LOOC

Lymphatic mapping Of Oropharyngeal Cancer

Supported by:

NIHR Efficacy and Mechanism Evaluation (EME) Programme

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Full title of study	Lymphatic mapping Of Oropharyngeal Cancer
Short title	LOOC
Version and date of protocol	4.0 dated 01 November 2023
Sponsor:	University College London (UCL)
Sponsor protocol number	Edge 127659
Funder (s):	Medical Research Council (MRC)
Clinicaltrials.gov no:	NCT04498221
Intervention:	Lymphatic mapping
Single site/multi-site:	Multi-site

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Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1	09SEP2019	Clare Schilling	
2	15MAY2020	Clare Schilling	REC comments
3	03 March 2022	Reka Novotta	Updated site list, replaced SITU with NCITA, and removed fhSPECT from sub-study.
4	01NOV2023	Clare Schilling & Ingrid Potyka	Addition of radiotracer 99mTc- human albumin colloidal particles to the choice of radiotracers, error correction in Table 2

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, the Data Protection Act (2018) and General Data Protection Regulations, the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator _____

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UCLH Signature Date

Sponsor _____

UCL Sponsor Representative

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Contents

List of abbreviations

AJCC	The American Joint Committee on Cancer
CI	Chief Investigator
CRF	Case Report Form
CRN	Cancer Research Network
CT	Computed Tomography
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EUA	Examination under anaesthetic
fhSPECT	Freehand single-photon emission computed tomography
GA	General anaesthesia
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
HPV	Human Papilloma Virus
HSA	Human Serum Albumin Nanocolloids
ISF	Investigator Site File
ITC	Individual tumour cells
LOOC	Lymphatic mapping Of Oropharyngeal Cancer
MDT	Multidisciplinary Team Meeting
MRI	Magnetic resonance imaging
NHS R&D	National Health Service Research & Development
OC	Oral Cancer
OPC	Oropharyngeal cancer
OPSCC	Oropharyngeal squamous cell cancer
p16	Tumour suppressor protein that inhibits cyclin-dependent kinase 4A
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
REC	Research Ethics Committee
SENT	Sentinel European Node Trial
SITU	Surgical & Interventional Trials Unit
SLN	Sentinel lymph nodes
SN	Sentinel node
SNB	Sentinel node biopsy
SOP	Standard Operating Procedure
SPECT	Single-photon emission computed tomography
TMG	Trial Management Group
TNM8	Tumour Node Metastasis (TNM) - 8th Edition
TSC	Trial Steering Committee
UCL	University College London
VEGF	Vascular endothelial growth factor

1 Trial personnel

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2 Summary

Objectives:	• Validate lymphatic mapping protocol in OPC using new technology (fhSPECT) with radiotracers (Lymphoseek, Human Serum Albumin Nanocolloids) • Establish lymphatic drainage pattern and occult metastatic rate in the contralateral neck in OPC
Type of trial:	Prospective multicentre cohort study to understand the lymphatic drainage pattern in 150 patients with unilateral neck metastases from oropharyngeal cancer
Trial design and methods:	The study has two phases: the imaging phase and the surgical phase. **1. IMAGING PHASE (n=75):** Develops an imaging protocol to establish lymphatic drainage pattern in a population of patients with proven unilateral neck metastasis from OPC during routine examination under anaesthetic. Four peritumoural injections of radiotracer are given followed by freehand SPECT (fhSPECT)scan under GA. SPECT/CT scan (gold standard for lymphatic mapping) will be carried out the next day. Outcomes – rate of contralateral drainage. Accuracy of fhSPECT Vs. SPECT/CT. Number of contralateral nodes on SPECT/CT will be used as the denominator in calculating the sensitivity of fhSPECT in independently verified images. fhSPECT should achieve sensitivity >94%. Minimum of 20/75 patients demonstrate contralateral drainage to proceed to surgical stage. Imaging substudy: Develops a secondary imaging protocol in case of <94% sensitivity of intraoperative fhSPECT Twenty patients from imaging phase with easily accessible tumours will be invited to undergo a second imaging Intervention. A single injection of radiotracer is given in clinic followed by SPECT/CT. Comparator – SPECT/CT performed in initial phase Outcome – Sensitivity of outpatient imaging (single injection, fhSPECT and SPECT/CT) compared to gold standard (SPECT/CT from initial phase). Acceptability of outpatient injection compared to under GA. **2. SURGICAL PHASE (n=75):** feasibility of surgically staging the contralateral neck A new study group of patients will be invited to participate. During EUA excision of contralateral nodes identified on imaging* is undertaken (sentinel node biopsy). Serial sectioning of excised (sentinel) nodes to identify micrometastasis. Outcome is occult metastatic rate of contralateral nodes (positive sentinel node biopsy). Contralateral drainage rate will be identified in the imaging phase, expected SNB positive rate of excised nodes 25-40%. Outcome of this study will prove feasibility of future research in which management of the contralateral neck is based on surgical staging
Trial duration per participant:	4 weeks
Estimated total trial duration:	54 months
Planned trial sites:	• University College London Hospitals NHS Foundation Trust • St George's University Hospitals NHS Foundation Trust • NHS Greater Glasgow & Clyde • Royal Marsden Hospital, London • Aintree University Hospital, Liverpool

