy start and finish plus number of cycles received (if applicable), dates of CRT start and finish plus number of cycles received.

Patient weight, site infections, x-rays (associated with tube placements) and pH problems requiring NG tube placement. Feed related hospital admissions (dates from/to), access to dietetic services (and dates), district nurse visits (and dates), visits to accident and emergency (and dates), hospital admissions (and dates and whether nutrition related or not), information from panoramic radiograph, dental chart, periodontal and oral hygiene assessment plaque scores, oral opening measurement and oral dryness.

** Observation of recruitment discussions meetings will take place during the recruitment phase of the trial

15. Data Handling & Record Keeping

Data will be collected from patient screening and study visits on paper and electronic Case Report Forms and questionnaires. Paper documentation at sites will contain patient initials, unique trial number, gender and dates of birth. These papers will be stored securely at the sites.

Feasibility trial data will be entered onto a secure password protected validated clinical data management system based at the study coordinating centre. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. The quality and retention of study data will be the responsibility of Vin Paleri, CI.

All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

Local Caldicott approvals will be obtained at all sites for data transfer by fax and email and data entry onto the trial clinical data management system by participating site staff.

Each site will also keep a secure separate log locally to link patient names and contact details to unique patient identifiers for the purposes of local trial administration (e.g. drafting appointment letters, telephoning patients etc as required). Addresses and contact details of randomised patients will also be stored in the secure password protected trial data management system.

Local site staff will work closely with the researcher conducting the in depth qualitative patient interviews (only conducted on a subset of patients) to identify appropriate patients and assist the researcher in organising either telephone or face to face interviews.

16. Statistical Considerations

16.1 Statistical Definitions and Analysis Plan

The primary outcome measure is feasibility as defined in section 10.6. As a feasibility trial, analysis will be predominately descriptive. As a randomised trial, primary analysis will be based on the intention to treat principle with analysis groups based on the group allocated at randomisation and all randomised patients being included in the analysis. As a feasibility trial, the extent of missing data will be assessed and reported and analysis of clinical outcomes may also be carried out on a complete-case basis.

Rates will be calculated as defined and reported with 95% confidence intervals. Recruitment, compliance, retention will be reported as a cumulative rate at the end of the follow-up phase. Recurrence and mortality will be reported as a cumulative rate and during patient follow-up. Rates will be reported by randomised treatment allocation.

Patient survival time (overall and disease free) will be calculated from the date of randomisation to the date of death from any cause (overall survival) or the date of documented clinical disease progression (disease free survival), patients being censored at the date last seen alive and progression free. Survival will be reported descriptively as median (with 95% confidence intervals) estimates calculated using the method of Kaplan and Meier³².

Questionnaire scores will be calculated and transformed as recommended by the specific research groups (MDADI, EORTC, SF-36). Scores will be reported longitudinally over time (mean with 95% CI) as raw scores and change from baseline as conditional scores, conditional on patient survival.

Quality adjusted survival estimates, simultaneously investigating global quality of life scores and overall survival, will be reported descriptively as mean quality adjusted survival calculated using the method of Billingham³³.

Nutritional parameters will be reported longitudinally over time descriptively as i) mean with 95% CI (or median with IQR) for BMI and weight and ii) categories reported as a proportion of the number of patients randomised within each treatment group.

Oral health parameters will be reported similarly but at the end of patient follow-up.

Planned Subgroup Analysis will be conducted descriptively reporting within the subgroups defined by i) induction chemotherapy plans at randomisation (planned, not planned), ii) age at randomisation (≤ 60 yrs, > 60 yrs) and iii) patients with severely reduced levels of swallowing (yes, no).

Interim Analysis will be conducted according to the statistical analysis plan and in line with the DMC charter. DMC review is planned at recruitment of 20 and 40 patients.

16.2 Sample Size considerations

Recruitment is dependent on the number of patients approached but should be no lower than 50%. The upper limit of the 95% confidence interval for the proportion of patients recruited should exceed 50%.

Target recruitment is sixty patients in total. If 120 patients were approached and 50% were recruited (60 patients randomised to treatment) the 95% confidence interval for the recruitment rate would have width $\pm 9\%$. This would provide a good level of accuracy to assess the acceptability of the recruitment rate.

