SEND Trial

The role of selective neck dissection used electively in patients with early oral squamous cell carcinoma (tumour stage T1 and T2) and no clinical evidence of lymph node metastases in the neck

TRIAL PROTOCOL (SEND 001)
Version 17 – 1 December 2011

Chief Investigator: Mr Iain Hutchison

Co-investigators: Mr Allan Hackshaw, Dr Marjon van der Pol, Mr Ian Martin, Dr Kim Piper, Dr Gareth Thomas, Mr Keith Webster, Dr Julie Olliff, Prof Ania Korszun, Dr Muy-Teck Teh, Dr Ahmad Waseem, Prof Edward Odell

Any questions relating to this protocol should be addressed to:

Fran Ridout
Facial Surgery Research Centre
St. Bartholomew's Hospital
West Smithfield
EC1A 7BE
TEL: 020 346 55743 / 57336 / 55755

Fax: 020 346 56755

This document describes the SEND trial and provides information about treatment policy and procedures for entering patients into the trial. The protocol should not be used as a guide for the treatment of patients outside the trial. If corrections or amendments are necessary an updated protocol will be circulated. Centres entering patients for the first time are advised to contact the Facial Surgery Research Centre (FSRC) to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the FSRC in the first instance.

This trial will adhere to the principles outlined in the Research Governance Framework. It will be conducted in compliance with the protocol, the Data Protection Act (DPA Z6364106) and other regulatory requirements as appropriate.

Contents

1 Trial Summary	
Title	The role of elective neck dissection in patients with early oral squamous cell carcinoma and no clinical evidence of lymph node metastases in the neck (SEND)
Design	Multicentre randomised controlled trial
Aims	1. To determine whether the use of a selective neck dissection used electively (hereafter referred to as SEND) on all patients presenting with T1 and T2 tumours and no clinical evidence of neck metastasis (N0) improves survival, disease-free survival and loco-regional disease control rates. 2. To determine how SEND and complex reconstruction affect quality of life (QoL) and mental health. 3. To determine whether the use of SEND on all patients presenting with T1 and T2 tumours and clinically N0 necks represents a cost-effective use of resources.
Population	652 patients with T1 or T2 oral cavity squamous cell carcinoma and no clinical evidence of neck metastases
Main outcome	Overall survival.
Secondary outcomes	1. Disease-free survival 2. Local and regional recurrence 3. Completeness of resection at the primary site. 4. Patients' QoL (EORTC QLQ-30 & H&N module) at 6, 12 and 24 months from treatment. 5. Costs to NHS, patients and carers/families. Incremental cost per life year saved and/or per quality adjusted life year (QALY).
Eligibility	• Patients with T1 or T2 oral squamous cell carcinomas (SCC) at the primary site; • No clinical or preoperative imaging evidence of neck node metastases; • An intention to treat with surgery as the primary modality; • Patients who do not have another synchronous tumour or previous oral or pharyngeal SCC • No technical, medical or anaesthetic difficulties which preclude the patient's treatment in one arm of the trial; • No requirement by the surgeon to open the neck for reconstructive purposes; • Age 16 years or over; • Capable of giving written informed consent;
Treatment arms	326 patients in each arm 1. Resection of primary tumour with simultaneous elective neck dissection at presentation with or without reconstruction. 2. Resection of primary tumour alone and salvage treatment of the neck if neck metastases develop.
Duration	Total duration 96 months
Additional studies	• Later pathological and genetic studies. • Follow-up studies for patients who want to choose their treatment (NON SEND) or who are not considered to be suitable for entry into a randomised trial (SEND NR).

2 Background

Neck lymph nodes are the first line of metastasis for oral squamous cell carcinoma (SCC). As many as a third of patients who die from oral SCC die with persistent or recurrent disease in these nodes (Kalnins et al 1977). Eliminating neck disease is therefore regarded as being vitally important (Leipzig 1982). Pathology studies have shown that even when the neck has no clinical or radiological evidence of metastases (N0), 30-35% of patients will actually have occult disease in their cervical nodes (Shah 1990, Woolgar 1996). This figure could be an underestimate as conventional pathological sectioning may miss up to 28% of micrometastases (Ross et al 2004).

These findings have generated a trend towards performing SEND during resection of the primary tumour. This trend is most marked for tumours of T2 or above even when there are no detectable metastases in the neck (N0) prior to surgery (Hughes et al 1993). This policy has also been fuelled by the perceived need to reconstruct the oral defect, created by removing the primary, with distant pedicled or free microvascular flaps (MVF). It is believed that this use of reconstructive techniques improves patients' speech swallowing and diet and therefore their quality of life (QoL) (Urken et al, 1991, Blackwell 1999). It is necessary to open the neck for both these reconstructive techniques so an opportunistic SEND is performed. Also some tumours are difficult to access and completeness of resection may be compromised if a mandibulotomy is not performed. With mandibulotomy the neck is also opened and SEND is performed. However, the use of SEND may have a negative impact on QoL in terms of visible scars, numbness of the neck skin and the possibility of ipsilateral shoulder weakness (Shah 2001, Kuntz 1999, Laverick et al 2004). It is therefore unclear what the overall impact of SEND is on QoL. In addition, there are other important variables that need to be taken into account when analyzing QoL outcomes. For example, individuals with a history of depression have a significantly higher mortality and poorer QoL outcome (Stommel et al 2002; Raison et al 2003).

There are also resource implications. Performing SEND in addition to a resection increases operating time and length of hospital stay. Conversely, treating neck metastases early may reduce overall treatment costs as evidence suggests treating necks later substantially increase treatment costs due to the need for further surgery and post-operative radiotherapy (NHS Centre for Reviews and Dissemination 2004).

There is some evidence from case series, which suggests that more radical treatment policies including pursuing SEND in N0 necks, confers a survival benefit. Memorial Sloan Kettering's results for 3 successive decades from the 1960s to the 1980s for all stages of disease demonstrate a dramatic sequential improvement in survival, which could be attributed to a lower threshold for pursuing neck dissection (Callery et al 1984, Franceschi et al 1993). Survival and disease control data from surgeons using the Liverpool Head & Neck Database (Magennis 2002) also supports this view as their results with radical surgical treatment for all stages are better than national statistics. There seems little doubt from these studies that surgical advances have resulted in improvement in survival but these studies do not have a comparative group and the exact factors responsible for this success are not absolutely clear.

Some retrospective studies have compared SEND with surveillance and salvage treatment of the neck if disease develops, but these have yielded conflicting results (Yuen et al 1997, Haddadin et al 1999, Yii et al 1999). Only 3 prospective randomised studies have compared SEND in clinically N0 necks with no active treatment of the neck at presentation (Vandenbrouck et al 1980, Fakih et al 1989, Kligerman et al 1994). None of these were adequately powered (75, 35 and 67 patients respectively) and the results were inconclusive.