Planned Participant Identification Centre (PIC) sites:	• St Bartholomew's Hospital, London • The Royal London Hospital, London • Whipps Cross University Hospital, London
Total number of participants planned:	150
Main inclusion/exclusion criteria:	**Inclusion** • Adults aged 18 or over • New diagnosis of OPC - all anatomical subsites and HPV status accepted • Unilateral metastatic nodes equating to AJCC TNM8 clinical staging N1-N2b for P16 negative and N1 for P16 positive patients. **Exclusion** • Suspicious bilateral nodes on imaging • Previous radiotherapy or surgery to the neck • Second primary oropharyngeal tumours • Distant metastasis (e.g. lung, bone) • Pregnancy and lactation • Inability to give informed consent • Allergy to lymphatic tracers
Statistical methodology and analysis:	LOOC assesses a new technique and thus effect size is difficult to estimate. Moreover no comparative data is useful as prior studies are all based on frank metastasis rather than "at risk" or occult metastasis rate. Extrapolating from oral cancer model our sample size is pragmatically based on number of eligible cases seen and minimum cases required to establish a baseline lymphatic pattern. **1) Validating image protocol** 75 patients will be assessed with both imaging procedures (fhSPECT and SPECT/CT) with SPECT/CT being considered the gold standard. This will allow us to estimate the sensitivity and specificity of fhSPECT (as well as PPV and NPV) with corresponding confidence intervals. The agreement between fhSPECT and SPECT/CT will be recorded as either agree/disagree. We both require and expect that the agreement will be high. With 75 patients an expected agreement of 96%, an exact 95% confidence interval will have a total width of approximately 10%. In addition, we will have 80% power to demonstrate that the agreement exceeds 88% using a one-sided test at the 5% significance level Analysis consists of sensitivity and specificity of fhSPECT and summarising the agreement between fhSPECT and SPECT/CT. Exact confidence intervals will be calculated for these proportions. We will investigate variation between sites with respect to surgical performance. Two independent assessors will consider each pair of scans. We will investigate the agreement between these assessors and quantify the corresponding intra-class correlation. **2) Surgical Phase** 75 patients will be considered for SNB. Of these, 20-30% (15-23 patients) will have sentinel nodes on the opposite side of the neck. We will quantify this proportion with an exact 95% confidence interval, (75 patients, CI +/- 11%).

3 Background and Rationale

What is the problem being addressed?

This exploratory surgical imaging study was developed to address patient concerns and published evidence showing increasing unmet need in treatment of patients with oropharyngeal cancer. Studies show there is no consensus in the optimum treatment for the node negative contralateral neck. Most evidence is based on case series comparing the outcomes of unilateral versus bilateral treatment, with significant heterogeneity of the modality used (conventional/robotic surgery, conformal radiation, Intensity-Modulated Radiation Treatment). However, all show morbidity (dysphagia, feeding tube dependency, taste, xerostomia, and neck lymphoedema) is significantly improved when only one side of the neck is treated.

Currently a phase II feasibility study of de-escalation in HPV positive oropharyngeal cancer (PATHOS ClinicalTrials.gov identifier NCT02215265) is supported by Cancer Research UK. Here all patients receive ipsilateral neck dissection and then are stratified to one of three arms of adjuvant treatment based on histological features of the tumour and nodes. The primary outcome was swallow function (MDADI score). The feasibly study has completed recruitment and has now moved to a phase III trial with non-inferiority of survival as the outcome.

We have discussed LOOC with the Co-Chief investigator of PATHOS who was enthusiastic about the complimentary information our study will provide regarding contralateral spread and has agreed to act as Chairperson for our DMC. There is no conflict between the two studies as interventions related to LOOC are undertaken at the time of diagnostic biopsy, prior to potential recruitment to PATHOS.

LOOC is an early phase oncology imaging study which will evaluate the utility of new technology for staging the contralateral neck. The results can then be rapidly translated to late phase prospective clinical trials in which treatment decision can be based upon the outcome of staging by sentinel node biopsy.

Why is the research important in terms of improving the health of the public and/or to patients and the NHS?

Treatment of oropharyngeal squamous cell cancer (OPSCC) is associated with significant morbidity. Traditionally prophylactic treatment of the contralateral clinically node negative neck is undertaken when the estimated risk of involvement is greater than 20%. Patients undergoing bilateral neck treatment often require long-term supportive care for swallowing dysfunction because of changes to the swallowing-related organs (pharyngeal muscles, larynx, salivary glands, and oesophagus). Dependence on feeding via gastrostomy or very limited oral diet is common. Reducing the impact of treatment on long-term function is key in patients with OPSCC who have a good prognosis and tend to be young and fit at presentation.

Unilateral neck treatment has a clear benefit in protecting swallow function and thus improving quality of life. This study is the first step in developing a technique to accurately stage the contralateral neck and thus spare the majority of patients from undergoing unnecessary treatment to the unaffected neck. If successful, this has major implications for improving survivorship for these patients, who are increasing in number with rising incidence of the disease. The impact for the NHS will be immediate and long lasting. Surgical time and inpatient stay will be reduced, as will acute admissions for dehydration during radiotherapy. Fewer patients will require percutaneous feeding, thus reducing complications. The impact upon allied health professionals – speech and language therapists and dieticians including provision of dietary supplements will also be reduced.

Furthermore by developing a reliable imaging protocol for lymphatic mapping of deep tumours in LOOC, there will be easy translation to other head and neck cancers such as salivary gland, thyroid and larynx. There may also be translation to other deep body cavity tumours such as the lung and prostate gland where there is controversy about the exact extent of nodal resection required and nodal relapse is a major cause of treatment failure.

Evidence explaining why this research is needed now (how does the existing literature support this proposal?)

The mechanism of reliability of lymphatic mapping to sentinel nodes was described in 2003. Functional lymphatic imaging studies were undertaken in tumour and control footpads of mice. Tracer showed in the

sentinel node within two minutes of injection compared to 30 minutes for the control. Histologically sentinel nodes had c-Myc oncogene overexpression stimulating VEGF-C and D to induce lymphangiogensis in the node, causing a 23-fold increase in lymphatic tracer drainage. Lymphatic mapping reveals and active pre-metastatic process directing lymphatic flow to specific nodes. Human studies in oral cancer showed patient injected and imaged on two separate occasions a week apart had drainage to identical nodes.

LOOC study will allow a choice of lymphatic mapping radiotracer, 99mTc- human albumin colloidal particles or 99mTc-Lymphoseek. 99mTc- human albumin colloidal particles are standard radiotracers which accumulate within lymph nodes. These have a large body of evidence supporting efficacy in the mapping of sentinel nodes from oral cancer and more recently has been used to map lymphatic drainage in cN0 OPC patients under GA (de Veij Mestdagh et al, 2018). In this study patients were imaged by SPECT/CT 3-6 hours post injection with a contralateral drainage rate of 20%.

