THE MOSES STUDY

Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the management of the unknown primary squamous cell cancer in the head and neck

Protocol version:	V4.2
Date:	18 March 2022
Sponsor:	The Royal Marsden NHS Foundation Trust Fulham Road, London SW3 6JJ, United Kingdom
CCR number:	CCR5065
IRAS number:	256047
Funders:	Oracle Cancer Trust: GAL_RMH131218 Biomedical Research Centre: W94505-B062
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This protocol follows the format recommended by WHO found at "Recommended format for a Research Protocol" found at http://www.who.int/rpc/research_ethics/format_rp/en/ and the template provided by the Health Research Authority at https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/.

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1 Version history

Version	Date	Version
0.1	9/1/19	Sponsor application
1.0	5/4/19	Amendments following CCR review
1.1	9/7/19	Amendments following REC review
2.0	3/10/19	Update of database management procedures
2.2	1/7/20	CRF and consent clarifications following COVID-19
2.3	26/10/20	Addition of anonymised histology reports
3.0	03/06/21	Clarification to recruitment target, amendment to inclusion/exclusion criteria
3.1	10/09/21	TBM Sample Recruitment period updated
4.1	01/10/21	Extend recruitment target, recruitment period, follow-up duration, and molecular analysis
4.2	18/03/22	Updated sample shipment details

2 Table of acronyms

Acronym	Meaning
CCR	Committee for clinical research
CH	Conventional histology
CRF	Case report form
CT	Computed tomography
CUP	Cancer of unknown primary
EBV	Epstein Barr virus
FNAC	Fine needle aspiration cytology
GCP	Good clinical practice
H&E	Haematoxylin and eosin stain
H&N	Head and neck
HNC	Head and neck cancer
HNSCCUP	Head and neck squamous cell carcinoma of unknown primary
HPV	Human papilloma virus
ICF	Informed consent form
IRAS	Integrated research application system
MDADI	M. D. Anderson Dysphagia Inventory
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MTA	Material Transfer Agreement (Part of HRA Statement of Activities)
PET CT	Positron emission tomography and computed tomography
PIS	Participant information sheet
REC	Research ethics committee
RMH	Royal Marsden Hospital
RVI	Royal Victoria Infirmary, Newcastle (laboratories)
SAE	Stamped addressed envelope
SCC	Squamous cell carcinoma
SOP	Standard operating protocol
SSS	Step serial sectioning
TBM	Tongue base mucosectomy

3 Project summary

Study title	Evaluation of the role of tongue base MucOsectomy and Step sErial Sectioning in the management of the unknown primary squamous cell cancer in the head and neck.
Short title	The MOSES Study.
Study design	Multicentre prospective observational cohort study, incorporating histopathological and molecular tissue analysis.
Study setting	UK centres performing TBM to for suspected HNSCCUP.
Study participants	Patients with suspected head and neck squamous cell carcinoma of unknown primary (HNSCCUP) undergoing tongue base mucosectomy (TBM).
Planned sample size	100.
Follow-up duration	5 years.
Planned study period	Until recruitment of planned sample size.
Aim	To understand the current management of suspected HNSCCUP patients undergoing TBM in the UK, including adequacy of current histology, functional and oncological outcomes, and disease biology.
Objectives	Primary: • To establish if step serial sectioning (SSS), compared to conventional histology, improves identification of a primary site in TBM and tonsil specimens in suspected HNSCCUP. Secondary: • To compare the pick-up rate of primary cancers in TBM specimens between surgical methods (robotic vs laser vs endoscopic). • To prospectively evaluate swallowing function and pain scores after TBM. • To understand patient views and experiences of undergoing TBM for suspected HNSCCUP. • To report time-to-event data for local, regional and distant disease recurrence, and mortality. • To assess the molecular makeup of patients with suspected HNSCCUP undergoing TBM.
Methods	• Identification of patients prior to TBM surgery. • Step serial sectioning histology performed on tongue base and tonsil tissue (if available) to compare to conventional histology results. • Functional follow-up using patient completed questionnaires for pain and swallowing function (MDADI) at baseline and intervals up to 5 years. • Clinical oncological follow-up recorded for up to 5 years. • Exploratory molecular analysis of tongue base, tonsil (if available) and cervical metastatic tissues.
Expected outcomes	• Increased identification of single and multi-focal primary cancers on SSS. • Reasonable recovery of functional outcomes after TBM surgery prior to administration of radiation therapy. • Acceptance of TBM and SSS amongst suspected HNSCCUP patients. • Greater understanding of the molecular make-up of suspected HNSCCUP.