Therefore, in the absence of systematic reviews or randomised controlled trials that show that SEND for N0 necks at presentation improves survival, the management of the N0 neck is still debatable. The proponents of SEND contend that it is therapeutic in the 30-35% of patients who have occult metastases and that early treatment of these subclinical metastases improves regional disease control and survival and does not adversely affect QoL in the 65-70% of patients with histologically N0 necks. A contrary view states that SEND is overtreatment in the 65-70% of patients who have histologically confirmed N0 necks and that waiting until patients present with overt neck disease and treating the neck at that stage does not adversely affect ultimate disease control or survival.

The fundamental question is: "are we under-treating the 30-35% of early primary oral SCC patients if we delay a neck dissection until they have overt neck disease; or are we over-treating the 65-70% of patients who do not have neck disease if we perform an SEND at presentation?" There are no randomised controlled trials addressing this question. Patients will continue to receive treatment based not on scientific principle but the belief of the surgeon.

The role of sentinel node biopsy (SNB) has been investigated extensively in other tumours including melanoma and breast cancer. At the moment there is conflicting evidence for its role in oral SCC (Nieuwenhuis et al 2002, Ross et al 2004). The role of sentinel node biopsy in oral SCC may be answered by a current EORTC study. There are several reasons why it is not appropriate to use sentinel node biopsy in our study. Firstly, it would only duplicate the EORTC study. Secondly, not all of our participating centres have access to the nuclear medicine facilities necessary to run a SNB study. Thirdly, opening the neck to perform SNB would invalidate the whole of the control/ intensive surveillance arm of our study. Fourthly, current SNB studies are assessing the value of nuclear medicine and dye techniques as an investigative tool to identify the first echelon lymph node for metastatic spread (sentinel node) whereas our study is assessing the therapeutic value of a treatment protocol involving SEND in the N0 neck. Both studies are important but for very different reasons.

3 Trial Design

The trial will be a two-arm randomized trial:

Arm A: Patients will be allocated to have resection of the primary tumour with neck dissection
Arm B: Patients will be allocated to have resection of the primary tumour only

The estimated recruitment period is 4 years with 4 years of follow-up from the time the last patient has been entered into the trial.

3.1 Sample Size

The 5-year survival rate is about 65% in patients with T2 disease undergoing resection of the primary alone. The results from the 3 small randomised trials and retrospective studies (Yuen 1997, Haddadin 1999) suggest a survival rate of 80% among patients undergoing elective neck dissection; a difference of 15%. We propose that our trial be powered to show a conservative difference of 10% or more (equivalent to a comparison of median survival of 96 vs 144 months, based on an exponential distribution), and a trial length of 8 years (4 years recruitment and 4 years follow-up). Therefore, the sample size is 620 (310 in each arm) with 80% power and 2-sided level of statistical significance using the logrank test. To allow for a 5% drop-out rate we aim to recruit 652 patients.

3.2 Outcome measures

Primary: overall survival
Secondary: disease-free survival, local and regional recurrence, completeness of resection, adverse effects, quality of life, emotional and psychological measures and financial costs

3.3 Statistical analysis

Overall survival and disease-free survival time will be taken from the date of randomisation to date of death, first recurrence or last follow-up. Kaplan-Meier curves will be used to examine survival in each of the surgical arms, and compared using the logrank test. Cox regression will be used to adjust for pre-specified factors such as age, tumour stage and size. The main analyses will be on an intention-to-treat basis. Risk factors for the development of metastatic disease will be examined by logistic regression using several pre-defined variables (such as age, prior medical and psychiatric history, tumour size, and other markers which may be examined as part of a future translational research project for which separate ethical approval will be sought).

Quality of life will be examined using the EORTC QLQ-C30 questionnaire and the module for Head and Neck cancer. These questionnaires will be completed at baseline and 6, 12 and 24 months after treatment. Scores will be compared between the two surgical arms using either parametric or non-parametric methods depending on the distribution of the data observed.

A cost-utility analysis will be conducted which compares the two interventions in terms of both costs and health outcomes expressed in Quality Adjusted Life Years (QALYs). Data on costs to the NHS (including treatments, investigations, and consultations) will be collected from patient records supplemented by patient questionnaires. NHS resource use will be costed using appropriate unit costs, taken from published sources (e.g. NHS reference costs). QALYs will be derived using data from the EQ-5D administered as part of the main study. Responses to the EQ-5D will be converted in health state utilities using UK population tariffs. The type of economic evaluation performed will depend upon the findings. If the two surgical procedures are similarly effective then cost-minimisation analysis will be performed. If one is more costly and more effective (in terms of survival and/or quality adjusted life years) then either an incremental cost-effectiveness and/or a cost-utility analysis will be performed. The results of the economic analyses will be presented as point estimates of mean incremental costs, life-years saved, QALYs and cost per life-year saved and per QALY gained. Incremental cost-effectiveness data will be presented in terms of cost-effectiveness acceptability curves.

4 Patient Eligibility

4.1 Inclusion criteria

1. Patients with T1 or T2 oral SCC at the primary site. (ICD9 codes: 141, 143,144,145,146,149.)
2. No clinical or preoperative imaging evidence of nodal involvement in the neck (N0 neck)
3. Surgery is the primary mode of treatment
4. Age 16 years and over
5. Capable of giving written informed consent

4.2 Exclusion criteria

1. Cancer of the lip (ICD9 code 140)
2. Previous oral or pharyngeal SCC
3. Other synchronous tumour
4. Technical, medical or anaesthetic difficulties which preclude patients being entered into one of the trial arms

5. Where the surgeon assesses that the patient needs reconstruction that necessitates opening the neck
6. Those patients whom the multi-disciplinary team meeting considered to be medically, socially or psychiatrically unfit for surgery as first line treatment.
7. Those patients where the patient expresses a preference for non-surgical treatment

5 Patient screening

5.1 Initial consultation with surgeon

Patients for whom the surgeon makes a provisional diagnosis of oral SCC will be preliminarily assessed for trial entry by:

- Measuring the maximum tumour dimension in cm by palpation, using callipers and a ruler
- Clinical assessment of the neck for metastatic nodes to produce a TNM stage
- Histological diagnosis of oral SCC will be confirmed by biopsy of the primary and further staging of the neck by imaging according to local availability
- Standard haematological, biochemical, respiratory and cardiological investigations

The patient will be given an appointment to attend the multidisciplinary clinic (MDC) accompanied by a close relative or friend. Prior to the patient's appointment at the multidisciplinary clinic the surgeon will:

Confirm the diagnosis of oral SCC T1 or T2 tumour at the primary site with no clinical or imaging evidence of neck metastases (N0).