Lymphoseek has additional properties to aid retention in the sentinel node via binding to macrophage CD206 mannose receptor. The advantage of clearing the injection site rapidly and selectively retention in the sentinel node is important in LOOC where we aim to image the sentinel nodes in theatre minutes after injection. Scatter and 'shine-through effect' in traditional tracers can impair immediate imaging, but Lymphoseek has not been compared with traditional tracers within the intraoperative setting. Over a longer protocol Lymphoseek has shown impressive results in reducing the false negative rate for SNB in oral tumours from 9% to 2.56%.

Review of the literature reveals a small number of case reports using freehand SPECT (fhSPECT) for intraoperative SNB. In one series 23 oral cancer (OC) patients had a 98% sentinel node detection rate by fhSPECT Another series of 66 patients with (OC) identified 94% of the sentinel nodes by fhSPECT.

Drug posology, specifically radiation dose is considered similar with Lymphoseek and 99mTc- human albumin colloidal particles.

The research team has performed a blinded study comparing intraoperative SN imaging fhSPECT to pre-operative SPECT/CT in 50 OC patients. Sentinel node biopsy using fhSPECT alone was superior to SPECT/CT (false negative rate 5.3% vs. 15.8% respectively).

Currently there are no reports using Lymphoseek or fhSPECT in oropharyngeal cancer but the outlined data above are used as proof of concept.

4 Objectives

LOOC is a phase II surgical imaging study for oropharyngeal cancer. The overarching aim and objective is to establish the lymphatic drainage pattern and occult metastatic rate in the contralateral neck.

The study is divided into two phases; imaging and surgery.

1.Imaging phase (n=75):

Purpose: Imaging protocol validation and establishing drainage pattern

Population – Patients with proven unilateral neck metastasis from oropharyngeal tumours

Intervention – During routine EUA 4 x peritumoural injection of lymphatic mapping tracer followed by freehand SPECT scan

Comparator – Following day SPECT/CT scan (gold standard for lymphatic mapping)

Outcome – Rate of contralateral drainage. Accuracy of fhSPECT compared to SPECT/CT. Number of contralateral nodes on SPECT/CT will be used as the denominator in calculating the sensitivity of fhSPECT by

independently verified images. fhSPECT should achieve sensitivity >94% minimum of 20/75 patients to demonstrate contralateral drainage to proceed to the surgical stage.

Imaging substudy:

Purpose: Develop back-up imaging protocol in case of failure of fhSPECT Population –20 patients from imaging phase with easily accessible tumours (e.g. soft palate, tonsil)

Intervention –single intratumoural injection of radiotracer in clinic SPECT/CT performed up to 24 hours later

Comparator – SPECT/CT performed at the imaging phase

Outcome – Sensitivity of outpatient imaging (single injection, fhSPECT and SPECT/CT) compared to gold standard for lymphatic mapping. Patient acceptability.

2. Surgical phase (n=75)

Purpose: Feasibility study of surgical staging of the contralateral neck Population – same as those in the imaging phase

Intervention – Excision of contralateral nodes identified on imaging *(fhSPECT or SPECT/CT*) during routine EUA. Serial sectioning of excised (sentinel) nodes to identify micrometastasis.

Comparator - none

Outcome – Occult metastasis rate of contralateral nodes. (positive sentinel node biopsy). Contralateral drainage rate identified in imaging phase, expected SNB+ rate of contralateral nodes 25- 40%.

Results of the surgical phase of this study will prove the feasibility of future studies in which management of the contralateral neck can be based upon surgical staging by SNB.

Additional information:

*Imaging used will depend on outcome of the imaging phase.

"Go" and "No Go" gate: Analysis at the end of imaging phase.

If fhSPECT found to be >94% then GO

If fhSPECT <94% sensitive and alternative (outpatient injection) not acceptable to patients NO GO.

Project does not proceed to surgical phase.

5 Trial design

LOOC is a multicentre prospective non-randomised phase II surgical imaging study. This study comprises two stages.

Patients with newly diagnosed (cervical) metastatic oropharyngeal cancer will be considered for recruitment.

Typical route to diagnosis is neck lump proven as metastatic squamous cell carcinoma on ultrasound guided fine needle aspiration cytology (FNAC). Oropharyngeal mass (primary tumour) is identified on subsequent clinical examination. All such patients undergo standard cross sectional imaging (MRI and/or CT) to stage the primary tumour and neck (as per national guidelines) and are presented at a Multidisciplinary Team Meeting (MDT).

The investigating team are members of local MDT and will identify potential patients at these weekly meetings.

MDT will normally recommend examination under anaesthetic (EUA). It is during this routine procedure the trial intervention (lymphatic mapping) will opportunistically take place.

Inclusion

- Adults aged 18 or over
- New diagnosis of OPC - all anatomical subsites and HPV status accepted

- Unilateral metastatic nodes equating to AJCC TNM8 clinical staging N1-N2b for P16 negative and N1 for P16 positive patients.

Exclusion

- Suspicious bilateral nodes on imaging
- Previous radiotherapy or surgery to the neck
- Second primary oropharyngeal tumours
- Distant metastasis (e.g. lung, bone)
- Pregnancy and lactation
- Inability to give informed consent
- Allergy to lymphatic tracers

Planned interventions

1. Imaging phase – Trial interventions:

a) At start of EUA four submucosal peritumoural injections of radiotracer administered under direct vision.

b) At end of EUA procedure freehandSPECT scan of contralateral neck undertaken (declispeSPECT, Surgiceye GmBH). Total procedure including scanning adds 15-30 minutes to anaesthetic time.

c) Following recovery from EUA (up to 24 hours later) imaging by conventional SPECT/CT undertaken in nuclear medicine department. If patients wish they can go home overnight between the injection and the scan. Any additional travel costs will be reimbursed.