16.3 Issues relating to the design of the phase III trial

The aim of this feasibility trial is to assess all possible parameters which inform power calculations for a definitive trial including consideration to possible primary outcomes including incidence of dysphagia, as measured by CTC, and dysphagia related quality of life, as measured by MD Anderson Dysphagia Inventory (MDADI) HNSCC-specific self report scale (variation and differences in change from baseline over time). This information will be used to inform the design, choice of primary outcome and clinically significant difference or effect size and approach to the analysis, including consideration of mortality, of the future definitive trial.

The decision to move to a phase III trial will be based on:

1. Adequate timely recruitment with a 50% recruitment rate. We have identified the statistical reasoning behind this in the detailed project description.

2. Completeness of outcome measurement (MDADI at 6 months): Excluding those individuals who die during the study period. Primary outcome data successfully collected should be greater than or equal to 80%.
3. Economic criteria of EVOI to suggest further research likely to be worthwhile

17. Qualitative data management and analysis:

Interviews and recruitment discussions will, with consent, be audio-recorded, 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. Data will be managed using NVivo software. The analysis will be theoretically-informed by Normalization Process Theory³⁰ and will be conducted according to the standard procedures of rigorous qualitative analysis³⁴ including open and focused coding, constant comparison, memoing³⁶, deviant case analysis³⁷ and mapping³⁸. We will undertake independent coding and cross checking and a proportion of data will be analysed collectively in 'data clinics' where the research team share and exchange interpretations of key issues emerging from the data.

17.1 Relationship between process evaluation and feasibility trial:

Findings will be regularly fed back to the study team and appropriate changes made to study processes during the lifetime of the study. For example, if the pre-pilot work identifies a problem with the coherence of the feasibility trial to one group of professionals, then additional awareness raising/education sessions or materials will be developed.

18. Health Economic Considerations

18.1 Within Trial Health Economics

For the definitive economic evaluation costs to patients and their families/carers, the NHS and personal social services will be elicited. Within the feasibility study we will develop the tools necessary to elicit these costs. Specifically, we will develop data collection forms and questionnaires to capture use of hospital and primary care services and patient/family/carer costs. These data collection tools reflect our existing item bank of questions, web based resources e.g. www.dirum.org and experience from other RCTs of nutritional interventions e.g. the recent SIGNET trial²⁸ but will be tailored to reflect the needs of the study participants and to ensure that there is no double counting of the use of service.

Data will not be statistically analysed in this element but rather summarised descriptively for completeness of data collection

18.2 Model based economic evaluation and value of information analysis

In an exercise that will initially run parallel to the trial but will then incorporate the finding from the feasibility trial an economic model will be developed that will estimate the costs, effects and relative cost-effectiveness of the alternative methods of nutritional support. It will

take the perspective of the UK NHS and personal social services (PSS) and discounting in the base case will be at 3.5%.³⁹. In addition as is described below it will estimate the expected value of information and expected value of sampling information. These latter pieces of information will be used to make the economic case for funding a definitive trial and to assist in the design of that trial.

The methods to parameterise the model are described below but in order to represent uncertainty around costs, effects and cost-effectiveness and to enable the value of information analysis probabilistic sensitivity analysis will be performed using Monte Carlo simulation. All uncertainty surrounding estimates of input parameters will be informed by appropriate distributions. Modelling will conform with recommendations for best practice including those developed for economic evaluation models⁴⁰

Structure of the economic model: Disease pathway and treatment pathways for patients undergoing chemoradiation for head and neck cancer will be developed. The treatment pathway will start with the choice of nutritional support. These pathways will be based upon the material prepared for the feasibility study and advice from the key stakeholders involved in the study. Following recommendation for best practice these care pathways will be used to develop a mathematical model covering the period of initial intervention and the costs and consequences of any subsequent outcomes including further interventions.

Derivation of cost data: Information on the precise description of the resources required for each intervention will be based upon data derived from the feasibility study. From participants recruited to the trial we will estimate costs for each method of nutritional support. Given the small study size these data will be imprecise and this imprecision will form a key input into the analysis. Further cost data will be required on subsequent management these data will be identified with the help of members of the study group and a search of the economic literature. Unit costs will be taken from appropriate routine sources e.g. NHS reference costs, British National Formulary for drugs, etc.