Confirm that the patient fulfils entry criteria.

Inform the research nurse or site coordinator (RN) that an eligible patient will attend the MDC.

Confirm the treatment plan at the multidisciplinary meeting.

5.2 Imaging criteria for the diagnosis of neck node involvement by metastases

A number of CT, Ultrasound and MR criteria have been proposed that suggest the presence of squamous cell carcinoma metastasis to cervical nodes and will be used in the study as exclusion criteria. The MRI scan should ideally be performed using T1 weighted sequences which are fat suppressed following Gadolinium enhancement.

The two main criteria used are size and the presence of central necrosis or nodal non-homogeneity. Lymph nodes measuring more than 11mm long axis diameter in the jugulo-digastric 8 mms in the retro-pharyngeal region and 10mm elsewhere in the head and neck on CT or MRI will be considered to be involved by metastases and excluded. On Ultrasound level 2 nodes greater than 8mm in short axis diameter and 7mm for the rest of the neck will be considered to be involved by metastases and excluded.

Clusters of 3 or more nodes which have a minimal axial diameter of 8mm (9mm in the jugulo-digastric region) in the drainage area of the primary tumour should also be considered as suggestive of metastasis and the patient excluded from the study.

The presence of central necrosis on CT, MR or US or abnormal enhancement following intravenous contrast on CT or MR should be considered pathological whatever the size of node and the patient excluded from the trial. Abnormal peripheral or parenchymal blood flow with loss

of the normal lymph node morphology on US should be considered pathological whatever the size of the node.

Criteria For Assessing Positive Neck Nodes (diameter greater than)			
	Jugulo-digastric Region	Retropharyngeal	Remainder of Neck
CT/MRI	11mm	8mm	10mm
Ultrasound	8mm	-	7mm

5.3 Multidisciplinary clinic

The surgeon will:

- Explain the diagnosis to the patient and supporting relatives or friends and solicit questions pertaining to treatment.
- Introduce the patient to the RN and explain that the RN will discuss the trial treatments.
- If the surgeon does not wish to enter a patient into the trial the RN will collect and enter the patient's details into a screening log including the surgeon's reason for non-recruitment.
- The RN will discuss the trial with the patient and any supporting relatives or friends privately in a quiet room, informing them of the trial treatments and the objectives, benefits and risks of participation. The RN will also provide the patient with an information sheet in clear, simple language (Appendix 2) and a contact number**.** The RN arranges a subsequent appointment for the patient with the surgeon and allied health professionals.

5.4 Informed consent

Patients must be allowed ample time to enquire about details of the study and to decide whether or not to participate. Two copies of the consent form (Appendix 2) must be completed, signed and dated by the participant and the surgeon. One copy is to be given to the patient and one to be kept in the Trial Site File. A photocopy should also be kept in the patient's medical notes. Patients should not be recruited into the study less than two days prior to treatment.

5.5 Randomisation

Following consent, patients will be registered with the trial centre and flagged by the Office for National Statistics (ONS) cancer registry. They will then be randomised. The RN will call the Facial Surgery Research Centre to determine which treatment the patient receives. The RN informs the patient and surgeon of which treatment the patient will receive and answers any further queries.

CONTACT DETAILS
The SEND Trial Coordinator, Facial Surgery Research Centre,

TEL: 020 346 55743 / 57336 / 55755

Fax: 020 346 56755
Office Hours: Monday-Friday 9.00am to 5.30pm

The randomisation method used will be minimisation, stratified by age group (<40, 40-64, 65+), tumour stage (T1 and T2) and surgeon.

5.6 Assessments before surgery

The RN will ensure that the following pre-treatment assessments are undertaken and recorded in accordance with standard operating procedures and trial specific guidance notes.

- Demographic and risk factors
- Medical history
- Tumour and investigative data (a modification of the Data for Head and Neck Cancer (DAHNO) and Liverpool databases)
- Quality of life measures: EORTC QLQ-C30 (Appendix 3) and head and neck module EORTC QLQ - H&N35 (Appendix 4)
- Measure of quality of life in economic evaluations - EQ-5D (Appendix 5)
- Optional speech therapy and dietician assessments according to local practice

6 Treatment details

6.1 Resection of primary tumour only

Surgery will be done through the open mouth. At the first therapeutic operation no neck incisions or neck surgery are allowed. The surgeon will aim for 10 mm clearance of tumour where possible at all margins and in all planes. Frozen section control may be used, but this is not mandatory. Reconstruction may be undertaken, but this must not involve any neck surgery. Permissible methods of reconstruction include skin grafts (split or full thickness) or local flaps.
All treatment details including operative, pathology (including tumour dimensions, characteristics and details of the margin clearance in mm.) and management variables must be recorded in accordance with standard operating procedures and trial specific database requirements.

6.2 Resection of primary tumour with synchronous neck dissection

The neck incision is left to the surgeon's discretion. The standard SEND, according to this protocol, harvests lymph nodes from levels I-IV including levels Ia and b and IIa and b. All lymphatic bearing tissue superior to the accessory nerve and all nodes up to the posterior border of the sternomastoid muscle should be removed in this dissection. However, a level I-III dissection and exclusion of level IIb may be carried out if the surgeon considers it to be more appropriate.

The omohyoid muscle and the posterior belly of the digastric muscle may be removed with the specimen or retained. All these decisions must be recorded. The antero-superior dissection is limited by the superior belly of the omohyoid muscle at the level of and inferior to the hyoid bone but above the hyoid bone includes both submental triangles. The superior border of the dissection is the lower border of the mandible. The internal jugular vein, sternomastoid muscle and accessory nerves are preserved and left in situ. The cervical plexus nerves may be sacrificed or preserved at the surgeon's discretion. All surgical boundaries and actions should be recorded.

If the primary tumour extends to the midline a SEND as above should be carried out on the side of tumour (ipsilateral). A neck dissection on the other side (contralateral) may be carried out in accordance with the surgeon's usual practice. A bi-lateral neck dissection may be carried out on patients whose primary tumour is centred on the midline where either side of the neck has an equal risk on metastasis. The surgeon may choose to carry out an in-continuity resection of the primary tumour with the neck dissection, or a discontinuous neck dissection. The surgeon may choose to perform a mandibulotomy for access to the primary tumour. The use and technique of reconstruction is left to the surgeon's discretion.

All surgical procedures in SEND are part of the standard clinical workout.