Imaging substudy:

a) Subgroup of patients (n=20) whose tumour is easily accessible without general anaesthetic will be invited to receive a second dose of radiotracer in the clinic 4-10 days after initial injection. This will give time to recover from EUA and the previous dose will be completely removed. Patients are selected on basis of ease with which the injection can be delivered. It is mandatory that nodal drainage was shown on SPECT/CT (desirable if this was contralateral but not essential).

b) Second dose delivered by a single injection after application of topical anaesthetic spray, followed by SPECT/CT. A questionnaire will ask patients to reflect on how the experience compared to the procedure under GA. The injection and scan will take place in the outpatient department and will take up to two hours to complete.

2. Surgical phase

Follows immediately from imaging phase if specified outcomes are met. Surgical protocol informed by outcomes of prior phase. Either:

i) Intraoperative peritumoural tracer injection, fhSPECT imaging of contralateral SN in the theatre under a single general anaesthetic.

or

ii) Single intratumoural injection in outpatient setting, followed by fhSPECT and conventional SPECT/CT. Proceed to EUA and SNB within the next 24 hours followed by

iii)Sentinel node biopsy of contralateral nodes during EUA (no additional general anaesthetic). SNB follows standardised procedure. Skin incision made directly over the position of nodes. Node identification using hand held gamma probe (Tc99m) and confirmed ex-vivo. Nodes sent for serial step sectioning at 150 micron intervals. Alternate sections stained immunohistochemical analysis.

Presence of viable individual tumours cells (ITC) or greater are considered metastatic nodes.

Result of the SNB will be discussed with the patient and oncology team prior to further treatment but recommendation is based on the MDT decision. This study is not powered to recommend changes in treatment based on SNB result.

Proposed outcome measures

Imaging phase

• Rate of contralateral drainage. fhSPECT and SPECT/CT images reviewed by two independent assessors. Sum of non-duplicated contralateral hotspots taken as the true contralateral drainage rate. Minimum of 20/75 patients must demonstrate contralateral drainage to proceed to surgical stage.

• Accuracy of fhSPECT compared to SPECT/CT. Number of contralateral nodes on SPECT/CT used as denominator in calculating sensitivity of fhSPECT by independently verified images.

Each assessor fulfills a case report form (CRF) per case with three simple questions:

Are there contralateral nodes on SPECT/CT? – no/yes (record neck level)

Are there contralateral nodes on fhSPECT?- no/yes (record neck level)

Do the contralateral nodes co-localise? - yes/no

If Contralateral nodes are shown in SPECT/CT but not fhSPECT this will be recorded as false negative result (unless these can be attributed to second echelon nodes) for fhSPECT and vice versa. Contralateral drainage on either modality will be recorded as true positive result.

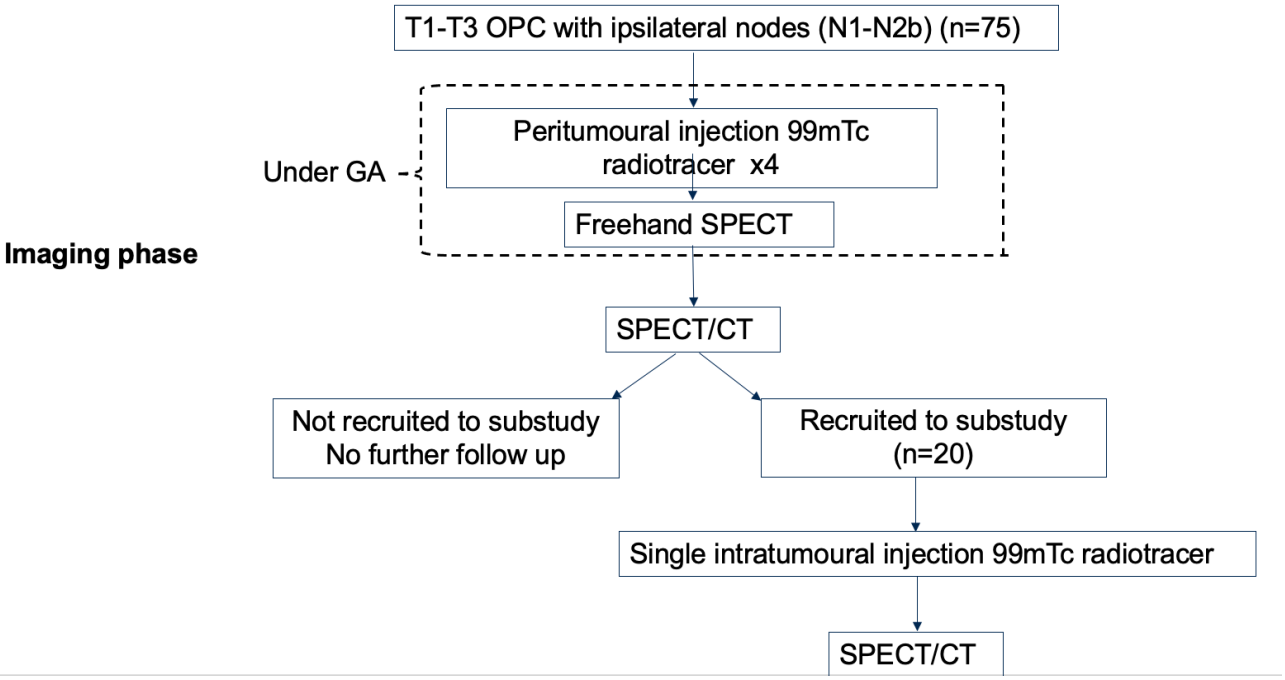
fhSPECT should achieve sensitivity >94% compared to SPECT/CT.

Assessment and follow up

The study procedures are very safe but all patients will be screened for adverse reactions following the final scan or the day following SNB and all complications will be reported according to GCP guidelines. No long-term follow up is planned.

The patient care pathway is summarised in Figure 1 and the assessments are summarised in Tables 1-3.

