Head & Neck 5000 Protocol

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CONTENTS

BACKGROUND

Head and neck cancer (H&N) accounts for around 7,000 cases per year in England and Wales [1] and the incidence of oral cancer appears to be increasing [2]. The two-year all cause mortality is around 35% [3] and this has not improved until recently [4]. The incidence and survival is affected by the individuals' socioeconomic status [5, 6]. The treatment is resource intensive and multi-disciplinary and currently the services for H&N are being centralised.

In 1995 the Calman-Hine report on commissioning of cancer services identified the need for multidisciplinary team working and centralised services to improve the quality of care for people with cancer [7]. This report led to the development and publication of the UK National Health Service Cancer Plan in 2000 [8]. This plan outlined a comprehensive strategy to tackle cancer in England and the Department of Health commissioned a series of evidence-based "Improving Outcomes Guidance" reports (IOG) on all major cancers. The IOG for H&N was published in 2004 [9]. As a result cancer networks are reviewing and centralising services for H&N. One UK based audit of H&N suggested that markers of quality of care (e.g. multi-disciplinary care and availability of a Chest X-Ray) are associated with improved survival [3]. A survey of clinical resources available to head and neck patients in 2004 reported that multi-disciplinary team working was evident in all centres but that there were staffing shortages, delays in complex investigations and problems with access to intensive care beds and oncological care, especially radiotherapy [1]. The impact of the different models of centralized care adopted and the consequences of the publication of the H&N IOG in H&N have not been formally evaluated.

Multi-disciplinary working tends to further increase health service costs as teams require time to meet and discuss cases and to agree, implement, document and review management plans [10]. The centralisation of care to a smaller number of larger centres has resource and logistic implications for both users and service providers. It is therefore crucial that practice within these cost-intensive services is both clinically effective and cost effective in order to ensure that patients are receiving the best quality care and that NHS resources are being used efficiently.

AIM

The overall aim of the study is to evaluate the outcome of centralisation in Head & Neck cancer.

OBJECTIVES

The overall objective of the study is to recruit a clinical cohort of 5,000 people with Head & Neck cancer and then follow up this cohort actively for one year and passively through flagging thereafter with planned formal survival analysis at two years.

Specifically, the objectives are to:

1. Compare morbidity and mortality outcomes across different centres.
2. Compare quality of life outcomes across different centres.
3. Describe the individual economic cost of head and neck cancer care.
4. Identify prognostic indicators for head and neck cancer.
5. Create a resource for translational and applied research in head and neck cancer.

RESEARCH MANAGEMENT

This section describes the research management and governance of this project.

Details of sponsor

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Safety reporting

As this is an observational study we are only collecting adverse events directly related to study related procedures. Adverse events will be reported according to U H Bristol Research Adverse Event Policy.

Monitoring and audit

The study will be monitored and audited in accordance with U H Bristol Trust policy. All study related documents will be made available on request for monitoring and audit by UH Bristol and the relevant Research Ethics Committee.

Data protection

Data will be collected and retained in accordance with the Data Protection Act 1998. All data and blood and tissue samples retained will be identified only by the patients study number and initials. Data will be stored in restricted access areas within the Trust.

Storage of records

Study documents (paper and electronic) will be retained in a secure location during & after the study has finished. All anonymised study data will be retained for at least 25 years following the end of the study. Paper records may be sent off site to be archived at the sponsors designated offsite archiving facility following study completion.

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical study when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

Ex-gratia payments may be considered in the case of a claim.

Ethics & R&D approvals

The study will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval.

Research governance statement

This study will be conducted in accordance with the Research Governance Framework for Health and Social Care and Good Clinical Practice.

METHODS

This section describes the process of conducting the research study. The sections outline the participants eligible to take part in the study and the recruitment and data collection process, including the protocol for collecting biological samples.

Setting

The potential participants will be recruited via the Head & Neck centres that agree to participate in the study in England, Wales and Scotland.

New sites will continue to be approached and encouraged to join the study.

