Head & Neck 5000 Follow-up Study

Short Study Title: H&N5000 Follow-up Study

Protocol V1.2 17-10-16

Sponsor Reference Number: DE/2016/5060

IRAS Number: 211454

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's Standard Operating Procedures, and other regulatory requirements.

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

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: ..... Date: 26/10/16

Name (please print): SESSILA BISSET

Position: RESEARCH OPERATIONS MANAGER

Chief Investigator:

Signature: ..... Date: 27/10/2016

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Head & Neck 5000 Follow-Up Study Management Group

Name	Job Title	Role in Study
Prof A Ness	Professor of Epidemiology, School of Oral & Dental Sciences, University of Bristol	Chief Investigator
Dr A Waylen	Senior Lecturer in Social Sciences, School of Oral & Dental Sciences, University of Bristol	Psychology measures
Miss K Hurley	Senior Research Nurse, Head & Neck 5000, University Hospitals Bristol	Project Manager
Prof S Thomas	Professor in Oral and Maxillofacial Surgery, School of Oral & Dental Sciences, University of Bristol	Clinical liaison
Dr M Pring	Consultant Senior Lecturer in Oral Maxillofacial Pathology, School of Oral and Dental Sciences, University of Bristol	Pathology liaison
Mr C Penfold	Research Associate in Statistics, University of Bristol	Statistician
Mr S Toms	Database Manager, University of Bristol	Database Manager

The Study Management Group will meet every month throughout the study. The meetings will review study participation, data return, data entry progress, data quality, study findings and the dissemination of results.

Contents

List of Abbreviations

DAHNO	Data for Head and Neck Oncology
H&N5000	Head & Neck 5000 Study
HES	Hospital Episode Statistics
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human Papillomavirus
HRA	Health Research Authority
HSCIC	Health and Social Care Information Centre
MDT	Multidisciplinary Team
PHE	Public Health England
QoL	Quality of Life
REC	Research Ethics Committee
SCC	Squamous cell carcinoma

1. Background

Head and neck cancer (HNC) remains a significant cause of mortality and morbidity worldwide [1] . Globally, it is the sixth leading cause of cancer and accounts for 5% of all cancer mortalities [2]. Despite considerable advances in diagnosis and treatment, survival remains poor. The five year survival rate varies between cancer sites, but ranges from between 26% for hypopharyngeal cancer to 87% for thyroid cancer [3].

Tobacco smoking and alcohol consumption are key risk factors for head and neck cancer and account for around 75% of all cases [4]. The risk for smokers is estimated to be approximately 6-fold over that of never-smokers and this risk increases in a dose-response manner with duration and extent of smoking [5, 6]. Alcohol is an independent risk factor but consumption seems to work synergistically to enhance the risk of HNC associated with tobacco use, especially in the case of heavy drinkers [7].

In addition to these long-established risk factors, human papillomavirus (HPV) infection has recently been identified as a major etiologic factor for a subset of head and neck squamous cell carcinomas (HNSCC) - carcinomas arising from the oropharynx [8-10]. HPV-related HNSCCs are usually seen in young-onset cases [11]. People with HPV-positive HNSCC have a better prognosis than those with HPV-negative tumours, i.e. tobacco- and alcohol-related carcinomas, largely because they respond better to chemoradiotherapy [12].

Typically, prognosis for people with HNC depends on the stage of the disease at presentation. [1] Treatment given during the early stages of the disease (stage I/II) is relatively successful and outcomes are typically good [13]. However, late presentation is not uncommon which in part explains why survival rates have taken so long to show any marked improvement.

A further reason for poor survival rates is that people who present with HNC also frequently have underlying health problems, associated with high-risk behaviours such as heavy smoking and alcohol consumption. Common ailments include cardiovascular, pulmonary and hepatic diseases [14, 15]. Comorbidities such as these are reported to present in 21–35% of people with HNC [16], which is disproportionately higher than in any other cancer group with the exception of lung cancer. HNC survival has been shown to be directly affected by the severity of comorbidity [17], first and foremost because it has a profound effect on the treatment options that are available.

Comorbidity has also been shown to impact on quality of Life (QoL) in people with HNC. There has been a growing interest in QoL as a predictor of overall survival in people with cancer in recent years. Strong associations between QoL and short-term survival have already been reported in breast cancer [18], lung cancer [19, 20] and melanoma [21]. Whilst the body of research on QoL issues in head and neck cancer is accumulating rapidly [22-24], there remains a need for further research examining long-term survival outcomes in large clinical cohorts.