6.3 Pathology and adjunctive treatment

Following consent and prior to or at induction of anaesthesia all patients will have 20ml of blood collected for immediate centrifuging in the laboratory and later transport to the study tissue bank at St. Bartholomew's Hospital, London. During surgery the surgeon will take fresh tissue from the primary tumour for snap freezing and ultimate transport to the tissue bank. A small piece (approximately $2mm^3$) of "normal" tissue is required as a control and should be removed from the margin of the tumour and processed alongside the tumour sample. Ideally, all samples should be frozen in the theatre complex to aid preservation of DNA and RNA. In some centres, where the pathologist is available for snap freezing within 30 minutes of the dissection and finds this process preferable, the pathologist may snap freeze the tissue samples. If no facility for snap freezing is available, tissue samples may be stored and preserved in RNA*later*. The site of the fresh tissue biopsy and control tissue will be under generic guidance generated by the trial pathologists.

The main pathology specimen (primary tumour alone or primary tumour with neck dissection) will be pinned or sutured to sponge, cardboard or cork to clearly identify the 3 dimensional spatial relationship of the tumour and levels of lymph node groups and transported according to local guidelines. Alternative methods of maintaining the spatial relationship of lymph node groups by level may be permissible with prior approval from the trial pathologist and Chief Investigator. For those patients who fall into the salvage node group, where possible, a fresh sample from a metastatic node should be snap frozen as above. The remainder will be retained with the rest of the main specimen for standard examination and processing using guidance produced by the trial pathologists and the Royal College of Pathologists minimum data set for oral cancer. If there is insufficient tissue for both diagnostic and pathology requirements of this protocol, then diagnostics will take priority.

The local pathologists will send a copy of the post-operative pathology report to the trial centre. They will also send a copy of H&E slides from all blocks and one block of the tumour (to be returned to the host centre at a later date) to the trial pathology panel where a panel member will examine the slides and generate a central standardized trial pathology report for all trial patients, when funding for this aspect of the trial has been agreed.

Where resources or facilities for the preparation and storage of samples are not currently available, alternative arrangements may be made with the prior agreement of the Trial Pathologist (Dr. Kim Piper) and the Chief Investigator. In these circumstances, the clinical

protocol may be undertaken independently until appropriate arrangements for the trial pathology are in place.

If there is evidence of extra-capsular spread in the neck specimen or two or more positive nodes are revealed, the neck should be treated with radiotherapy. If the pathology shows that margins are involved, the surgeon may either re-operate or arrange post operative radiotherapy, chemotherapy or any combination of these 3 treatment options. The management of close margins will be left to the surgeon's discretion. All these subsequent treatment variations should be recorded.

7 Post-operative assessments

The RN will ensure that all details of recurrence, metastasis or metachronous primary and special investigations are recorded in accordance with standard operating procedures and trial specific database requirements.

7.1 Routine assessments

The patient will be examined by the surgeon to exclude recurrence, metastasis or metachronous primary. These assessments will be carried out monthly in year 1, two monthly in year 2, three monthly in year three and then four monthly until the end of the trial as is normal practice. Investigations may be arranged at the surgeons' discretion according to their normal practice, at any visit, if recurrent, metastatic or new disease is suspected.

7.2 Quality of life and psychological assessments - 6, 12 and 24 months post treatment

EORTC QLQ-C30 assesses the quality of life of cancer patients. The patient will complete the EORTC QLQ-C30 and the head and neck cancer module EORTC QLQ - H&N35.

7.3 Quality of life and psychological assessments following treatment for relapse

Patients will complete the EORTC QLQ-C30 and EORTC QLQ - H&N35 prior to re-treatment and at 6, 12 and 24 months post treatment.

7.4 Economic evaluation

EQ-5D is a standardised instrument for use as a measure of quality of life in economic evaluations. Patients will complete the EQ-5D at baseline, 6 months, 12 months and 24 months post treatment. A self-completion Health Service Use questionnaire will be completed every 2 months, during the first 24 months post treatment, to enable costs to the NHS to be monitored. At 6 months, a supplementary health economic questionnaire will be completed by the patient.

7.5 Side effects/adverse events

Any side effects observed or reported by patients will be recorded at the time of surgery, immediately after surgery and for 6 months post trial treatment. The following side effects will not be recorded as adverse events as they are included in the quality of life assessments;

- scarring of the neck
- shoulder restriction
- numbness of neck
- neck pain
- effect on speech
- effect on swallowing/eating

8 Safety Reporting

8.1 Serious Adverse Events

A serious adverse event (SAE) should be reported to the trial centre where in the opinion of the investigator the adverse event was related to the study procedure (i.e. allocated surgery) and that the event was an unexpected result of the procedure (not listed below as an expected adverse event).

For this trial, the conditions listed below will not need to be reported as SAEs, because they are expected sequelae of the study treatments. However, these must still be recorded as an adverse event in line with trial specific SOP's.

airway complications
haemorrhage
haematoma
anastomosis failure
fistula
flap loss
nerve damage/division
pulmonary embolism
stomal stenosis
chyle leak
wound dehiscence
wound infection
severe pain
donor site infection
donor site tissue loss
donor site loss of function
alcohol withdrawal complications
long term inability to eat
PEG feeding
PEG feeding complications
chest infection
chronic aspiration
congestive failure
DVT
septicaemia

SAE reports should be submitted within 24 hours of the investigator becoming aware of the event, using the SAE form and in line with trial specific SOP's. SAEs should only be reported up to 6 months following the patient's initial surgery in the trial.

9 Trial administration

9.1 Trial management group

A trial management group (TMG) including all co-investigators will be set up. The TMG will meet regularly with the trial co-ordinator and report to Cancer Research UK on the progress of the trial. The trial centre (Facial Surgery Research Centre) will be responsible for the day-to-day management of the study.

9.2 Data monitoring committee

The role of the DMC is to provide independent advice on the progress of the trial. They may request interim analyses on recruitment, safety and efficacy at their discretion. The following members have been recruited:

Professor Jack Cuzick (CRUK Mathematics, Statistics & Epidemiology Laboratory, Wolfson Institute of Preventive Medicine)
Professor Jeffrey Tobias (Oncology, University College London)
Professor Paul Speight (Oral Pathologist, Sheffield)

9.3 Trial steering committee

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman.

9.4 Role of trial centre

The trial centre (Facial Surgery Research Centre) will be responsible for the day-to-day management of the study and will collaborate closely with Allan Hackshaw (CRUK & UCL Cancer Trials Centre) to ensure that the trial is run in accordance with the appropriate regulations, including obtaining ethical approval and registering the trial, randomisation, the reporting of side effects and monitoring the trial's progress.

9.5 Investigator responsibilities

Individual investigators should seek Local Research Ethics Committee (LREC) and Research and Development (R&D) approval. They are then responsible for recruiting patients, adhering to the most recent version of the protocol (taking into account any updated safety information and protocol amendments) and the safe conduct of the study.

9.6 Protocol amendments

The trial management group will agree protocol amendments prior to submission to the Main Research Ethics Committee (MREC). All investigators will be kept informed of all amendments.