Figure 1 Patient care pathway



ANALYSIS OF RESULTS, STOP GO:NO GO

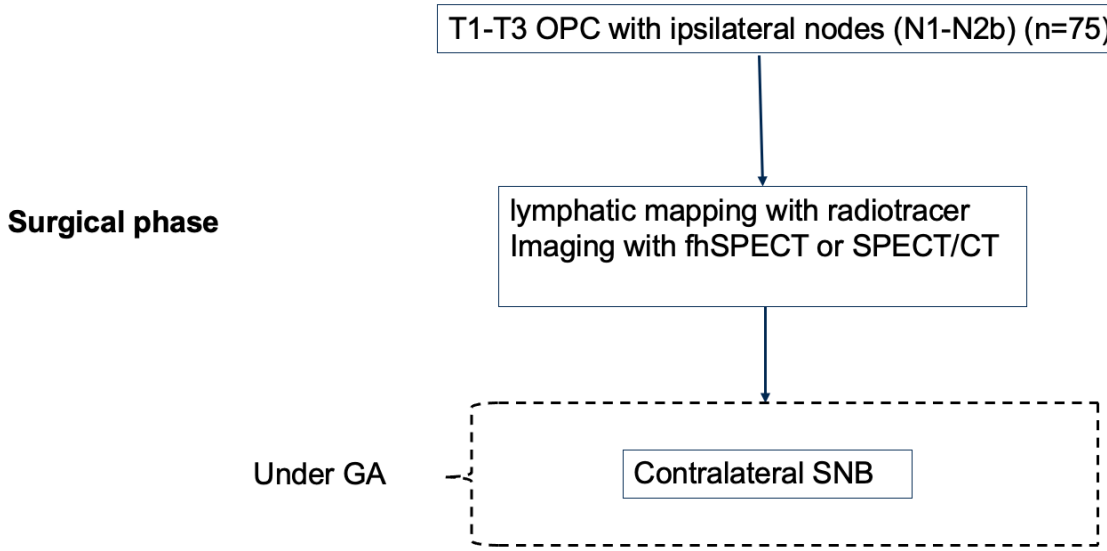


Table 1 Table of assessments – Stage 1 Main Group

Assessments	**Screening**	**Baseline**	**Examination day**	**Examination day + 24h**
All Stage 1 Patients (n=75)				
Inclusion and exclusion criteria	x			
Consent	x			
Registration		x		
Demographic data		x		
Medical history		x		
Concomitant medications		x		
Tumour characteristics		x		
Examination under anaesthesia (standard of care)			x	
Injection of radiotracer and fhSPECT scanning			x	
Sentinel node imaging by SPECT/CT up to 24 hours post injection				x
AE reporting			x	x

Table 2 Table of assessments – Stage 1 Subgroup

Assessments	**Screening**	**Baseline**	**Examination day**	**Examination day + 24h**	**Examination day + 4–10 days**
Stage 1 Subgroup (n=20)					
Inclusion and exclusion	As per Stage 1 main group				
Consent					
Registration					
Demographic data					
Medical history					
Concomitant medications					
Tumour characteristics					
Examination under anaesthesia (standard of care)					
Injection of radiotracer and fhSPECT scanning					
Sentinel node imaging by SPECT/CT up to 24 hours post injection					
AE reporting					x
Local anaesthesia					x
Intratumoural injection of radiotracer					x
SPECT/CT scan					x
Patient Acceptability Questionnaire					x

Table 3 Table of assessments – Stage 2

Assessments	Screening	Baseline	Scanning day*	Examination Day
Stage 2 Patients (n=75)				
Inclusion and exclusion criteria	x			
Consent	x			
Registration		x		
Demographic data		x		
Medical history		x		
Concomitant medications		x		
Tumour characteristics		x		
Outpatient radiotracer injection followed by SPECT/CT *			x*	
Examination under anaesthesia (standard of care)				x
Injection of radiotracer and fhSPECT scanning*				x*
Excision of contralateral nodes identified on imaging				x*
AE reporting			x	x

*These procedures will depend on the results of Stage 1.

6 Selection of Participants

6.1 Inclusion

- Adults aged 18 or over
- New diagnosis of OPC - all anatomical subsites and HPV status accepted
- Unilateral metastatic nodes equating to AJCC TNM8 clinical staging N1-N2b for P16 negative and N1 for P16 positive patients.

6.2 Exclusion

- Suspicious bilateral nodes on imaging
- Previous radiotherapy or surgery to the neck
- Second primary oropharyngeal tumours
- Distant metastasis (e.g. lung, bone)
- Pregnancy and lactation
- Inability to give informed consent

- Allergy to lymphatic tracers

6.3 Recruitment

Patients diagnosed with OPC who fulfil the inclusion/exclusion criteria will be identified during MDT meetings and in outpatient clinics.

6.4 Informed consent

Patients who fulfil the eligibility criteria will be provided with a patient information sheet (PIS) by the investigator or a designated appropriately trained member of the research team, who will be present to answer any questions regarding the aims, methods, anticipated benefits and potential hazards of the trial. They will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

The person taking consent will be suitably qualified and experienced, and will have been delegated this duty by the PI on the Staff Signature and Delegation of Tasks log.

Potential participants will be offered sufficient time (at least 24 hours) to consider the study, allowing time for discussion with family/friends/GP. The participant will be given the opportunity to ask questions and to be satisfied with the responses prior to written consent being taken. No study procedures will be conducted prior to the participant signing the study consent form. Following consent, the patient will be enrolled in the study and allocated a unique pseudo-anonymised subject number. A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the investigator site file and a copy placed in the medical notes. The PIS and consent form will be reviewed and updated if necessary throughout the study (e.g. where new information becomes available) and participants will be re-consented as appropriate.

7 Product/Interventions

Lymphatic mapping of the drainage of OPC

8 Study procedures

8.1 Pre-intervention assessments

No study specific procedures will be needed to be carried out to assess eligibility. All information required to determine eligibility will be available from the standard medical records and identified as specified above either during MDT meeting or at outpatient clinics.

Relevant clinical information will be recorded in the CRFs. Data recorded will include:

- Demographics
- Relevant medical history
- Concomitant medication
- Tumour characteristics including size, type, grade, TNM stage, p16 status

8.2 Participant registration

Consented, eligible participants will be registered by completing the study's online registration form.