Participants

Inclusion criteria:

a) Every patient with a **new** head and neck primary cancer seen or discussed at the MDT meeting or clinic will be eligible for inclusion into the study, including those enrolled in other studies or trials.

b) Patients with an unknown primary, and those without a histological diagnosis, are eligible if the MDT decision is that the primary is likely to be a head and neck cancer and the patient is aware of the clinical decision.

c) Patients age 16 or over

Exclusion criteria

Patients who meet the following criteria are excluded from the study:

a) Participants who are considered to meet the criteria for mental incapacity or vulnerability set out in the mental capacity/ vulnerable adult act.

b) Patients who do not have cancer of the Head & Neck

c) Patients who have a recurrence of their cancer of the Head & Neck.

d) Patients with lymphoma

e) Patients with a secondary head and neck tumour.

f) Patients with skin cancer

g) Carcinoma in Situ where there is no evidence of invasion (these patients will only be eligible if a clinical diagnosis of cancer has been made by the MDT)

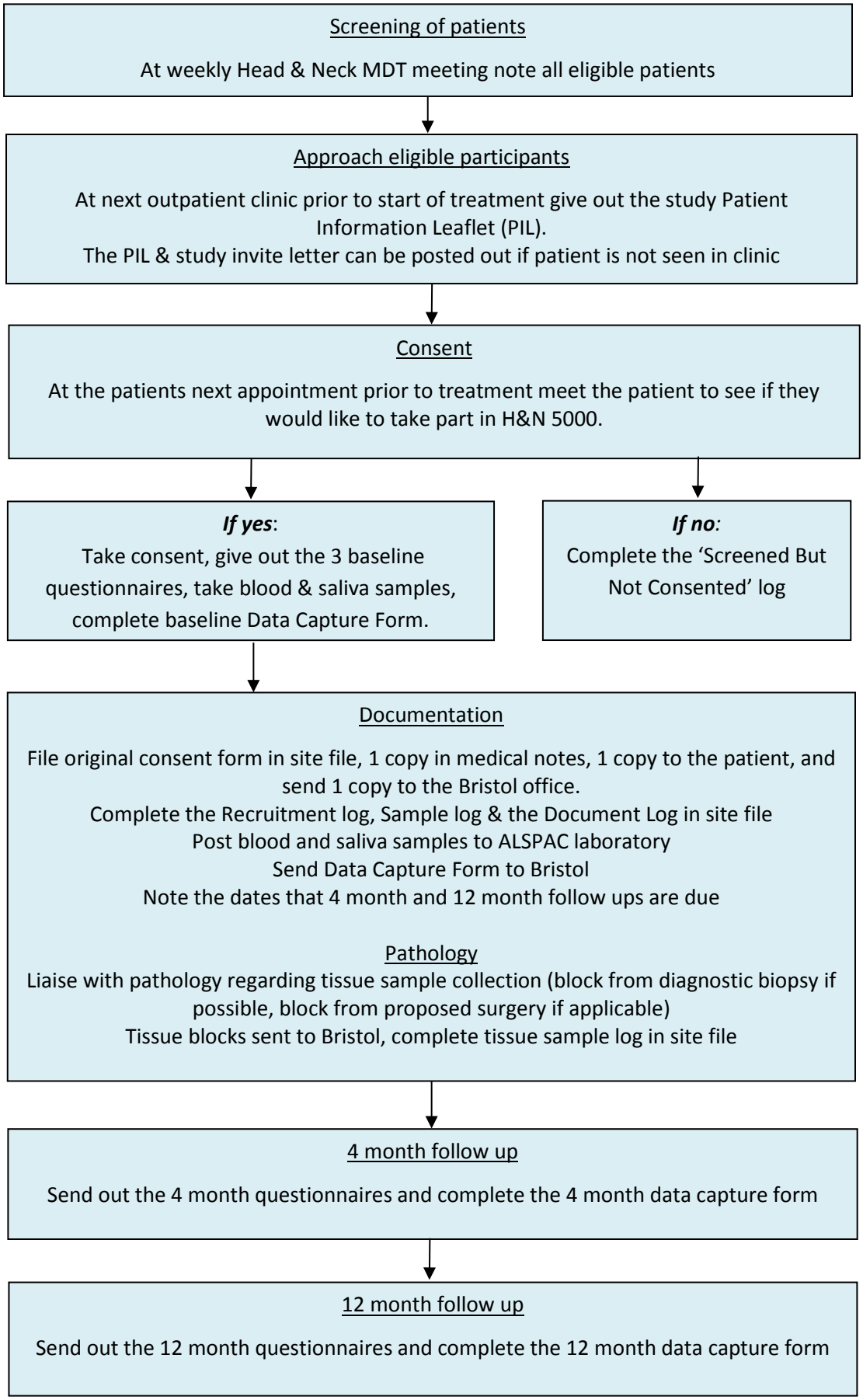
h) Patients who have already commenced their cancer treatment (with the exception of those whose treatment is also their diagnostic procedure)