9.7 Publication policy

Members of the Trial Management Group will form the basis of the writing committee, and will be responsible for the first publication of the trial results. All collaborating centres will be acknowledged. Further publications based on data from the trial should be agreed by the writing committee.

10 Regulatory issues

The trial will be run in accordance with the Research Governance Framework.

10.1 Sponsorship

Queen Mary School of Medicine (QMUL) and Dentistry, University of London is the main sponsor for all study sites.

10.2 Audits and inspection

The study may be subject to inspection and audit by QMUL.

10.3 Indemnity and compensation

Non negligent harm: Queen Mary School of Medicine and Dentistry, University of London (as sponsor) will provide insurance against claims for compensation for injury caused by participation in this clinical trial (i.e. non negligent compensation). Patients wishing to make a claim should address their complaint in writing to the chief investigator.

Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in this study. Queen Mary School of Medicine and Dentistry, University of London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

10.4 Ethical approval

The Trial Centre will obtain approval from the Main UK Research Ethics Committee. The trial protocol must be submitted to each participating hospital's LREC. The Trial Centre will require a copy of the LREC approval letter before accepting patients into the trial. The trial will be conducted 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.

10.5 Patient consent

Consent to enter the trial must be sought from each patient only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed patient consent should be obtained. The right of the patient to refuse to participate without giving reasons must be respected. After the patient has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage, if he/she feels it is in the patient's best interest, but the reasons for doing so should be recorded. In these cases the patients remain within the study for the purposes of follow-up and data analysis. All patients are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

10.6 Patient confidentiality

Patient's identification data will be required for the registration process. The trial centre will preserve the confidentiality of patients taking part in the study and is registered under the data protection act.

11 References

Blackwell KE (1999) Unsurpassed reliability of free flaps for head and neck reconstruction. *Arch Otolaryngol Head Neck Surg* **125**: 295-299

Callery CD, Spiro RH, Strong EW (1984) Changing trends in the management of squamous carcinoma of the tongue. *Am J Surg* **148**: 449-454

Fakih AR, Rao RS, Patel AR (1989) Prophylactic neck dissection in squamous cell carcinoma of oral tongue: a prospective randomized study. *Semin Surg Oncol* **5**: 327-330

Franceschi D, Gupta R, Spiro RH, Shah JP (1993) Improved survival in the treatment of squamous carcinoma of the oral tongue. *Am J Surg* **166**: 360-365

Haddadin KJ, Soutar DS, Oliver RJ, Webster MH, Robertson AG, MacDonald DG (1999) Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. *Head & neck* **21**: 517-525

Hughes CJ, Gallo O, Spiro RH, Shah JP (1993) Management of occult neck metastases in oral cavity squamous carcinoma. *Am J Surg* **166**: 380-383

Kalnins IK, Leonard AG, Sako K, Razack MS, Shedd DP (1977) Correlation between prognosis and degree of lymph node involvement in carcinoma of the oral cavity. *Am J Surg* **134**: 450-454

Kligerman J, Lima RA, Soares JR, Prado L, Dias FL, Freitas EQ, Olivatto LO (1994) Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. *Am J Surg* **168**: 391-394

Kuntz AL, Weymuller EA, Jr. (1999) Impact of neck dissection on quality of life. *Laryngoscope* **109**: 1334-1338

Leipzig B, Hokanson JA (1982) Treatment of cervical lymph nodes in carcinoma of the tongue. *Head Neck Surg* **5**: 3-9

Magennis, P (2002) Mortality, causes and place of death in head and neck cancer - Liverpool Head and Neck Cancer Database (LHND) User Group 1995-2002. *Br J of Oral and Maxillo Surg* **40**: 359-360

NHS Centre for Health and Dissemination (2004) Management of Head and Neck Cancer. *Effective Health Care*. **5**, 1-11.

Nieuwenhuis EJ, Castelijns JA, Pijpers R, van den Brekel MW, Brakenhoff RH, van dW, I, Snow GB, Leemans CR (2002) Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node? *Head & neck* **24**: 282-289

Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. Biol Psychiatry 2003 54:283-94

Ross GL, Soutar DS, Gordon MacDonald D, Shoaib T, Camilleri I, Roberton AG, Sorensen JA, Thomsen J, Grupe P, Alvarez J, Barbier L, Santamaria J, Poli T, Massarelli O, Sesenna E, Kovacs AF, Grunwald F, Barzan L, Sulfaro S, Alberti F (2004) Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial. *Ann Surg Oncol* **11**:

Shah JP (1990) Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. *Am J Surg* **160**: 405-409

Shah S, Har-El G, Rosenfeld RM (2001) Short-term and long-term quality of life after neck dissection. *Head & neck* **23**:

Stommel M, Given BA, Given CW. Depression and functional status as predictors of death among cancer patients. Cancer 2002 May 15;94(10):2719-27.

Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Parker R, Schaefer J, Som P, Shapiro A, Lawson W, . (1991) Functional evaluation following microvascular oromandibular reconstruction of the oral cancer patient: a comparative study of reconstructed and nonreconstructed patients. *Laryngoscope* **101**: 935-950

Vandenbrouck C, Sancho-Garnier H, Chassagne D, Saravane D, Cachin Y, Micheau C (1980) Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. *Cancer* **46**: 386-390

Woolgar JA (1996) Carcinoma of the tongue: pathological considerations in management of the neck. *J R Soc Med* **89**: 611-615

Yii NW, Patel SG, Rhys-Evans PH, Breach NM (1999) Management of the N0 neck in early cancer of the oral tongue. *Clinical otolaryngology and allied sciences* **24**:

Yuen AP, Wei WI, Wong YM, Tang KC (1997) Elective neck dissection versus observation in the treatment of early oral tongue carcinoma. *Head & neck* **19**: 583-588

APPENDIX 1. STUDY FOLLOW UP SCHEDULE

	Pre-Treatment		Surgery	Post Treatment																		
Procedure / Assessment	Prior to Registration	Registration / Randomisation		Month 2 & 4	Month 6	Month 8 & 10	Month 12	Month 14	Month 16	Month 18	Month 20	Month 22	Month 24	Month 27	Month 30	Month 33	Month 36	Month 40	Month 44	Month 48	Month 54	Month 60
T Staging	x																					
Tumour Biopsy / Histology	x																					
Tumour Dimensions	x																					
CT/MRI/US	x																					
Initial Assessment	x																					
Consent Form		x																				
Patient Demographics		x																				
EORTC QLQ-C30#		x			x		x						x									
EORTC QLQ-H&N35#		x			x		x						x									
EQ-5D#		x			x		x						x									
Supplementary Health Service Use Questionnaire					x																	
Health Service Use Questionnaire				x	x	x	x	x	x	x	x	x	x									
Head and Neck Exam				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tissue and blood samples			x																			
Complications / Adverse Events			x	x	x																	
Disease Status				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

= to also be completed at time of relapse and at 6, 12, 24 months after re-treatment

APPENDIX 2. PATIENT INFORMATION SHEET AND CONSENT FORM

TO GO ON HOSPITAL HEADED PAPER

The role of neck gland removal in the treatment of patients with small mouth cancers (tumour stage T1 and T2) where there is no obvious evidence of secondaries in the neck glands.