Derivation of utilities: For the cost-utility analysis effects/benefits will be estimated in QALYs. For each health state a health state utility will be defined. The data will come from the feasibility trial and a focused search to identify utility data, including a search on the CEA Registry (<https://research.tufts-nemc.org/cear/default.aspx>). The estimates used within the model will be based upon the best available data, ideally derived using SF-6D (as the SF-36 will be used within the feasibility study and can be used to derive SF-6D scores). Nevertheless, such data may not be readily identifiable and data from other sources along with judgements as to how that measure compares to SF-6D scores will be used.

Epidemiological and relative effectiveness data: The main source of evidence to inform the probabilities required for the model will be the existing systematic reviews and other literature summarised in the background section of this application. From these sources information on the likelihood of key events described in the economic model will be sought. Additional focused searches will be conducted as necessary to identify the best available evidence relevant to the UK NHS for such probabilities.

Estimation of relative efficiency: The results of the economic model will be presented as a cost-utility analysis (CUA). In the CUA, mean costs, mean QALYs, incremental costs and QALYs will be presented.

Uncertainty: It is possible that sufficient data to populate the model will not be identified. In such a case threshold values will be explored where data is missing by varying estimates through a range thought plausible (based on advice of the stakeholders involved in the study). Within a probabilistic analysis a plausible distribution will be assigned to this range (which may include a uniform distribution to indicate that we do not know what value a parameter might take within a specified range). Deterministic sensitivity analyses will be carried out to test for the effect of assumptions and variability⁴¹ such as the impact of changes in discount rates. The probabilistic sensitivity analysis will also be undertaken for both the base case analysis and, where sensible, all deterministic sensitivity analyses allowing presentation of results in a series of cost-effectiveness acceptability curves (CEAC). Estimates of costs and QALYs will be calculated as the expectation over the joint distribution of the parameters. Relevant distributions will be informed by the systematic reviews and meta-analyses, other literature or expert opinion according to best practice⁴²

Value of information analysis: Identification of future research needs: We anticipate that the economic model will only provide preliminary data on the relative effectiveness and cost-effectiveness of the different methods of nutritional support. The main purpose of the model will be to help inform decisions about the direction of future research. Within the economic component of this study this will be explored using variants of value of information analysis.
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We will initially estimate the expected value of perfect information (EVPI) and expected value of removing uncertainty surrounding specific parameters or groups of parameters to identify where further research should focus on identifying more precise and reliable estimates of specific pieces of information e.g. relative effectiveness, costs, utilities etc (the expected value of partial perfect information, EVPPI). EVPI and EVPPI can be interpreted as the value of eliminating a wrong decision and it places an upper value on conducting further research overall (EVPI) or a specific area of information (EVPPI). EVPI and EVPPI at an individual level can be estimated directly from the model but will need to be combined with information on the number of people who could benefit from the gastrostomy tube feeding over the expected lifetime of the project. As these two factors are uncertain sensitivity analysis will be used to explore alternative assumptions. If relatively small values are obtained for EVPI and EVPPI (although we note that this is a judgement) then this suggests that no further research is necessary or no further research is required to obtain 'better' estimates for specific groups of parameters.

A judgement will be formed based upon the findings the EVPI analysis as to whether a move to the analytically complex, expected value of sampling information (EVSI), will be made. EVSI provides further information on the value of removing some of the existing uncertainty and also explicitly takes into account the cost of generating that future research to estimate the expected net benefit of sampling. Specifically, in this study we will explore the use of this

approach to identify, from an economic perspective, the optimal trial design. Such methods have only very rarely been used to determine the size of randomised controlled trials and therefore following the recommendations of forthcoming guidance the findings of this analysis will be used along with other information to determine the sample size for a future definitive trial ⁴⁷

19. Compliance and Withdrawal

19.1 Assessment of compliance

Where feasible, study visits will coincide with routine clinical follow-up, to enhance the likelihood of good compliance. Follow up visit windows of +/- 1 week should ensure capture of outcome data.