Head and Neck 5000 (H&N5000) is a large observational study of people with head and neck cancer from across the United Kingdom [25]. Recruitment began in April 2011; by the time it closed in December 2014, 5511 people from 76 separate centres agreed to take part, making H&N5000 one of the largest studies of its kind.

The study is exceptional in bringing together clinical data, patient-reported outcomes and biological samples in a single co-ordinated resource for translational and prognostic research.

At baseline, participants were asked to provide both a blood and saliva sample and to complete questionnaires on health and lifestyle, quality of life and sexual history. A clinical data capture form was completed for each participant. Where possible a tissue sample, either from the diagnostic procedure or from the operation to remove the primary tumour, was collected. The local sites also sent an anonymised copy of the participant's histopathology report. No further biological samples

were requested from participants, but follow-up questionnaires were sent out at four months and twelve months after the individual joined the study.

The follow-up questionnaires repeated many of the questions included in the baseline questionnaire apart from those enquiring about previous sexual behaviour. Additional questions were included on fear of recurrence at both four and twelve months and questions on late radio-toxicity at twelve months. As before, the research staff abstracted information on diagnosis and treatment from the hospital medical records onto a short data capture form at four and twelve months.

2. Aims & Objectives

The H&N5000 Follow-up Study aims to describe the social, lifestyle and clinical outcomes in people with head and neck cancer and relate these to baseline characteristics from the original Head & Neck 5000 study.

The primary objective is collect further outcome data on H&N5000 participants who have been in the study for a minimum of three years. The secondary objectives are:

1. To send out a follow-up questionnaire on patient-reported outcomes to be completed by participants who have been in the study for a minimum of three years.
2. To characterise three to five year morbidity and mortality outcomes in the H&N5000 cohort.
3. To combine clinical and lifestyle data collected on H&N5000 participants at baseline, 4 months and 12 months with 3 year data to identify predictors of HNC outcome.
4. To explore the long-term psychological impact of living with a head and neck cancer diagnosis.
5. To determine the individual economic cost of HNC three to five years after a head and neck cancer diagnosis.

3. Study Design

This is a multi-centre cohort follow-up of the Head & Neck 5000 study. All 76 study sites that recruited patients to the Head & Neck 5000 study will be eligible to join the Follow-up Study. The list of sites who took part in Head & Neck 5000 and the list of sites taking part in the Follow-up Study can be found on the H&N5000 website www.headandneck5000.org.uk

As in the original Head & Neck 5000 study, data will be collected by patient questionnaire, collection of information from the medical notes on the study Data Capture Form and linkage to national clinical databases such as those held by Public Health England, DAHNO, HES & HSCIC.

4. Eligibility Criteria

Inclusion criteria:

1. Participants recruited into the original H&N5000 cohort.
2. Participants who have been in the H&N5000 study for a minimum of 3 years

Exclusion criteria:

1. Participants who did not consent to be approached regarding further research.
2. Participants withdrawn from the H&N5000 study.
3. Participants who are now considered to meet the criteria for mental incapacity or vulnerability set out in the Mental Capacity Act 2005.

5. Participant Identification

Informed consent was provided by participants when they enrolled into the H&N5000 study. Consent was wide-ranging and participants were asked to specify whether:

- They were happy to complete questionnaires that include questions on subjects such as health and lifestyle.
- They gave permission for the research team to collect additional information about them from their medical notes and via linkage to health-related records including disease registries.
- They gave permission for researchers to contact them in the future regarding further studies.

The central H&N5000 office will use the study database to prepare a list of eligible participants who:

- have been in the H&N5000 study for a minimum of three years
- consented to further contact from researchers
- have not withdrawn from the H&N5000 study

In order to recruit to this follow-up study the central Bristol H&N5000 team will send the study numbers of eligible patients to the study sites for further eligibility checks. The study sites will run checks against their hospital databases and clinic letters to see if there is any reason why the individuals should not be contacted, for instance if they are too unwell to participate, or more recent mortality data has been obtained. The results of these local checks will be sent back to the central Bristol team using the eligibility log, and where no apparent or recorded reason to withhold the questionnaire is detailed by local checks, an updated patient's address will be recorded on the study 'Address Form' and sent by post to the central Bristol office so that the Follow-up Study pack can be posted out.