A unique pseudo-anonymised subject number will be generated. This number will be used to identify all patient data and tissue samples for the study.

8.3 Intervention procedures

Consented, eligible participants will undergo the following procedures.

1. Imaging phase – Trial interventions:

a) At start of EUA, four submucosal peritumoural injections of investigator's choice of 99mTc-human albumin colloidal particles or Lymphoseek (99mTc-Tilmanocept) will be administered under direct vision.

b) At end of EUA procedure, freehandSPECT scan of contralateral neck will be undertaken (declispeSPECT, Surgiceye GmBH). Total procedure including scanning adds 15-30 minutes to anaesthetic time. In the case of no drainage on the initial fhSPECT scan, a further scan can be undertaken after an additional 15 minutes.

c) Following recovery from EUA (up to 24 hours later), imaging by conventional SPECT/CT will be undertaken in nuclear medicine department. If patients wish they can go home overnight between the injection and the scan. Any additional travel costs will be reimbursed.

Imaging substudy:

a) Subgroup of patients (n=20) whose tumour is easily accessible without general anaesthetic will be invited to receive a second dose of the same radiotracer in the clinic 7-10 days after initial injection. This will give time to recover from EUA and the previous dose will be completely removed. Patients are selected on basis of ease with which the injection can be delivered. It is mandatory that nodal drainage was shown on SPECT/CT (desirable if this was contralateral but not essential).

b) Second dose will be delivered by a single injection after application of topical anaesthetic spray, followed by SPECT/CT. A questionnaire will ask patients to reflect on how the experience was when compared to the procedure under GA. The injection and scan will take place in the outpatient department and will take up to two hours to complete.

2. Surgical phase

This follows immediately from imaging phase if specified outcomes are met. Surgical protocol will be informed by outcomes of prior phase and will be either:

i) Intraoperative peritumoural tracer injection, fhSPECT imaging of contralateral SN in the theatre under a single general anaesthetic.

or

ii) Single intratumoural injection in outpatient setting, followed conventional SPECT/CT. Proceed to EUA and SNB within the next 24 hours followed by

iii) Sentinel node biopsy of contralateral nodes during EUA (no additional general anaesthetic). SNB follows standardised procedure. Skin incision will be made directly over the position of nodes. Node identification using hand held gamma probe (Tc99m) and confirmed ex-vivo. Nodes will be sent for serial step sectioning at 150 micron intervals. Alternate sections will be stained immunohistochemical analysis.

Presence of viable individual tumours cells (ITC) or greater are considered metastatic nodes.

Result of the SNB will be discussed with the patient and oncology team prior to further treatment but recommendation is based on the MDT decision. This study is not powered to recommend changes in treatment based on SNB result.

8.4 Subsequent assessments and procedures

The study procedures are very safe, but all patients will be screened for adverse reactions following the final scan or the day following SNB and all complications will be reported according to the following protocol.

8.5 Samples

The samples will be assessed by a qualified and trained histopathologist for presence of cancer. Sample storage and disposal will follow the local hospital policy for storage of cancer biopsies.

The retention of pathology samples for patients is outlined in:
Records Management: NHS Code of Practice Part 1 (2006) and Part 2 (Second Edition,

2009). The UK Departments of Health, in this published code of practice covers record/tissue management policy, standards and
retention periods for pathology samples (usually 15 years)

In Scotland, the position is set out in
MEL(1993)152, which was the subject of consultation in 2005 followed by publication in 2008 and revision in 2012, of a code of practice essentially equivalent to that applicable in England: Scottish Government Records Management: NHS Code of Practice (Scotland) Version 2.1, 2012

8.6 Discontinuation/withdrawal of participants

Participants will be free to withdraw from the study at any time. No data or follow-up information will be collected in relation to participants from the date of withdrawal. The decision of a participant to withdraw from the study will be recorded in the CRF. All recorded data and samples processed prior to the date of withdrawal of consent for study participation will remain in the study database and continued to be analysed as per study protocol. In line with GDPR, participants' rights to access, change or move their information are limited, as these need to be managed in specific ways in order for the research to be reliable and accurate. On withdrawal from the study, information already obtained will be kept, no new data from date of withdrawal will be held.

8.7 Definition of End of Study

The expected duration of the study is 4 years from recruitment of the first participant. The end of study is the date of the last follow up of the last participant.

The study will be stopped prematurely if:

- This is mandated by the Ethics Committee
- Following recommendations from the Sponsor
- Funding for the study ceases
- The Chief Investigator in consultation with the clinical and scientific lead, decides that sufficient biopsies and data have been obtained to fulfil the scientific objectives of the study.

The Research Ethics Committee will be notified in writing within 15 days if the study has been concluded or terminated early.

9. Recording and reporting of events and incidents

The risks of the procedures are summarised in Table 4.

9.1 Assessment and Management of Risk

The table below (Table 4) summarises the risks and mitigations of all interventions above standard care that are to be performed.

Table 4 The risks and mitigations of all interventions above standard care

Interventio	Potential risk	Risk Management
Radiotracer	Hypersensitivity (patients)	1. Ask patients about prior reactions to drugs, especially dextran or modified forms of dextran and exclude patients who are allergic. 2. Observe for hypersensitivity signs and symptoms following radiotracer injection. 3. Have resuscitation equipment and trained personnel immediately available.