Patient consent, baseline questionnaires and blood and saliva collection are to be completed before the patient starts their treatment. An exception will be made to this rule where the patients diagnosis and treatment have been the same procedure (for example tonsillectomy or thyroidectomy). In this case recruitment and study baseline procedures should be completed within a month of the diagnostic procedure. In cases where there is no treatment procedure recruitment baseline procedures should be done as close to diagnosis as possible.

Research pathway

Below is a flow chart outlining the pathway through the research process. The diagram shows how patients will be contacted, the data that will be collected and the administrative tasks that need to be undertaken at each stage of the research process. The appendix lists the paperwork that will be completed.

Head and Neck 5000 Research Pathway



Recruitment and data collection

We will recruit a clinical cohort of 5000 patients from the participating MDTs. A designated research nurse (or health professional) will assist with patient recruitment and data collection at each of the participating MDTs.
The exact timing and framing of the approach may vary across centres as MDT clinics run differently. The proposed protocol for centres will be as follows:

1. Confirmed new diagnosis of head and neck cancer by MDT, eligibility criteria checked
2. Study information sheet given to patient in clinic after diagnosis has been given, but before treatment starts. Alternatively the patient information leaflet can be posted out with the study cover letter if required.
3. At the next appropriate clinic appointment before treatment begins consent taken, questionnaire pack provided and blood and saliva samples taken. Data Capture form completed.
4. Pathology department contacted regarding tissue specimen collection.

Screening:

The research nurse (or designated health care professional) will check with the Multidisciplinary Team and patient records that the diagnosis of head and neck cancer has been confirmed and the patient meets the study eligibility criteria.

Recruitment:

All eligible patients discussed at the MDT meeting will be asked by their clinical team to consider participating in the study. The research nurse, or a member of the Head & Neck clinical team, will then give or send out the study information leaflet to the patient. If the patient information leaflet is to be posted out it will be sent with the study approved introductory letter.

The research nurse will meet the patient (usually at a planned clinic) and will explain the proposed study and ask if they have any questions. If the patient agrees to participate in the study, consent (Appendix 4) will be obtained by the research nurse, or an appropriately delegated member of the research team. Consent will be taken the following areas: provision of a blood and saliva sample, permission to access stored tissue samples, data collection from notes, questionnaire participation and flagging with the NHS Information Centre (NHSIC). The research nurse will send a copy of the signed consent form to the central Head & Neck 5000 research team.