6. Study Procedures & Methods of Data Collection

All eligible participants will be sent a follow-up pack that will contain the following documents: an invitation letter, participant information leaflet, the 29-page study questionnaire, and a pre-paid return envelope. The packs will be sent out by the central H&N5000 office in Bristol, but if a study site would prefer to send the questionnaires to their patients this can be arranged following discussion with the central H&N5000 Bristol team.

6.1 Participant Invite Letter and Information Leaflet

All eligible participants will be sent a letter informing them about the Follow-up Study and inviting them to take part. They will have the opportunity to contact the research team to ask any questions that they may have before deciding whether or not to participate in the follow-up study.

The participant information leaflet will provide individuals with further details about the study and what their participation will require. It will be made clear in the information leaflet that participants are under no obligation to take part in the Follow-up Study and that their care will not be affected should they choose not to take part. The information leaflet will also make it clear that participants are free to withdraw from the study at any point.

6.2 Questionnaire

The H&N5000 Follow-up Study questionnaire will repeat many of the questions asked previously at twelve months: questions concerning anxieties, loss of function (such as speech or swallowing), treatment received, health economics, quality of life and late toxicity. There are some additional questions around comorbidities, use of feeding tubes, dental health, changes in eating behaviours and cancer recurrence. Participants will be asked to complete the questionnaire and send it back to the Bristol study team in a pre-paid envelope. If they have any queries about the questionnaire or how to complete it, they will be able to get in touch with the research team using the contact address and /or telephone number provided on the front page of the questionnaire. For those participants who have been identified as needing assistance with the questionnaires, the local research nurse will be available to meet the patient at their next routine hospital visit.

If the central study team have not received the questionnaire three weeks after posting it out, they will send a reminder letter along with replacement documents.

6.3 Data Capture Forms

As in Head & Neck 5000 the research staff at each site will extract clinical information about participants from their medical records and send this back to the central H&N5000 office using the Follow-up Study Data Capture Form. Site staff will make every effort to find as much of the clinical information as possible using patient notes, hospital databases, and information held by the patient's clinical team. The deadlines for return of completed Data Capture Forms will be agreed for each site at study set up.

6.4 Deceased patients

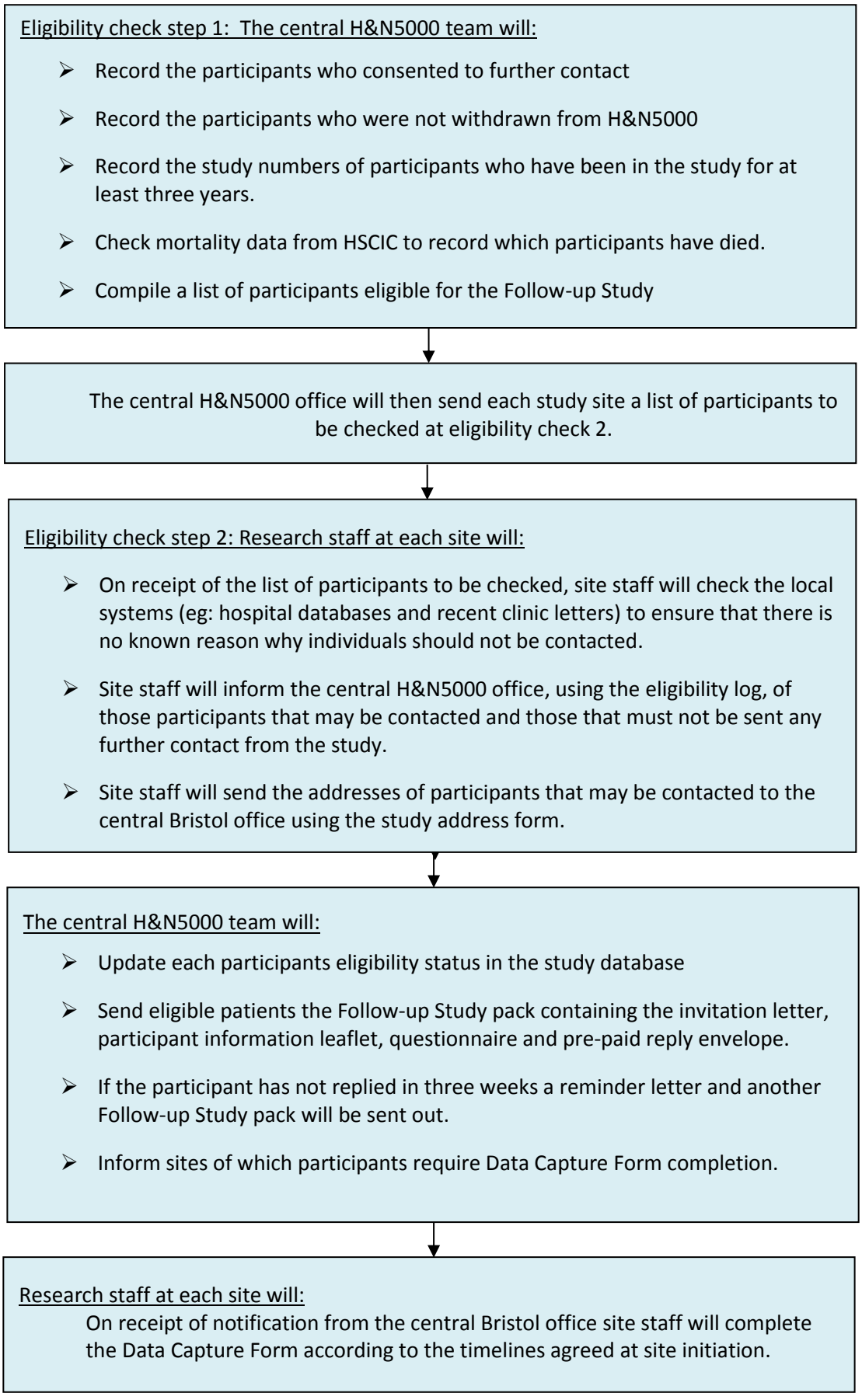
Where patients have died, a data capture form will be completed from the medical notes to the date of death.