Radiotracer	Adverse reactions (patients)	The most common adverse reactions (incidence < 1%) are injection site irritation and/or pain. We will check for pain and administer analgesics to patients as required.
Radiotracer / SPECT	Radiation exposure (patients)	1. The effective dose equivalent of radiation exposure to an average dose used in a 70 kg adult is about 0.30 mSV (30 millirem) in males and is about 0.33 mSV (33 millirem) in females. Patients are also exposed to an additional 200 millirem of exposure to CT scan. Therefore, the total radiation exposure per scan 230 millirem. Some patients (20/150 participants) will undergo two procedures. Therefore, such participants is exposed to an additional 460 millirem because of being involved in the project. The remaining 130/150 participants will be exposed to an additional 230 millirem because of being involved in the project. This is less than the average radiation exposure to a single CT chest. The average radiation exposure per year per individual due to background radiation is about 310 millirem. Therefore, the effective dose equivalent due to participation in the project is about 460/310 years or about 18 months of background radiation. To put this in context, the average radiation in a flight journey of about 1 hour at an altitude of 39,000 feet is about 0.006 mSV (0.6 milli rem). Therefore, the dose received is equivalent to 460/0.6 = 767 hours of air travel.
Radiotracer / fhSPECT	Additional operation time	Total procedure including scanning adds 15-30 minutes to anaesthetic time. In the case of slow drainage after intraoperative injection a second scan can be taken 10-15 minutes after the initial scan. The participants included in the study are those who are fit for major surgery. Therefore, the addition of the 15 to 30 minutes of time will not increase the risk significantly.
Sentinel node biopsy	Additional surgical procedure under GA and related wound complication including infection, bleeding, lymph collections	Qualified and trained doctors (surgeons and anaesthetists) will perform the procedure to minimise the risk due to GA and wound complications related to the biopsy.
Radiotracer / SPECT	Radiation exposure (healthcare professionals)	1. Use waterproof gloves, effective radiation shielding, and appropriate safety measures when preparing and handling radiotracer. 2. Radiotracer will be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and who have received approved training. 3. CT scan will be performed by trained healthcare professionals, who are aware of the radiation exposure to CT scan and take adequate precautions to minimise their exposure.

The definition of adverse events is provided in Table 5.

Table 5 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

The participants are not anticipated to have any unexpected adverse events in this study. Should a subject have an adverse event related to the radiotracer, this will be recorded on the AE log.

The period of observation for events is until the following day of the procedure. AEs and SAEs will be recorded until the end of the period of observation.

It is not necessitated for expected AEs to be reported and it is not necessitated for an adverse event form to be filled out for an expected AE. It is not necessitated for expected AEs to be reported to the sponsor.

A list of expected AEs includes the following:

- Injection site irritation
- Pain
- Allergy to radiotracers

If any of these symptoms are accompanied by events consistent with the definition of an SAE as specified in Table 5, then the event will be considered an SAE.

NCITA should be informed of any SAE within 24 hours of the investigator becoming aware, please send completed SAE CRF to NCITA via email.

Unexpected, related SAEs should be reported to NCITA within 24 hours of the investigator becoming aware.

NCITA SAE email:

uclh.ncita.sae@nhs.net

This will then be escalated to sponsor.

Local sites may have specific R&D protocols for reporting SAEs, which should be followed in addition.

The SAE will be reviewed for seriousness, causality, severity and expectedness.

All SAE CRFs must be completed and the SAE logs updated. All SAEs must be followed up until a resolution is reached (i.e. recovered, recovering, recovered with sequelae, fatal, not recovered or unknown).

Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories listed in Table 6 will be used to define the causality of the adverse event.

Table 6 Categories for causality of the adverse event

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

Expectedness

The expected is defined as shown in Table 7.

Table 7 Expectedness of adverse event

Category	Definition
Expected	An adverse event which is consistent with the information about the procedure defined in this protocol.
Unexpected	An adverse event which is not consistent with the information about the procedure defined in this protocol.

Recording adverse events

All adverse events (AE) that occur during the period of observation (which is the next day after the procedure) should be recorded on the AE log. Expected and related events do not need to be reported.

Procedures for recording and reporting Serious Adverse Events

All reportable serious adverse events will be recorded in the medical records and the appropriate eCRF and the AE log.

10 Data management

10.1 Confidentiality

All personal identifiable data collected during the study will be handled and stored in accordance with the Data Protection Act (2018) and General Data Protection Regulations (GDPR) and all other applicable regulations and legislation. To preserve patient anonymity, only the allocated subject number and subject identifier will be recorded on the Case Report Forms (CRF).

Medical records (case-notes and hospital trust computer databases) may be accessed by the recruiting site for up to 4 years from the date of consent for the purpose of data clarification.

Information about participant demographics, medical history, and concomitant medication and tumour characteristics together with clinical follow up information will be made available to the study team.

10.2 Data collection tools and source document identification

Data will be collected from sites using electronic CRFs designed in MACRO.

Source data are contained in source documents (medical records, which include laboratory and other clinical reports, case-notes and hospital trust computer databases) and must be accurately transcribed onto the eCRF.

It is the responsibility of the principal investigator to ensure the accuracy of all data entered in the eCRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the study database.

10.3 Completing Case Report Forms

Data will be collected by electronic Case report forms (eCRFs) and will be verified using manual and electronic validation checks.

All eCRFs must be completed in a timely manner by staff that are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the eCRF.

10.4 Data handling

A member of the local study team will submit the data into the study database. Access to the eCRF system will only be provided to staff with relevant authority delegated to them on the site's delegation log.

At enrolment, participants will be given a unique subject number and data will be entered under this subject number onto the study database. No personal identifiable data will be stored on the study database. Any personal identifiable data will be stored on a dedicated secure study area, part of UCL's Data Safe Haven (DHS). This database is access controlled and only accessible to the study team, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

The study database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the study the database will be locked and retained on the servers of UCL.

Information linking participant identifiable data to the pseudo-anonymised subject number will be held locally by the study site. These will either be held in written form in a locked filing cabinet or electronically in a password protected form on hospital computers. After study completion this information will be securely stored by the sites for 20 years unless otherwise advised by the Sponsor.

The data will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent.

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles. UCL is the data controller; the UCL Data Protection Officer is Alex Potts, contactable at data-protection@ucl.ac.uk. The data processors are site staff specified on the delegation log. The study will be collecting the following personal data: Name, sex, ethnicity, age, medical history.

11 Statistical Considerations

11.1 Sample size calculations

LOOC assesses a new technique and thus effect size is difficult to estimate. Moreover no comparative data is useful as prior studies are all based on frank metastasis rather than "at risk" or occult metastasis rate. Extrapolating from oral cancer model our sample size is pragmatically based on number of eligible cases seen and minimum cases required to establish a baseline lymphatic pattern.