The trial management group will meet regularly to centrally review patient recruitment and subsequent rates of baseline and follow up visit completion and data capture; non-attendance for study visits and lack of data capture will prompt reminders to local site investigators by telephone or email.

19.2 Withdrawal of participants

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study intervention if s/he judges this to be in the patient's best interests. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

There are two withdrawal options:

1. Withdrawing completely (i.e. withdrawal from both the study treatment and provision of follow-up data).
2. Withdrawing partially (i.e. withdrawal from study treatment [including a request to move to another treatment arm] but continuing to provide follow-up data by attending clinic and completing questionnaires).

At the start of the study consent will be sought from all participants to retain all data collected up to the point of withdrawal. At the time of withdrawal participants will be asked if they would be happy for the reason for the decision to withdraw to be recorded.

20. Data Monitoring, Quality Control and Quality Assurance

20.1 Discontinuation rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring & Ethics Committee and/or Trial Steering Committee, Sponsor, regulatory authority or ethics committee concerned.

The Trial Steering Committee and data monitoring committee will each advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

20.2 Monitoring, quality control and assurance

The trial will be managed through the Trial Management Group (TMG) (membership listed in project contacts section).

The Principal Investigators will be responsible for the day-to-day study conduct at sites.

Newcastle Clinical Trials Unit will provide day-to-day support for the sites and provide training through Investigator meetings, site initiation visits and routine monitoring visits.

Quality control will be maintained through adherence to NCTU SOPs, study protocol, the principles of GCP, research governance and clinical trial regulations.

An independent data monitoring (DMC) will be convened to undertake independent review (membership listed in project contacts section). The purpose of this committee will be to monitor safety. At the first meeting, the DMC will agree on its charter of operation, and possible adoption of a formal stopping rule for safety. They will also determine a schedule for further meeting(s) taking into account that this is a feasibility trial.

A Trial Steering Committee (TSC) will be established to provide overall supervision of the trial (membership listed in project contacts section). The committee will meet twice during the first year of the study and then again at the end. A written charter will be agreed and used by the DMC and TSC.

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by NCTU. The main areas of focus will include consent, serious adverse events and essential documents in study.

Site monitoring will include:

- All original consent forms will be reviewed as part of the study file. All original consent forms will be compared against the study 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 investigator site file and study files will be checked.
- Source data verification of primary endpoint data and eligibility data for 10% of participants entered in the study.

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission.
- All documentation essential for study initiation will be reviewed prior to site authorisation.
- Review of consent form copies faxed to Newcastle Clinical Trials Unit (this will ensure that monitoring at site goes more smoothly and any problems with consent are picked up early and on an on-going basis).

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

The study may be subject to inspection and audit by 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.

21. Adverse Event Monitoring and Reporting

21.1 Definitions

Adverse event (AE): Any untoward medical occurrence in a subject to whom a study intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, “treatment” includes all interventions (including comparative agents) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Related AE: An AE that results from administration of any of the research study procedures. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a study procedure qualify as ‘related adverse events’. The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality:

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e definitely, probably or possibly related) are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the main REC and other bodies will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Unexpected Adverse Event: An adverse event that is not listed in the study protocol as an expected occurrence in the circumstances of this trial.

Serious Adverse Event (SAE): an untoward occurrence (whether expected or not) that:-

- Results in death
- Is life-threatening (refers to an event in which the subject was at 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)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Severity (intensity) of Adverse Events and Adverse Reactions

Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, severe):

- Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
- Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

An AE may be severe but not serious.

21.2 Expected adverse reactions:

Most adverse events that occur in this study, whether they are serious or not, will be expected due to the nature of the condition under study, side effects of routine NHS CRT treatment and also the study tube feeding interventions (which are also standard NHS treatments).

Expected AEs are summarised in the table below.