6.5 Withdrawals

All participants have the right to withdraw from the Follow-up Study at any point. In the event that an individual decides not to continue in the study, their wishes will be recorded on the study withdrawal form. The form will record whether the individual wishes to withdraw from the study entirely, or whether they no longer wish to take part in certain sections of the study. Participants may withdraw from part or all of the three sections of the study: data collection from medical notes, questionnaire completion and linkage to national databases such as those held by Public Health England, DAHNO, HES & HSCIC. If withdrawing from one or two sections only they may remain in the study for any remaining data collection.

The form will be completed by the central H&N5000 team following notification by the participant of their decision to withdraw. If a participant has contacted local site staff to discuss withdrawal the local site staff will contact the central Bristol team as soon as possible to report the withdrawal.

6.6 H&N5000 Follow-up Study Pathway:



7. Protocol compliance

Accidental protocol deviations can happen at any time. They must be reported to the Chief Investigator and Sponsor immediately by completion of the Protocol Deviation Form.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach of the protocol.

8. Data Management

The source data for the Data Capture Forms will be the patients' medical records. Data will be collected by a member of the research team using the study Data Capture Form (DCF). The form will be in paper format. The completed original Data Capture Forms will be stored at site and a copy of the Data Capture Form will be sent to the H&N5000 office in Bristol by post; pre-paid return envelopes will be provided. Patient completed questionnaires will also be returned to the central Bristol office using postage paid envelopes. All DCF and questionnaire data will be entered in to the study specific, password-protected, Access database sited on the University Hospitals Bristol NHS Foundation Trust network. The database will be backed up automatically on a daily basis as part of University Hospitals Bristol NHS Foundation Trust IT department procedures. The database will have automatic range and logic checks to reduce data entry errors.

A sample of 25% of Data Capture Forms will be checked by the central H&N5000 team against source data. This will be performed over a minimum of 10 sites. The percentage of source data checks will be increased within a site if error rates of over 10% are found. The number of sites checked may also be increased if common errors are found across sites. Source data checks may involve anonymized source data sent from sites to the H&N5000 office, for example an anonymized MDT report.

A random sample of 25% of questionnaire and Data Capture Form data will be checked by the central study team, against entries within the database to check for data entry errors. The percentage will be increased if error rates of over 10% are found.

Where data on the Data Capture Form appear inconsistent or inaccurate, or are missing, a data query will be raised. Automatic data query reports generated through the database will be run initially once a fortnight, and sent to sites by e-mail. Further cross checks on data will be performed by clinical staff from the central Bristol team. The clinical checks will be performed on a minimum of the first 25 DCFs sent in by each site. These checks will review data to look for inconsistent or inaccurate data not covered by the automatically generated query reports. Where necessary the automatically generated query reports will be updated as a result. Queries raised during the clinical checks will be sent to sites by e-mail, where possible in connection with the automatically generated queries.