4 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 SOPs, and other regulatory requirement.

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 publicly 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:

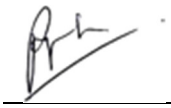
Print Name: _____

Signature: _____

Date: _____

Chief Investigator:

Print Name: Vinidh Paleri

Signature: 

Date: _____

5 Rationale & background information

Approximately 5% of head and neck cancer (HNC) present with a neck metastasis with no clinically evident primary site.[1,2] Patients undergo clinical examination and cross-sectional imaging to attempt to identify this primary site.[3] If the origin of the cancer is still not apparent, then FDG PET combined with CT can be used. A proportion of these patients will still not have their primary cancer identified. In these instances, patients would have traditionally undergone a panendoscopy including bilateral tonsillectomy and random biopsies, including of the tongue base. More recently, a surgical procedure called tongue base mucosectomy (TBM) has been used to remove all the mucosa and lymphoid tissue from the back of the tongue in an attempt to improve on the low diagnostic yield seen in random tongue base biopsies.[4]

Currently, treatment strategies for CUP in H&N are not standardised. Management plans can vary from no radiation therapy addressing potential primary sites, with a watch and wait policy, to Elective Mucosal Irradiation (EMI) which can lead to significant early and late morbidity. Identification of the primary site has a number of potential advantages. The primary site may be completely excised with an adequate margin, in which case it may be suitable for single modality therapy. There may also be a significant negative psychological burden if the primary cancer has not been identified or addressed. Conversely, a positive margin in the resected specimen could indicate escalated therapy, with concomitant chemotherapy, if it felt to be inadequately excised (the procedure is diagnostic not oncological). Further, the identification of multicentric primary sites may also lead to an increased radiation field compared to if this added information were not available. The benefit of TBM is, as such, yet to be fully established.[4,5]

Human papilloma virus (HPV) is thought to play a significant role in many of these cancers presenting as CUP.[6,7] Smaller or involuted primary foci are known to be more common in HPV related cancers which may be contributing to the apparent incidence of these unknown primaries, or occultomas as they may also be called. A histological technique called step serial sectioning (SSS) allows examination of tissue specimens in greater detail than conventional histology. It has not previously been used to investigate the primary site in head and neck cancer but the oropharyngeal tissues that potentially harbour these small primaries make a sensible target to pioneer its usage. It is hypothesised that utilising SSS on tonsillectomy and TBM specimens may increase the identification rate of the primary site and may subsequently affect recommended management.

Currently, we do not understand why some cancers present with cervical metastases with no evident primary site. There has been an explosion in genomics research in many cancers, but this remains an understudied area in head and neck cancer. There are currently no treatments available to patients with head and neck cancer based on genomic insights. This study aims to begin to address the unmet need of patients who present with these poorly understood cancers and to provide a starting point for more detailed investigations into the relationships between cancer genomics and clinical outcomes.

6 Study aim and objectives

6.1 Aim:

To understand the current management of suspected HNSCCUP patients undergoing TBM in the UK, including adequacy of current histology, functional and oncological outcomes, and disease biology.

6.2 Primary objective:

- To establish if step serial sectioning (SSS), compared to conventional histology, improves identification of a primary site in TBM and tonsil specimens in suspected HNSCCUP.