Questionnaires

The research nurse will give the patient a questionnaire to complete, or complete with the patient if they are unable to do so alone, with questions on socio-economic status (including occupation, education and housing) and lifestyle (including smoking and alcohol intake) to be completed at the clinic where possible (Appendix 5). This questionnaire can be taken home and returned by stamped addressed envelope if the patient does not wish to complete it in clinic. The research nurse will inform the patient about the sexual history questionnaire; due to the sensitive nature of the questionnaire the research nurse will ensure that the information is given in a confidential setting. They will give the patient the option to complete in clinic or take it home for self completion together with a prepaid envelope for this questionnaire (Appendix 6). If a patient needs help with completing the sexual history questionnaire, they will be asked if they would like to answer these sensitive questions with the help from the research nurse or if they would prefer not to complete the questionnaire. If a translator is required, the sexual history questionnaire will not be provided. A questionnaire pack (Appendix 7) that includes questions on psychological status and general as well as cancer specific quality of life questions [11, 12] will be given to the participant to be completed either in clinic, or in their home environment and sent back to the research team in the provided prepaid envelope. Additionally at the Bristol site, a second baseline questionnaire package will be provided (Appendix 8). The research nurse will make a record of each patient who requires assistance with questionnaire completion and/or requires an interpreter. The research nurse will send a copy of the signed consent form together with the clinical information and baseline questionnaire to the research team in Bristol, who will enter the data onto a database. The research team will send a reminder to participants if they have not returned the questionnaires within two weeks. If further reminders are required, the research nurses will contact the participants by phone.

Data Capture Forms

Data will be collected from the medical notes of patients who have consented to the study at baseline, 4 months and 12 months. The Data Capture Forms are to be returned to the central Head & Neck 5000 office not later than one month after the scheduled time points. The follow up time points are dated from the date of consent.

Blood, Saliva and Tissue Samples

The collection of blood, saliva and tissue samples is described in the biological sample collection protocol below. These samples are to be collected at baseline only and are not returned to sites. If a patient does not wish samples to be collected they may continue in the study for questionnaire completion and data capture only.

Baseline questionnaires and blood and saliva sample collection are to be completed before the patient starts their treatment. The exception to this is where the patients diagnosis and treatment have been the same procedure (for example tonsillectomy). In this case recruitment and study baseline procedures should be completed within a month of the diagnostic procedure. In cases where there is no treatment procedure recruitment and baseline procedures should be done as close to diagnosis as possible.

Follow Up:

The research team will receive regular cancer/death notifications from the NHSCR and the NHSIC. The registers will notify us of subsequent cancer registrations and mortality among cohort members throughout the study. Where sites have become aware that a patient has died they will notify the Head & Neck 5000 team in Bristol. A mortality form is to be completed by site staff for each deceased patient.

At 4 months, we will review the mortality data, and ensure that no patient who has died is contacted. We will also ensure that any patient that has withdrawn from the study will not be contacted. The follow up questionnaires are to be sent out by the local sites where possible. Where the central Bristol site is sending out the follow up questionnaires the research team will send out the contact list to the research nurse 1-2 weeks before we contact the patient, who will check that there is no reason why the patient should not be contacted, for example the patient has recently died or is too ill to participate. The research nurse at site will extract clinical information about participating patients from the medical notes and send the information back to the research team using the 4 month follow up data capture form (Appendix 9). The local site or the central research team will send out the 4 month questionnaire pack (Appendix 10) that includes questions about concerns, loss of function (such as speech or swallowing), treatment received, health economics and quality of life. Participants will be asked to complete the questionnaires and send them back to the research team in the provided prepaid envelope. The participants in Bristol will receive a second questionnaire pack with further questions about appearance and quality of life (Appendix 11). The research team will send a reminder letter to participants if they have not returned the questionnaires within two weeks. If further reminders are required, the research nurses will contact the participants by phone after one month of sending the questionnaire pack. For those patients that have been identified as needing assistance with the questionnaires, the research nurse will contact them directly. The collected data will be entered into the database by the central Head & Neck 5000 research team.