9. Statistics and Data Analysis

We will describe morbidity, mortality and psychological outcomes three to five years after a diagnosis of HNC. Morbidity outcomes will be described using the ACE-27 scale of co-morbidities, mortality will be described as overall mortality and mortality at 3-years, and psychological outcomes will be described using continuous scales from the Hospital Anxiety and Depression Scale and the 'Fear of

Recurrence' questionnaire. We will combine the clinical, lifestyle and patient reported outcomes measures (PROM) data we will collect at 3-5 years with data already collected at diagnosis, and at 4 and 12 months after diagnosis. We will use these repeated measures to explore associations between clinical and lifestyle factors, and HNC outcomes. Specifically we will use survival analysis models for time to event data (e.g. death and disease recurrence), logistic regression models for binary outcomes (e.g. death and disease recurrence at 3-years), and linear regression models for continuous outcomes (e.g. PROM scores derived according to published protocols).

10. Data Handling and Data Protection

The database will be designed so as to protect patient information in line with the Data Protection Act 1998. Study staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centres. The study participants will be identified only by their H&N5000 ID number and initials on the Data Capture Form and database. All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with the Data Protection Act 1998.

11. Monitoring and Audit

The study will be monitored in accordance with University Hospitals Bristol's Monitoring Standard Operating Procedure. All trial related documents will be made available on request for monitoring and audit by UH Bristol, the relevant Research Ethics Committee and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies. The monitoring plan will be developed and agreed by the sponsor. Local study sites may also be subject to monitoring according to their local NHS Trust policies.

12. Research Governance & Authorisations

The study will be performed subject to favourable opinion/authorisation/permission from all necessary regulatory and other bodies. This includes but is not limited to REC, HRA, and NHS trusts. This study will be conducted in accordance with Good Clinical Practice and the Research Governance Framework for Health and Social Care.

13. Storage of Records

Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All essential documents, including patient records and other medical record source documents will be retained for a period of 5 years following the end of the study. Where study related information is documented in the hard copy medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where date is 5 years after the last patient last visit. Where electronic records are in use Trust policy will be followed.

Study questionnaires and Data Capture Forms will be retained for 20 years as further follow up work may be carried out in the future with this cohort.

14. Sponsorship & Finance

The study is sponsored by University Hospitals Bristol NHS Foundation Trust who assume overall responsibility for the conduct and management of the study.

The study is jointly funded by money from:

- Professor Andy Ness NIHR Senior Investigators Award
- A Cancer Research UK grant awarded to Professor Richard Martin.
- Research Capability Funding awarded to Professor Andy Ness

Patients will not receive payment for participating in this study. Sites participating in this study will not receive payment from the Head & Neck 5000 study, but will attract support costs through the UKCRN portfolio.

15. Indemnity

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 trial 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 trial. 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.

16. Reporting and dissemination

We will disseminate our research findings at national and international conferences and via original research articles published in high-end peer-reviewed journals. We will also make research findings available on the H&N5000 study website.

17. References

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18. Appendices

18.1 Protocol Amendments

Amendment Number	Protocol version number & date	Author(s) of changes	Details of changes made	Date of ethical approval
Original ethics application	1.1 02-08-16	Prof A Ness	Section 13 altered to show that DCF and questionnaires will be retained for 20 years	04/08/2016
1	1.2 17-10-16	K Hurley	Telephone numbers updated for C Wood & K Hurley. Version numbers updated in section 18.2	Minor amendment

18.2 List of Current Study Documents

Document	Version Number	Date	Required at local sites?
Data Capture Form	1.1	17-10-16	Yes
Data Capture Form Completion Guidelines	1.0	12-07-16	Yes
Eligibility Log	1.0	12-07-16	Yes
Address Form	1.0	12-07-16	Yes
Participant Invitation Letter	1.0	12-07-16	No (unless by prior arrangement with H&N5000 team)
Participant Information Leaflet	1.1	17-10-16	No (unless by prior arrangement with H&N5000 team)
Questionnaire	1.1	17-10-16	No (unless by prior arrangement with H&N5000 team)
Reminder Letter	1.1	17-10-16	No (unless by prior arrangement with H&N5000 team)
Protocol Deviation Form	1.0	12-07-16	No. Form to be completed by central H&N5000 team
Withdrawal Form	1.0	12-07-16	No. Form to be completed by central H&N5000 team