6.3 Secondary objectives:

1. To compare the pick-up rate of primary cancers in TBM specimens between surgical methods (robotic vs laser vs endoscopic).
2. To prospectively evaluate swallowing function and pain scores after TBM.
3. To understand patient views and experiences of undergoing TBM for suspected HNSCCUP.
4. To report time-to-event data for local, regional and distant disease recurrence, and mortality.
5. To assess the molecular makeup of patients with suspected HNSCCUP undergoing TBM.

7 Study design and setting

7.1 Study design

Multicentre prospective observational cohort study, incorporating histopathological and molecular tissue analysis.

[Qualitative descriptive study with thematic analysis].

7.2 Study setting

UK centres performing TBM to for suspected HNSCCUP.

8 Patient eligibility criteria

8.1 Population

Suspected HNSCCUP patients, with a diagnosis of squamous cell cancer from cervical lymph node biopsy, with the primary disease presumed to be of head and neck origin, who have not had the primary site identified by either clinical examination or cross-sectional imaging (CT/MRI) including PET CT.

8.2 Inclusion criteria

- Aged 16 or over
- Both sexes
- Cervical metastatic SCC, confirmed with cytology or biopsy, undergoing TBM for identification of primary site

8.3 Exclusion criteria

- Primary site identified by any means prior to being indicated for TBM
- Patients undergoing targeted biopsies or resections
- Patients known to have a history of previous H&N cancers
- Patients known to have undergone previous radiation to the H&N region

9 Study procedure and methodology

9.1 Patient identification

Patients will be identified from the MDT lists from participating centres which will be screened weekly by local leads. Those satisfying inclusion and exclusion criteria will be approached to take part.

Additionally, for the patient interview qualitative component, local teams may mention the study to patients who have been previously treated with tongue base mucosectomy during their routine follow up appointments. The MOSES study team will not approach any of these patients directly. Adverts will also be places at peopleinresearch.org and at mosesstudy.co.uk for people to self-refer.

9.2 Consent

Once identified, eligible patients may be approached by the usual care team or research nurse either remotely or in person. No additional outpatient appointments or patient contacts should be required. Patients will be provided with copies of the **Patient Information Sheets** (PIS) and **Informed Consent Forms** (ICF). Appropriate time will be given to patients to read and digest the information. Written consent will be taken by an appropriately trained member of the clinical team or a research nurse.

Re-consent

Following the implementation of protocol v4.1, patients who had already consented using ICFs prior to v3.0 may be re-approached, by an appropriately trained member of the local team, to re-consent to the study to be able to participate in the extended follow-up and molecular analyses.

Qualitative interviews

For the Qualitative Interviews, consent may be completed remotely by the patient and the MOSES team. As with face-to-face consent, the Patient Information Sheet should be provided, and the patient given adequate opportunity to ask questions about participation in the study. An electronic copy of the consent form will be stored in the Trial Master File by the Sponsor.

9.3 Functional outcomes and pain scores.

Patient will be asked to complete 10 sets of questionnaires: at baseline (pre-operatively); and post-operatively at 3 weeks, 6 weeks, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months. Patients will be asked to record their pain score at its worst, at its least and most of the time, on a Numeric Rating Scale. They will be asked to assess their swallow function by completing a M. D. Anderson Dysphagia Inventory (MDADI). Questionnaires may be completed in person, via post or

remotely (including telephone, video-call or electronic form) and returned to the MOSES team on the contact email provided.

9.4 Dataset and case report form (CRF)

The following fields will be recorded on the CRF (please see the MOSES CRF document for full list):

- Demographics
- Medical history
- Surgical history
- Investigations
- Peri-operative outcomes
- Conventional histology result
- Initial treatment plan
- Pain and swallowing function scores
- SSS histology result
- Oncological status, including disease recurrence and primary emergence
- Management of further disease
- Participation in clinical trial(s)

Data collected on the CRF can be used as source data.