Sponsor: Queen Mary College University of London
Version Date: 10/10/2011

Patient Information Sheet, Version 11

Simplified Title: The role of selective neck dissection in early oral cancer treatment

Protocol Number: **SEND-001**

Doctor in Charge of Study: **Insert name of Principal Investigator**

Study Location(s): **Insert name of institution**

Invitation Paragraph

You are invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read this carefully. Our staff will help you and give you more information if you need it. You can also discuss it with others if you wish. Take time to read it and decide what you would like to do.

Purpose of study:

This study will compare 2 everyday surgical treatments for early mouth cancer. These treatments do not use any new or untried methods. Both of these treatments have a high chance of curing mouth cancer.

Mouth cancer, like all cancers, can spread. In mouth cancer this is usually to the lymph glands in the neck. These small cancer cells are called secondaries. They are usually found by looking or feeling or by using special scans. Research shows that 3 out of 10 patients with early mouth cancer have these small hidden secondaries in the neck glands that can't be seen, felt or even shown on special scans.

If we find secondaries in the neck we remove some of the lymph glands at that side of the neck. This is to remove these 'secondaries' and to help prevent the cancer from spreading. This is called 'selective neck dissection'.

We cannot tell which of our patients has these hidden secondaries, so this has led to uncertainty over whether we should remove the neck glands on all patients at the same time as removing their mouth cancer. There is currently no universally accepted evidence to show whether this is best for the patients or whether it is just as good to operate at a later date if and when secondaries develop.

We want to know

- If it is better to remove the glands at the same time the mouth cancer is removed, even if it does not seem that there are any hidden secondaries (selective neck dissection)

or

- Should we wait until we know that there are definitely secondaries and then remove them.

Why have I been chosen?

You have been chosen to take part in this research because**:**

There is no evidence that your cancer has spread to your lymph glands. However, this means that we cannot tell which is the best treatment. We are doing a study with 652 patients with the same condition as you. We are doing it in hospitals all over the UK and your surgeon thinks you are very suitable to take part.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. You would be free to withdraw at any time and without giving a reason. A decision to withdraw will not affect the standard of care you receive.

If you do not decide to take part in this trial, your surgeon will treat you as he/she normally would, probably by using one of the 2 procedures in this research study.

What will happen to me if I take part?

All the preparation and planning of your treatment will follow the normal standard procedures.

Surgery

All patients will have surgery to remove the primary cancer in their mouth completely. Half the patients will also have a selective neck dissection (surgery to remove the neck glands) at the same time. You will have an equal chance of having either treatment. It is important that neither you nor your doctor should choose which of the 2 treatment options you receive. The choice of which treatment you will receive will be made by the study's computer on a random basis. This is the only change to standard treatment practice and is done to ensure there is no bias and that the results of this research are scientifically sound and accepted by all surgeons and patients worldwide.

Tissue samples

We will ask your permission to collect 4 teaspoons (20 ml) of your blood at the time of surgery for future research. We will also ask you to allow us to store some of the removed cancer at the Human Tissue Resource Centre (HTRC) at St. Bartholomew's Hospital, London so that we can conduct research on this material in the future as new investigations or treatments become available. A small piece of normal tissue (about the size of a match head) will be removed from the edge of the tumour. This may be used in future research to compare with tumour cells. A saliva sample will also be collected.

You may, if you wish, donate blood, tissue and saliva samples even if you do decide not to take part in SEND.

Questionnaires

You will be asked to complete some questionnaires assessing your quality of life and emotional and psychological well-being after signing the consent form and 6, 12 and 24 months after your surgery. You will also be asked to complete a short questionnaire every 2 months following your surgery. This will ask you about visits you have made to hospitals or your GP. It will also ask you about any medicines that you have been prescribed. These questionnaires should take less than half an hour to complete. The questionnaires are for research purposes only, so you will not receive the results.

Follow-up visits

All mouth cancer patients are asked to attend clinics regularly for 5 years after their operation. The frequency of your visits will not change because you are participating in this study. You will be asked to attend the clinic once a month for the first year, once every two months for the second, and then once every three or four months for the remaining years. At some of these clinics a researcher will ask you questions about your health, symptoms, and level of physical and social functioning. Your surgeon may ask you to attend occasional clinics during the 6^{th}, 7^{th} and 8^{th} years following your treatment.

Further treatment

If you do not have a neck dissection at the same time as your mouth cancer is removed you may have this operation later, if you develop secondaries in your neck glands.

What is the procedure that is being tested?

We are comparing the two most commonly used surgical treatments for small mouth cancers. One treatment involves removing only the primary mouth tumour. The other involves removing the primary mouth tumour and carrying out a selective neck dissection at the same time.

We want to see:

- Which one may be better at preventing the cancer returning
- Which one might help people to live longer
- Which one helps you to live a more comfortable life

Is there any alternative to these treatments?

For patients with small mouth cancers such as yours, surgery is the usual treatment. Anti-cancer drugs (chemotherapy) are not, on their own, prescribed for mouth cancer but they may be used before or after surgery. Radiotherapy (similar to X-rays, but with more side effects) may also be used either on its own or before or after surgery.

What will happen to any samples I give?

The tumour and some of the tissue around it will be removed from your body. It will be examined in the pathology laboratory, following standard practice, to ensure that the cancer is eliminated. With your consent we would also like to take small parts of this tissue for special research analysis.

If you do consent to the use of your tissue and blood for laboratory studies we would also seek your permission to store the samples and use them for future research. All new research work will be subject to ethical approval. You will not be required to undertake any additional tests or make any extra visits to hospital.

The part of your sample, which is used to confirm that your cancer has been removed, will be stored in accordance with national guidelines and forms part of your medical record. The part of the sample taken for research will be stored securely in accordance with Medical Research Council guidelines (currently for ten years after the research has been completed). Any results from tests carried out on your sample are likely to be published in the medical literature, but individual patients will not be identified in these publications.

All your samples will be stored with a code number that does not contain any details about you although it will be possible to link the specimen with your study data so that researchers can, if necessary, compare the results of their analyses with the clinical results of the SEND trial.

Future research may include genetic analyses, which could help us understand how these tumours develop and spread. There is a need to learn about the genetic basis of these tumours, which might help us improve the diagnosis and treatment of mouth cancer in the future. The results may not benefit you personally, but should help future generations.