At 12 months, we will review the mortality data, and ensure that no patient who has died is contacted. We will also ensure that any patient that has withdrawn from the study will not be contacted. As before, the follow up questionnaires are to be sent out by the local sites where possible. Where the central Bristol site is sending out the 12 month follow up

questionnaires the research team will send out the contact list to the research nurse, who will check that there is no reason why the patient should not be contacted, for example the patient has recently died or is too ill to participate. The research nurse will extract clinical information about participating patients from the medical notes and send the information back to the research team using the 12 month follow up data capture form (Appendix 12). The local site or the central research team will send out the 12 months questionnaire pack (Appendix 13) that includes questions about concerns, loss of function (such as speech or swallowing) treatment received, health economics and quality of life. Participants will be asked to complete the questionnaires and send them back to the research team in the provided prepaid envelope. The participants in Bristol will receive a second questionnaire pack with further questions about appearance and quality of life (Appendix 14). The research team will send a reminder letter to participants if they have not returned the questionnaires within two weeks. If further reminders are required, the research nurses will contact the participants by phone one month after the questionnaire was sent. For those patients that have been identified as needing assistance with the questionnaires, the research nurse will contact them directly. The collected data will be entered into the database by the research team.

Where the 4 & 12 month follow up questionnaires are to be sent out by the central Head & Neck 5000 office the patients name and address must be sent to the Bristol office at baseline by using the study 'demographic form'.

Patient withdrawals

Where a patient wishes to withdraw from the study the research nurses will ascertain to what degree the patient wishes to withdraw from the study. Patients may withdraw from a section of the study (e.g. sample collection or questionnaire completion) and remain in the study for all other study procedures. Where a patient wishes to withdraw from an aspect, or all, of the study a withdrawal form will be completed and sent to the central Head & Neck 5000 team in Bristol.

Biological Sample Collection Protocol

This section describes the protocol for collecting biological samples. For this study we will ask patients for consent to cover blood and saliva collection for the research and access to excess tissue not required for diagnosis or treatment. A hierarchy of access protocol will be followed to ensure that local diagnostic tissue banks have first access to tissue, with Head and Neck 5000 only receiving access to additional tissue where available.

Sample Processing and Analysis

As part of Head &Neck 5000 we will test the blood and tissue samples for Human Papilloma Virus (HPV) so that we can get a more accurate picture of how the virus is involved in head and neck cancer.
We will also look at metabolites and epigenetic biomarkers that are causally associated with head and neck squamous cell cancer progression or fatality. We will test the hypothesis that metabolomic and epigenetic profiles measured at the diagnosis of head and neck squamous cell cancer predict subsequent progression of the disease to metastases and can predict survival. We aim to look initially at 1000 incident squamous cell cancers from the cohort. DNA extraction and genetic analysis on blood, saliva and tissue will be performed on samples where the study participants have signed the relevant section of the consent form to allow this. We will also link to the National Institute of Dental and Craniofacial Research (NIDCR) funded project 'The role of germline and somatic DNA mutations in oral and oropharyngeal cancers' (grant reference: 1R01DE025712-01A1). This project aims to improve understanding of the genetic factors involved in oral and oropharyngeal cancer risks and outcomes. Anonymised samples & data from H&N5000 will be sent to the project which is run by the World Health Organisation International Agency for Research on Cancer.

Study samples may be sent to laboratories outside of UH Bristol (including overseas) for processing and for tests to be performed. All samples sent for analysis, and any data sent with the samples, will be anonymised and labelled with the H&N5000 study number.

Current study procedures for collecting and storing the blood, saliva and tissue samples as outlined below.

Samples

- 16 mls of venous blood, collected in 2 x EDTA tubes (10 and 6 mls in each).
  White cells for DNA extraction, and plasma for biochemical, proteomic and metabolomic measures.
- Saliva will be collected in a sterile container.
  For transcriptomic, biochemical, proteomic and metabolomic measures
- Tissue sample will be processed as formalin fixed paraffin embedded tissue.

Protocol for collection and processing of biological samples

Sampling

Samples will be collected from participants attending outpatient clinics at baseline.

Research nurses will follow the established consent process (outlined in the recruitment and data collection section above) and samples will be labelled with the patients study ID number and a numeric ID barcode label provided by the study.