9.5 Pseudonymisation

Each site will generate a unique study ID and use a 'key' to reference this to the NHS and hospital medical record number. This key will be stored locally at contributing trusts on an excel file on the hard drive of a secure NHS computer. The study key will be stored for the duration of the study and then destroyed in line with local processes for handling patient identifiable data. No patient identifiable data will leave the contributing trusts.

A case report form (CRF) will be created for each patient to record the above dataset including the unique study ID. This information will be shared with the central MOSES team via nhs.net mail to a central MOSES computer held at the Royal Marsden Hospital in the H&N office.

The central MOSES team will only receive and process pseudonymised data associated with the study ID. The central MOSES database will not record contributing sites by name so that individual cases are not linkable to their site of origin. The key to this information will be kept separately to the MOSES database.

Study ID will be formed from a three letter hospital code followed by a three digit consecutive number, e.g. RMH001, RMH002, etc.

9.6 Surgical technique

All centres known to be performing TBM in the UK will be invited to take part. The surgery will take part at the contributing centre adhering to their usual practices. This will encompass techniques using laser resection, endoscopically assisted techniques and resections using robotic systems. There is currently no standardised method for performing TBM. An affiliated project will look to generate a standard operating protocol (SOP) for TBM for potential future studies. The technique used in each case will be recorded on the CRF.

9.7 Handling of tissue specimens and histological processing

All tissue will undergo conventional histological processing at the local site and will be used to influence patient management by the local team according to local practices. The following tissues will then be requested to be sent by the local teams to RMH for further analysis:

- Oropharyngeal tissues from diagnostic surgeries attempting to identify the primary site (i.e., TBM specimens, and tonsils, if available)
- Cervical nodal specimens, from the diagnostic neck biopsies (fine needle aspiration cytology and/or core biopsies) and/or therapeutic neck surgeries, if available
- A buccal swab and/or blood sample (for germline DNA)

Where SSS is indicated (TBM and tonsil specimens, if available) the MOSES team will then send these tissues onto the RVI. Appropriate tissue handling practices will be observed. RMH uses FreezerPro Laboratory Management Software to facilitate handling and tracking of tissue specimens.

Anonymised histopathology reports will be requested from local centres. The macroscopic description will be used to orientate the submitted tissue blocks undergoing step serial sectioning.

Step serial sectioning

The paraffin blocks supplied from TBM and tonsil specimens will undergo step serial sectioning using the following method:

- Steps every 0.5mm with five serial 4μm sections taken.
- Each block will be processed in this way until the material is consumed.
- Slides will be stained with haematoxylin and eosin stain (H&E) and examined for signs of SCC.
- If an SCC is identified, then serial sections 2 and 4 will be submitted for HPV testing (p16 immunohistochemistry and high-risk HPV DNA in situ hybridisation).
- Serial sections 1 and 5 will be retained for repeat tests if required.
- The pathologist will compose a report and complete the relevant sections of the CRF.
- Unused material will be returned to the contributing centres if desired. Some material may be retained for further study, as detailed in the PIS and ICF.

Exploratory molecular analysis

Patients will be asked to provide buccal swabs and/or blood samples for germline DNA analysis. These samples may be provided at any time point following recruitment.

Packaging and sending

All MOSES blood and/or buccal swab samples should be collected, labelled, stored and shipped as detailed in the **MOSES Sample Collection Manual**.

The buccal swabs and/or blood samples will likely be obtained during a face-to-face contact as part of the patient's usual care pathway. In circumstances where samples cannot be obtained during a face-to-face contact, the local site team may send a **research pack** (supplied by the sponsor) to the participant, via post, containing the blood and buccal swab collection materials for those agreeing to re-consent. The pack will also contain the Cover Letter, PIS and ICF. The completed documents and sample collection materials may then be returned to the local site team using return labels, before being sent onto RMH as per the **MOSES Sample Collection Manual**.