No results from these blood and tissue tests will be available to you, but you are free to discuss any aspect of this with your surgeon.

Will I have to alter my lifestyle?

There is nothing specific that you have to do and participating in the study will not place any restrictions on your lifestyle. For example, you will be able to drive, drink,

play sport as normal and take your regular medication. You should follow your surgeon's advice about lifestyle choices whether or not you decide to participate in this study

What are the side effects of any treatment received when taking part?

During Surgery

The side effects and risks for either treatment are those of any surgery including blood loss or reaction to medication. You will receive the normal full explanation that is given to all patients prior to this surgery before signing the consent form for surgery. If you are also having neck dissection you will undergo a longer operation and the surgical incision will be on your neck.

Whichever procedure is selected for you, your surgeon may decide that your mouth needs reconstruction after he/she has removed the mouth cancer. He/she may take tissues and grafts from around your head and neck or from your chest, arm or leg to reconstruct your mouth. This is normal practice and is used for all patients whether they are in the study or not.

After surgery

If you have only the mouth cancer removed you will need to stay in hospital for a few days after your operation. If you have a neck dissection you will be in hospital for several more days.

Any wound takes time to heal after surgery, and the time needed to recover is different for each person. You may be uncomfortable for the first few days but medicines can usually control the pain. Before surgery, you should discuss the plan for pain relief with your doctor or nurse. After surgery, your doctor can adjust the plan if you need more pain relief.

It is common to feel tired or weak for a while. Also, surgery may cause tissues in your face to swell but this swelling usually goes away within a few weeks. Your treatment may affect your speech, chewing and/or swallowing.

If you are one of those patients having neck surgery to remove some lymph nodes, you will have more side effects. All of these patients will have neck scars. All of these patients are likely to experience areas of numbness and weakness of the neck. About a quarter of neck dissection patients will have stiffness or weakness of the shoulder on the side of the surgery.

What are the possible disadvantages and risks of taking part?

There are no specific risks in taking part in the study as both treatment approaches are standard treatments, although you may experience some of the side effects listed above.

If you have private medical insurance you should check with the company before

agreeing to take part in the trial, to ensure that your insurance is not affected in any way.

What are the possible benefits of taking part?

The results of this research will benefit all patients with mouth cancer in the future as it answers a specific area of uncertainty in our treatment planning. You will be helping determine best treatment practice for future patients. You may benefit if you have had the treatment that the results of this study prove to be the best.

What if new information becomes available?

Sometimes during the course of a research project, new information about the treatment that is being studied becomes available. If this happens, your research doctor will tell you about it and discuss with you whether you would like to continue in the study. If you decide to withdraw, your surgeon will make arrangements for your care to continue.

What happens when the research study stops?

Once the study is completed you will continue to be seen by your surgeon as part of your routine care.

What happens if there is a problem?

Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action. For further information or for initial concerns or disagreements please contact **(local details)**. You can also visit PALS by asking at any hospital reception.

Will my taking part in this study be kept confidential?

If you consent to take part in this study, all information collected about you during the course of the study will be kept strictly confidential. Details about you, the treatment you receive and your subsequent progress will be recorded in your medical notes and will be passed on to the Facial Surgery Research Foundation Trials Centre, which is registered under the Data Protection Act. These details will include your name, date of birth and hospital number. The information collected will be primarily to do with the treatment you receive, the side effects that you may or may not experience and your long-term state of health. In order to check that the information sent to them is accurate and that the study is being carried out properly, staff from the trial centre may wish to see your medical records. We will ask your permission to inform your GP of your participation in the study and may contact your GP for follow up information if you are unable to attend hospital appointments. We will also request

your permission to register your details with the Office for National Statistics (ONS) so that we may follow your health status.

What will happen to the results of the research study?

The results from the study will be published in medical and scientific journals. You will not be identified in any report or publication arising from this study.

Who is organising and funding the research?

Cancer Research UK is funding the study. Neither the surgeon conducting this research nor you own surgeon will receive any special or additional payment because you have agreed to participate in the study.

Who has reviewed the study?

Many of the UK surgeons specialising in mouth cancer, the National Cancer Research Institute (NCRI) Head and Neck Cancer Studies Group, Cancer Research UK and the International Academy of Oral Oncology have reviewed and approved this study.

Contact for Further Information

If you have any concerns or questions about this study please contact one of the medical team caring for you.

Consultant

Phone No……

Research Nurse or other trial support staff

Phone No……

CancerHelp UK provides general information for patients about cancer and its treatment on their website, www.cancerhelp.org.uk.

Cancer Research UK has cancer information nurses who provide a confidential service, Tel: 020 7061 8355 or 0808 800 4040, email: cancer.info@cancer.org.uk.

MacMillan Cancer Support provides support and counselling to help people living with cancer, Tel: 0808 808 0000, www.macmillan.org.uk.

(To go on hospital headed notepaper)

SEND Patient consent – Version 11 – 27/04/2009

The role of neck gland removal in the treatment of patients with small mouth cancers (tumour stage T1 and T2) where there is no obvious evidence of secondaries in the neck glands.

Patient's Full Name*: ……..…… Trial number: SEND-001
**please print name clearly*

Hospital No: ……..…….. Date of Birth: ……..

Please complete this section by initialling the boxes and then signing at the bottom of the page.

PATIENT CONSENT TO STUDY TREATMENT

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

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

3. I agree to complete some questionnaires as part of my participation in the study.

4. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from regulatory authorities or from the Barts and the London / Queen Mary University of London / Facial Surgery Research Foundation, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records

5. I understand that records maintained by the Office for National Statistics may be used to follow my health status.

6. I agree for my GP to be informed of my participation in the study.

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

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from Investigator)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Barts and The London NHS
NHS Trust

Queen Mary
University of London

CONSENT TO DONATION AND STORAGE OF RESIDUAL TISSUE FOR MEDICAL RESEARCH

Version 4, 10/10/2011

Study Title: **The role of neck gland removal in the treatment of patients with small mouth cancers measuring 1-3 cm in size where there is no obvious evidence of secondaries in the neck glands.**

Research Ethics Committee Reference:

Following surgery some residual (left-over) tumour tissue, and a small amount of normal tissue that can be used for comparison may be collected. This will be stored at the Barts and the London NHS Trust tissue bank and studied by researchers in the future after submission of a proposal to the SEND steering committee or its appointed sub-committee and peer scrutiny for approval of the scientific merits of the proposal. Research conducted on these samples may contain personal information but all such information will be anonymised at the end of any project, when the results are published, and you will not receive the results of any future research project. All staff undertaking future studies will abide by the Data Protection Act 1998 with any medical information relating to you being kept confidential. The blood, tissue and saliva samples collected during the SEND project may be given to external research organisations for approved medical research but the samples will not be sold, although costs will be recovered without any financial benefit to either you or to the researcher. Any residual tissue will be disposed of lawfully when it is no longer required.