Blood sample

a. The research nurse or phlebotomist will collect the blood samples in accordance with the local standard operating procedures for drawing blood.

b. Obtain 16 ml of venous blood, collected in 2x EDTA blood tube (10 and 6 mls in each).

c. The blood specimen will be transported by first class post in accordance with the approved regulations. Transfer kits will be provided by the central Head & Neck 5000 team.

Saliva sample

a. The patient should rinse his/her mouth with water several times prior to collection.

b. The patient should allow saliva to flow in the mouth and should empty saliva by spitting into the sterile empty screw-top container.

c. At least 1ml of saliva will be collected if possible.

d. The sample will then be transported by first class post in accordance with the approved regulations. Transfer kits will be provided by the central Head & Neck 5000 team. Only the transfer kits provided by the Head & Neck 5000 Bristol office are to be used for transport of specimens.

Samples will be posted to the Avon Longitudinal Study of Parents and Children (ALSPAC) laboratories in Bristol. All other personal data and information will be stored by the research team in the study coordinating centre. The samples will be shipped to the laboratory at ambient temperature by the next available first class post using the transfer kits provided. Samples taken on a Friday do not require refrigeration over the weekend. This is an established process, since DNA and plasma and serum samples suitable for biochemical analysis were successfully shipped to the ALSPAC laboratory from all over the UK in this way for the 1958 Birth Cohort Biomedical Sweep in 2002-2004 (http://www.b58cgene.sgul.ac.uk/report.php). Over 60% of samples arrived within 48hr and over 85% within 72hr.

Processing

On receipt samples will be logged into a database and blood samples will be separated by centrifugation (3500rpm for 10mins). The buffy coat layer will be stored for future DNA extraction. Up to 2.5ml of plasma per EDTA tube will be stored in a selection of 200ul and 500ul plasma aliquots. Saliva samples will be divided into up to four 1ml samples.

All samples will be frozen and stored at –80^{o}C in the ALSPAC biosample repository and details of the number of aliquots and location stored in the repository's stock control system. The freezers in the repository are alarmed and covered by a 24hr a day call out system. The ALSPAC laboratory and biosample repository are licensed by the Human Tissue Authority to store human tissue for research purposes.

Tissue samples

Tissue will be obtained in two ways:

1) From the diagnostic examination/biopsy of the primary tumour or pre-malignant lesion;
2) From the operation to remove the primary tumour.

A hierarchy of access protocol will be followed to ensure that local diagnostic tissue banks have first access to tissue, with Head and Neck 5000 only receiving access to additional tissue where available. If there is not enough tissue available for the Head & Neck study to be sent a block, this does not prevent the patient from entering the study. The Pathologist will select one representative paraffin embedded tumour block from the primary site and if applicable, one also from a matched lymph node metastasis. The tissue blocks required for the study need to be blocks showing the transition from normal to malignant tissue with details of the invasive front. The local Pathology department is also to send an anonymised (identified only with study number and initials) copy of the patients histopathology report with the tissue blocks and the completed anonymised H&N 5000 pathology request form.

The tissue will be processed as formalin fixed paraffin embedded tissue. The tissue sample will be sent to Head & Neck 5000 office, Bristol Dental School, Lower Maudlin Street, Bristol BS1 2LY. The confidentiality of the sample will be ensured by pseudonymisation and the samples will be stored in a cabinet in a restricted access laboratory at the Bristol Dental Hospital. The coding schedule will be kept separately from the samples in a secure location. Tissue samples are not returned to sites so must be surplus to clinical requirements. If tissue cannot be obtained this does not stop the patient from being in the study.
Tissue will be processed and stored in Tissue Micro Arrays (TMAs) to facilitate use of the samples in future ethically approved studies.

Questionnaires used

The baseline questionnaire will consist of a 4 –page questionnaire that can be nurse administered or self completed, and a 10-page self completed questionnaire. The 4-month questionnaire will consist of a 14-page self completed questionnaire and the 12-month questionnaire will consist of 16-page self completed questionnaire. For those patients that receive radiotherapy, they will complete an additional 5-page self completed questionnaire. Patients that are enrolled in the study at the Bristol centre will complete an additional 12-page self completed questionnaires (Your Quality of Life, Difficulties in Your Life, Your Appearance) at baseline, 4-months and 12-months.