<u>Expected Adverse events</u>			
<u>Cause of event</u>	Common & well understood consequences of treatment	Less common & unpleasant side effects	Rare events*
Chemoradiation	<ul style="list-style-type: none"> • Mucositis • Swallowing discomfort • Neutropenia • Skin inflammation • Loss of weight • Xerostomia • Thick secretions • dysgeusia 	<ul style="list-style-type: none"> • pain, pulpitis • localised reaction to bonding agents or filling materials • dental abscess • facial swelling 	<ul style="list-style-type: none"> • Mortality
Nasogastric tube placement	<ul style="list-style-type: none"> • Nasal discomfort, pain and inflammation • Throat discomfort, pain and inflammation • Tube blockage • Tube dislodgement 	<ul style="list-style-type: none"> • Re-insertion of tube • Difficulty determining tube position with pH paper • Nasal ulceration 	<ul style="list-style-type: none"> • Malplacement and feeding into the lung (a never event) • Mortality (never event)
Gastrostomy placement	<ul style="list-style-type: none"> • Local pain • Local inflammation • Local infection • Tube blockage 	<ul style="list-style-type: none"> • Loss of catheter tract 	<ul style="list-style-type: none"> • Procedure related mortality • Repeat procedure • Bowel perforation • Gastrointestinal haemorrhage • Gastrocutaneous fistula • Intra-abdominal abscess • Peristomal abscess • Peritonitis requiring surgery

*These rare expected events are serious and would be documented as serious expected adverse events.

21.3 Protocol Specifications

For purposes of this protocol:

- All adverse events will be recorded after the study intervention occurs and at follow up 1 (3 months post completion of CRT) and follow up 2 (6 months post completion of CRT) and categorised as to expectedness, relatedness and severity.
- Any serious adverse events (expected and unexpected) will be recorded throughout the duration of the trial up to and including the final follow up visit.
- Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.
- Serious adverse events exclude routine treatment (eg. CRT) or monitoring of the studied indication not associated with any deterioration in condition.
- Serious adverse events exclude the expected events as defined in the expected events section unless they are rare expected adverse events.
- Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.
- Serious adverse events exclude primary outcome measures, already documented and monitored within study (with the exception of death).

21.4 Recording & Reporting Serious Adverse Events or Reactions:

All adverse events and serious adverse events will be recorded on appropriate eCRFs and SAE forms.

All adverse events (unless expected and not serious in nature) should be reported on the study adverse event eCRF. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator or Senior Trial Manager in the first instance.

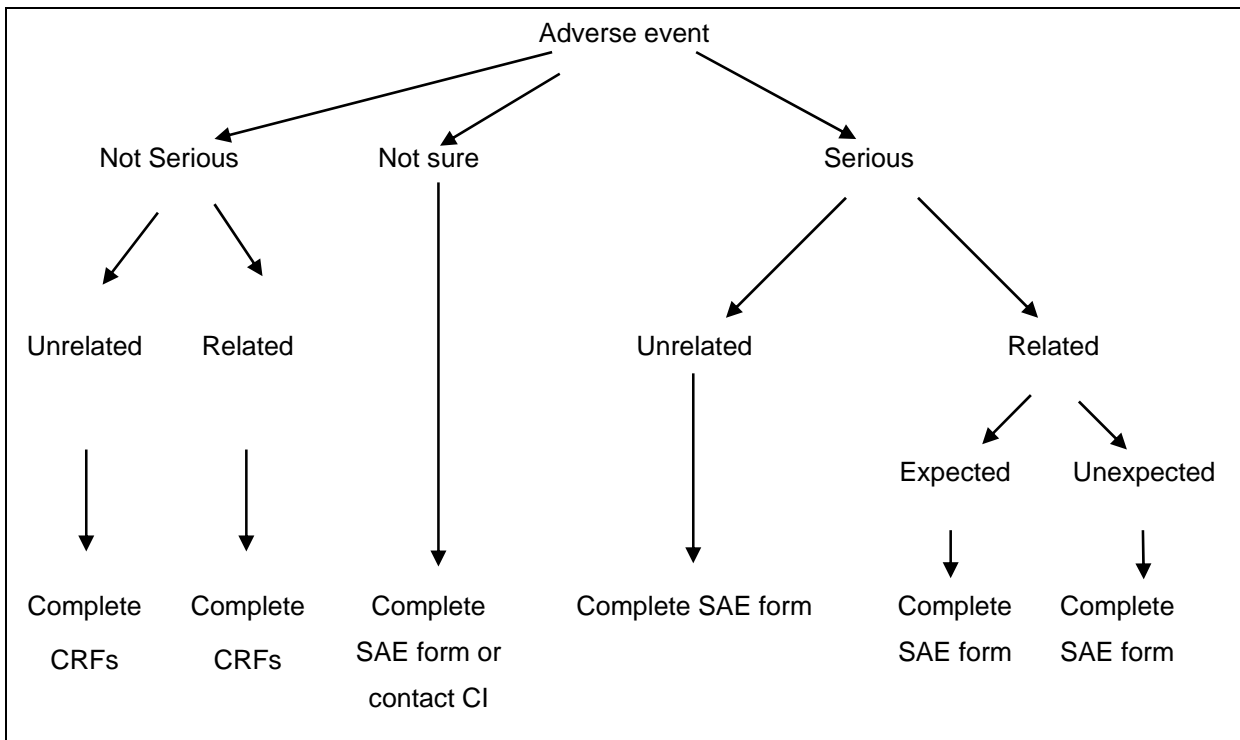
Adverse Event (AEs): All adverse events during study participation will be reported on the study adverse event eCRF. Severity of AEs will be graded on a three-point scale (mild, moderate, severe). Relation (causality) and seriousness of the AE to the treatment should be assessed by the investigator at site in the first instance. The individual investigator at each site will be responsible for managing all adverse events according to local guidelines.