All samples must be labelled with the participant's study identifier, date of birth and date of sample to enable cross-referencing. All samples should be sent by post to the following address:

Dr Ben O'Leary
2S8
Chester Beatty Labs
The Institute of Cancer Research
237 Fulham Road, London SW3 6JB

9.8 Qualitative methods and data outcomes

Patients eligible for inclusion in the prospective cohort study will also be asked on the consent form if they would be happy to be contacted by a trained member of the MOSES team to be interviewed about the following topics:

- Their views on the patient pathway to date.
- Their views on TBM.
- Their views on CUP in H&N and the psychological impact of not knowing the origin has been identified.
- Their views on the potential diagnostic improvements brought by SSS
- Their views on the possible escalation of treatment brought about by identification and incomplete removal of a primary
- Their views on robotic surgery in general

There is a separate patient information sheet and informed consent form for this qualitative component. Patients not consenting to be contacted regarding the above interviews will not be precluded from participation in the remainder of the study.

After appropriate training in qualitative research methodology, a core committee will meet to agree a final methodology, form a provisional topics list and suggest interview questions. We will then engage with a PPI group to assess topic lists and questions and to hold practice interviews with appropriate feedback. Patients will be recruited for one-to-one interviews at various stages of their treatment.

The interviews will be recorded, and a transcription of the conversation made. The transcription will be reviewed and coded using appropriate software. There will be interval thematic analysis and further recruitment/interviews until saturation (as per Francis method) before final thematic analysis [8]. No patient identifiable data will be recorded as per the methods above. Basic treatment information will be recorded alongside demographics to give context to the answers.

Following the COVID-19 pandemic, it was clarified with the sponsor that remote consent and conduct of qualitative interviews would be acceptable for appropriately informed and consenting patients.

10 Assessment timings

10.1 Summary tables

The following tables summarises the time points at which respective data fields will be gathered and returned:

Procedure		**Screening/ Day 0**	**3 wks.**	**6 wks.**	**3 mos.**	**6 mos.**	**12 mos.**	**24 mos.**	**36 mos.**	**48 mos.**	**60 mos.**
Local team	Eligibility	x									
	Informed Consent	x									
	Medical and surgical history	x									
	Investigation results	x									
	Conventional histology result		x								
	CRF Completion	Page 1-2	Pages 3, 4, 5				Page 6	ICF v3.0 and above Page 7	ICF v3.0 and above Page 8	ICF v3.0 and above Page 9	ICF v3.0 and above Page 10
Patient/ Local team	Pain questionnaire	x	x	x	x	x	x	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above
	MDADI questionnaire	x	x	x	x	x	x	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above

Return of data	**Screening/ Day 0**	**3 wks.**	**6 wks.**	**3 mos.**	**6 mos.**	**12 mos.**	**24 mos.**	**36 mos.**	**48 mos.**	**60 mos.**
Local team to return CRF to RMH	x	x				x	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above
Local team to return questionnaires to RMH	x	x	x	x	x	x	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above	ICF v3.0 and above
Local team obtain germline DNA samples (buccal swabs and/or blood samples)	Any time point									

in person or posted to patient	
Local team return tissues to RMH (TBM +/- tonsil specimens, cervical nodal specimens and buccal swab and/or blood samples)	Any time point

10.2 Pragmatic interpretation of timepoints

The timepoints above are intended to collect data at the following points in the patients care:

- Baseline Prior to TBM surgery
- 3 weeks Following TBM surgery
- 6 weeks Just prior to starting radiotherapy (if applicable)
- 3 months Just after completing radiotherapy (if applicable)
- 6 months -
- 12 months -

11 Data management

The study will require a database to store pseudonymised data. Patient data will be collected on a paper case report form (CRF) at each site. The CRF will contain no patient identifiable data and will be pseudonymised with a study ID. The CRFs will be sent to the MOSES team at RMH. This will be entered onto an excel spreadsheet held on an NHS trust computer at the sponsoring organisation, the Royal Marsden Hospital NHS Foundation Trust.