Question Set	Research Topic	Number of pages	Questionnaire pack
About You	Education, occupation [13] Income [14] EQ-5D-5L [15] Smoking [16, 17] Alcohol [16, 17]	4	Baseline, 4-month, 12-month
Your Outlook	Revised Life Orientation Test (LOT-R) [18]	1	Baseline, 4-month, 12-month
Your General Health	EORTC QLQ-C30 [19]	2	Baseline, 4-month, 12-month
Specific Aspects of Your Health	EORTC QLQ-H&N35 [20]	2	Baseline, 4-month, 12-month
Your Feelings	Hospital Anxiety and Depression Scale (HADS) [21]	2	Baseline, 4-month, 12-month
Your Diet	Semiquantitative Food Frequency Questionnaire [22]	1	Baseline, 4-month, 12-month
You and Cancer	Fears of Recurrence [23]	½	4-month, 12-month
Your Personal costs	Survey designed by Dr. Melissa Ke	2	4-month, 12-month
Your Quality of Life	The revised University of Washington (UW) QOL questionnaire. [24, 25]	2	In Bristol group at Baseline, 4-month, 12-month

Question Set	Research Topic	Number of pages	Questionnaire pack
Difficulties in Your Life	The Social Difficulties Inventory (SDI) [26]	2	In Bristol group at Baseline, 4-month, 12-month
Your Appearance	The Derriford Appearance Scale (DAS 24) [27]	6	In Bristol group at Baseline, 4-month, 12-month
Your Symptoms	Head and Neck Radiotherapy Questionnaire (Late Toxicity) [28]	5	For patients that receive radiotherapy , 12-month
Sexual History	Sexual History [29]	1	Baseline

PROCESS

1. The central research team will ensure that the research teams at each site have sufficient supplies of study materials. They will also arrange training for the research teams at each site.

2. The local research team will record all new Head & Neck cancer patients discussed at the MDT meeting who are not consented in to the study (Appendix 15). This is in order to describe the workload of the MDT and to allow us to assess the representativeness of the cohort. This list will be anonymised and will only contain the details specified below:

    a. Diagnosis (tumour site)
    b. Age
    c. Gender
    d. Reason patient not enrolled in study
    e. Date discussed at the MDT

The list of patients 'screened but not consented' will be sent to the central Head & Neck 5000 team on a monthly basis. Patients recruited to the study will be recorded on the recruitment log in the study site file.

3. Patients recruited into the study will be flagged with the NHS Information Centre (NHSIC) and followed for at least five years. The NHSIC will notify the research team of subsequent cancer registrations and mortality among cohort members.

4. The central Head & Neck 5000 research team in Bristol will enter questionnaire data and information from the data capture form into the study database.

5. The research team will update the database based upon the information provided via the flagging process from the NHSIC and the Office of National Statistics for each patient.

STATISTICAL ANALYSES

We will use multiple linear regression to compare continuous outcomes; logistic regression to compare dichotomous outcomes and Cox's proportional hazards to compare survival between different groups controlling for confounding factors. We will use random effects models or robust estimates to allow for clustering between centres.

We have calculated the power of this study based on survival differences across 4,000 participants. This allows for exclusions of rarer cancer types, withdrawals from the study, incomplete data and loss to follow up from the target total of 5,000 enrolled. We have assumed that patients are recruited from 10 centres (this allows for recruiting future centres who agree to enrol patients) and have allowed for a range of plausible centre level effects. If 2 year mortality is 35% and alpha is 0.05 we have 80% power to detect a difference in survival (according to an individual patient characteristic or a measure of the quality of care [31] they received split at the median) of around five percentage points for an intra-class correlation coefficient of 0.005 and of 10 percentage points for an intra-class correlation coefficient of 0.01.

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