Serious Adverse Event (SAEs): All SAEs during study participation shall be reported to the Chief Investigator or Newcastle Clinical Trials Unit within 24 hours of the site learning of its occurrence using an SAE form and the SOHO 66 reporting system. The initial report can if necessary be made to the trial management team by site investigators 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, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to study procedures should be assessed by the investigator at site, as should the expected or unexpected nature of the AE.

The Chief Investigator will ensure the Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor is notified of any SAEs in accordance with local trust policy. Serious Adverse Fatal and life threatening events that are related and unexpected should be reported to the main REC within 7 days of the Chief Investigator becoming aware of the event and all non-fatal events must be reported no later than 15 calendar days. This is the responsibility of the Sponsor (or authorised delegate).

Local investigators should report any SAEs as required by their local Research & Development Office.

Process for documenting Adverse Events and Serious Adverse Events:



Contact details for reporting SAEs and SUSARs
 Please send SAE form(s) via [Fax: 0191 580 0254]
 or
 Tel: [0191 208 7647] (Mon to Fri 09.00 – 17.00)

22. Ethics & Regulatory Issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Favourable ethical opinion from an appropriate REC and R&D approval will be sought prior to commencement of the study. Local approvals will be sought before recruitment may commence at each site. Newcastle Clinical Trials Unit will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures.

22.1 Confidentiality

Personal data will be regarded as strictly confidential. The study will comply with the Data Protection Act, 1998. All paper records, video recordings (of MDT meetings, patient and health professional interviews) and patient screening records will be kept in locked offices or filing cabinets with restricted access. Investigator Site Files will also be kept in secure offices with restricted access.

Caldicott approval will be obtained for transfer of patient identifiable data from sites to the study coordinators.

23. Insurance and Finance

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

UK National Institute for Health Research, HTA programme are funding the study.

24. Study Report / Publications

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

It is planned to publish this study in peer review articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site. All manuscripts, abstracts or other modes of presentation will be led by the Trial Management Group and circulated to the Trial Steering Committee and Funder prior to submission. Individuals will not be identified from any study report.

Participants will be informed of the study results at the end of the study. The research nurses at sites will send the lay summary of results to participants via post.

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List of Appendices

These documents are useful reference documents relevant to this protocol:

APPENDIX 1: TUBE Enrolment Flow Chart.

APPENDIX 2: TUBE: Flow chart for randomised patients

APPENDIX 3: EORTC QLQ- H&N35

APPENDIX 4: EORTC QLQ –C30

APPENDIX 5: Chen 2007: MDADI Development and validation publication

APPENDIX 6: Grade 1 pre-treatment dysphagia, as defined by Common Terminology Criteria for Adverse Events v4.0 (defined as: asymptomatic / symptomatic / able to eat regular diet). Information extracted from: <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>

APPENDIX 7: Performance Status Scale Publication