11.2 Planned recruitment rate

In each stage up to seventy-five patients will be recruited over 18 months at five major head and neck cancer centres. In addition a number of regional units have agreed to act as Participant Identification Centres (PIC). Each of the main centres see over 100 new OPC diagnoses per year.

11.3 Randomisation

This is a non-randomised study.

11.4 Statistical analysis

1) Validating image protocol

75 patients will be assessed with both imaging procedures (fhSPECT and SPECT/CT) with SPECT/CT being considered the gold standard. This will allow us to estimate the sensitivity and specificity of fhSPECT (as well as PPV and NPV) with corresponding confidence intervals. The agreement between fhSPECT and SPECT/CT will be recorded as either agree/disagree. We both require and expect that the agreement will be high. With 75 patients an expected agreement of 96%, an exact 95% confidence interval will have a total width of approximately 10%. In addition, we will have 80% power to demonstrate that the agreement exceeds 88% using a one-sided test at the 5% significance level.

Analysis consists of sensitivity and specificity of fhSPECT and summarising the agreement between fhSPECT and SPECT/CT. Exact confidence intervals will be calculated for these proportions. We will investigate variation between sites with respect to surgical performance. Two independent assessors will consider each pair of scans. We will investigate the agreement between these assessors and quantify the corresponding intra-class correlation.

Update: Due to interruption in Lymphoseek tracer supply in the UK during the trial period coupled with widespread staffing pressures on radio-pharmacy and nuclear medicine departments, a pragmatic decision has been made to add the choice of 99mTc- human albumin colloidal particles as one of the radiotracers allowed for this study. Prior to this amendment thirteen patients were included in the study in whom Lymphoseek was used as the radiotracer. Consequently, an additional review will be undertaken after thirteen cases undertaken with 99mTc- human albumin colloidal particles to compare (descriptively) performance in the initial fhSPECT scan. There have been no high-quality head-to-head comparisons of 99mTc- human albumin colloidal particles and Lymphoseek in any tumour group, although small studies have

shown that Lymphoseek may identify more sentinel nodes but without impact on the number of positive nodes identified (Ooms et al. 2023, Tokin et al. 2012). No studies report the sentinel node identification rate in 99mTc- human albumin colloidal particles or Lymphoseek under 1 hour post injection. Thus we will seek to compare SN identification rate on fhSPECT in two groups of thirteen patient to ensure there is no gross disparity at this early stage of lymphatic mapping. If 99mTc- human albumin colloidal particles do not match Lymphoseek performance (SN identification rate at up to 30 minute post injection) we will revert to Lymphoseek as the sole tracer.

2) Surgical Phase

75 patients will be considered for SNB. Of these, 20-30% (15-23 patients) will have sentinel nodes on the opposite side of the neck. We will quantify this proportion with an exact 95% confidence interval, (75 patients, CI +/- 11%).

12 Record keeping and archiving

At the end of the study, all essential documentation will be archived securely by the PI for a minimum of 20 years from the declaration of end of study.

Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements.

The sponsor will notify sites when study documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

13 Oversight Committees

13.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, the clinical and scientific leads for the study and NCITA operational team. The TMG will be responsible for overseeing the study. The group will meet at least every 6 months during the period of recruitment and annually during the follow-up period and will send updates to PIs.

The TMG will review recruitment figures, the ongoing progress of the scientific studies and any resulting necessity for modification of the characteristics of subjects to be recruited to the study and any consequent requirement for substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments.

The TMG will additionally submit periodic progress reports to the REC and Sponsor.

13.2 Other committees

A study-specific TSC and an independent DMC will be appointed. The CI will report on scientific progress to these committees. Each of these committees will meet at least annually to monitor the progress of the study and the safety of the study respectively.

14 Ethical requirements and Patient and public involvement (PPI)

This protocol and all associated patient materials have been reviewed by the patient representative and modified as a result of the feedback.

The study protocol, participant information sheet, consent form, GP letter and other supporting documents have been approved by the Health Research Authority and the Yorkshire & The Humber - South Yorkshire Research Ethics Committee. The protocol, all other supporting documents including amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

Before any NHS site may be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must receive NHS permission in writing from the Trust Research & Development (R&D). It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. The chief investigator will prepare the APR.

Within 90 days after the end of the study, the CI/Sponsor will ensure that the main REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The CI will supply the Sponsor with a summary report of the study, which will then be submitted to the REC within 1 year after the end of the study.

15 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the study. Risk will be assessed on an ongoing basis and adjustments made accordingly.

The degree of monitoring will be proportionate to the risks associated with the study.

A study specific oversight and monitoring plan will be established for studies. The study will be monitored in accordance with the agreed plan.

We will use both central monitoring and external site monitoring to maintain oversight of local research conduct.

Central monitoring - will use reports from the online clinical trial database to monitor metrics such as subject recruitment rate, data completion and rate of data queries to monitor the performance of local research sites. We will also monitor adverse event reporting and protocol deviations at regular management group meetings to maintain oversight of local research conduct. Furthermore, we will ensure that we maintain records of GCP training from site PIs and research teams.

Site monitoring - external clinical monitors with on-site monitoring expertise will be commissioned by the sponsor to monitor conduct at each site such as subject consent procedures, local site file document maintenance and adherence to regulatory governance and trial quality.

16 Finance

Funding for this study was awarded to Mrs Clare Schilling by NIHR EME(Application Reference 17/39/05).
None of the CI or other investigators and members of the TMG have any personal financial interest related to the study.

17 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this study without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this study shall provide negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

18 Archiving

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCL for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for 20 years and in line with all relevant legal and statutory requirements.

19 Publication policy

The results of this research will be published in academic journals. Authorship will reflect the individual contribution to research in line with standard academic practice. The contribution of the funders of this research and the clinicians contributing to the research will be acknowledged. All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings.

20 Intellectual property

No background intellectual property rights (including licences) is required and no commercially exploitable intellectual property is likely to be generated during this research.

Appendices

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