Patient Initials

I understand that I have given my consent voluntarily to the collection and storage of blood, tissue and saliva for future medical research and that I am free to withdraw my consent at any time ☐

I agree that the blood,tissue and saliva may be used for future genetic research but not for research that involves reproductive cloning, or be tested for inherited diseases without my express consent ☐

If you have any preferences or exclusions for use of the donated tissue, or any other comments, please include them here:

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

(Researcher)

APPENDIX 3. EORTC QLQ-30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ☐☐☐☐

Your birthdate (Day, Month, Year): ☐☐ ☐☐ ☐☐☐☐

Today's date (Day, Month, Year): 31 ☐☐ ☐☐ ☐☐☐☐

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 4. EORTC QLQ-H&N35

EORTC QLQ - H&N35

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

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

Please go on to the next page

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

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

APPENDIX 5. EUROQOL EQ-5D

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

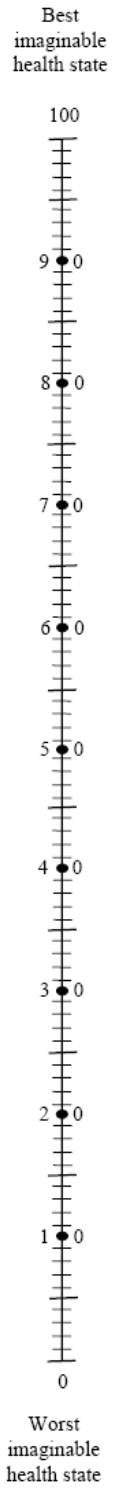
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 6. Health Service Use Questionnaire

Study Number | | | | | | |

CONFIDENTIAL

SEND trial

HEALTH SERVICE USE

2 MONTHLY PARTICIPANT QUESTIONNAIRE

Version 1, 5th March 2007

HOW TO FILL IN THIS QUESTIONNAIRE

Please try to complete the whole questionnaire. Most questions can be answered by putting numbers or a cross in the appropriate boxes. In a few questions you are asked to write some details.

Please print carefully within the boxes like this | 2 | 7 | **or like this** | X |

THIS FIRST SET OF QUESTIONS IS ABOUT ANY HOSPITAL ADMISSIONS AND/OR OUTPATIENT APPOINTMENTS YOU MAY HAVE HAD IN THE PAST 2 MONTHS

1a. Have you been admitted to hospital or attended outpatients for any reason during the last 2 months?

Yes ☐
No ☐

If **Yes,** please give details

_____

_____

_____

1b. Were you treated as an inpatient or an outpatient?

Inpatient ☐
Outpatient ☐

If you were treated as an **inpatient**, how many days did you spend in hospital? ☐☐

If you were treated as an **outpatient**, how many visits to hospital have you made? ☐☐

1c. Did you receive any medication? *(please specify type and length of treatment)*

_____

_____

_____

Please go to the next page

THIS SET OF QUESTIONS IS ABOUT ANY APPOINTMENTS YOU MAY HAVE HAD WITH YOUR GP IN THE PAST 2 MONTHS

2a. Have you been to see your GP for any reason during the last 2 months? Yes ☐ No ☐

b. How many appointments did you attend? ☐☐

c. How many times did your doctor visit you at home? ☐☐

d. Did you receive any medication? *(please specify type and length of treatment)*

_____

_____

THIS FINAL SET OF QUESTIONS IS ABOUT ANY OTHER HEALTH SERVICES YOU MAY HAVE RECEIVED IN THE PAST 2 MONTHS

In the last 2 months have you:

		If Yes: how many times?
seen a **Physiotherapist?**	☐ Yes ☐ No	..... times
seen a **Speech therapist?**	☐ Yes ☐ No	..... times
seen an **Occupational therapist?**	☐ Yes ☐ No	..... times
seen a **District nurse?**	☐ Yes ☐ No	..... times
seen a **Health visitor?**	☐ Yes ☐ No	..... times
seen a **Homehelp?**	☐ Yes ☐ No	..... times
Other (please specify):		
		..... times
		..... times

Thank you very much for your help. If you have any concerns you wish to discuss please contact Fran Ridout at the central trial office on 02076017582.

Once you have completed this questionnaire please hand it back to the research nurse.

APPENDIX 7. Health Service Use 6 month supplementary questionnaire

CONFIDENTIAL

SEND trial

HEALTH SERVICE USE

6 MONTH SUPPLEMENTARY QUESTIONNAIRE

HOW TO FILL IN THIS QUESTIONNAIRE

Please try to complete the whole questionnaire. Most questions can be answered by putting numbers or a cross in the appropriate boxes. In a few questions you are asked to write some details.

Please print carefully within the boxes like this | 2 | 7 | **or like this** | X |

THIS SET OF QUESTIONS ISABOUT THE OPERATION YOU HAD ABOUT 6 MONTHS AGO TO TREAT YOUR MOUTH CANCER

1a. How many days were you in hospital following the operation to remove your mouth cancer? | | |

1b. Did you move to another hospital as an inpatient before you went home? Yes ☐ No ☐

If Yes please give details including the name of the hospital, the reason for the move and the length of stay:

1c. How many days of paid work did you miss, because you were recovering from your operation? *(if you are retired or are not usually in paid work, please write N/A)* | | |

1d. Did you get paid as usual while you were in hospital and at home recovering from your operation? *(if you are retired or are not usually in paid work, please write N/A)* Yes ☐ No ☐

1e. If not, how many days of your usual pay did you lose? | | |

1f. Did this cause you or your family financial hardship? *If yes please give details below.* Yes ☐ No ☐

Please go to the next page

THIS SET OF QUESTIONS IS ABOUT THE ROLE OF YOUR RELATIVES OR FRIENDS FOLLOWING YOUR OPERATION

2a. Did any relatives take time off their normal paid work to look after you following your operation?

Yes ☐
No ☐

2b. Did any relatives take time off their normal paid work to look after a child or dependent relative that you normally care for, following your operation?

Yes ☐
No ☐

2c. Did any friend take time off their normal paid work to look after you following your operation?

Yes ☐
No ☐

2d. Did any friend take time off their normal paid work to look after a child or dependent relative that you normally care for, following your operation?

Yes ☐
No ☐

If you answered yes to any questions in section 2, did this cause you or your family financial hardship? *If yes please give details below.*

Yes ☐
No ☐

Thank you very much for your help. If you have any concerns you wish to discuss please contact Fran Ridout at the central trial office on 02076017582.

Once you have completed this questionnaire please hand it back to the researcher.

Patient Initials …… Signature…….. Date……..……