All patient identifiable data will remain at the local site subject to normal data governance practices. None will be sent to or handled by the project management team, except for those consenting to the qualitative study who agree to share their name and contact details on the main study ICF.

12 Statistics and data analysis

12.1 Sample size

No a prior sample size calculation was performed as initial funding limited recruitment to analysis of 60 specimens to undergo SSS. Meta-analysis shows a pickup rate of 58% for this cohort. We anticipate a potential increase pick up rate of around 10%.

- With 60 specimens, the 95% confidence interval boundaries around the pickup rate are +/-12.6% for 58% and +/-11.4% for 68%.

In anticipation of further funding, our sample size is increased to 100 to give greater confidence in the effect size.

- With 100 specimens, the 95% confidence interval boundaries around the pickup rate are +/-9.8% for 58% and +/-9.0% for 68%.

12.2 Study endpoints

For the Primary objective:

- Identification of cancer in the tonsillectomy or TBM specimen on histology.

For the Secondary objectives:

- To compare the pick-up rate of primary cancers in TBM specimens between surgical methods (robotic vs laser vs endoscopic).
    - Identification of cancer in the tonsillectomy or TBM specimen on histology.
    - We anticipate no significant disparity in pick up rate between methods with the limited number of cases in this study.
- To prospectively evaluate swallowing function and pain scores after TBM.
    - We anticipate no significant change in means from pain and MDADI scores between 0 and 6 week questionnaires. Results at 3 weeks are anticipated to be different as still recovering from surgery. Results up to 60 months will evaluate effects of any subsequent treatments and future recovery.
- To understand patient views and experiences of undergoing TBM for suspected HNSCCUP.
    - Qualitative thematic analysis therefore no quantitative end point.
- To report time-to-event data for local, regional and distant disease recurrence, and mortality.
    - Primary emergence rate of around 3% per year.
- To assess the molecular makeup of patients with suspected HNSCCUP undergoing TBM.
    - (Exploratory analysis)

12.3 Study duration

Recruitment of patients will continue until 100 patients are recruited and undergo TBM. The study duration will be extended as necessary until this target is met across all centres.

The study will remain open until the last patient to be recruited has completed their final 60 month follow-up. Thereafter, end of trial definition will be dependent on resolution of all data queries and completion of database entries in preparation for final statistical analysis and subsequent publication. Once these stages have been reached and the study paperwork is ready for archiving, a 'Declaration of End of Study Form' will be sent to RMH R&D and to the Research Ethics Committee (Health Research Authority) notifying them that the study is now concluded. A summary of the final research report will be provided to the Committee within 12 months of the conclusion of the study. This will report on whether the study achieved its objectives, summarise the main findings, and confirm arrangements for publication or dissemination of the research including any feedback to participants.

Summary of project timings (correct at time of drafting v2.2)

Date	Activity
Dec 2018	First draft of protocol
Jan 2019	Protocol submission to sponsor (CCR)
Feb 2019	CCR review
May 2019	Submission via IRAS
July 2019	REC/HRA approvals
Nov 2019	Opening of first sites
March 2020	COVID-19 disruption
October 2023	Completion of recruitment
October 2028	Completion of 60 month follow up for all patients

12.4 Analysis methods

Descriptive analysis only is anticipated. The rate of CH and SSS pick up will be reported in the overall specimens and separately in the sub-group of surgical methods with 95% confidence intervals. The pain scores and swallow recovery with MDADI scores will be reported using mean/median and standard deviation or range as appropriate at each time point of 0, 3 weeks, 6 weeks, 3 months, 6 months and 12 months, 24 months, 36 months, 48 months and 60 months. Similarly, score change between time points will be summarized in the same way. The primary and secondary analysis will be done when the complete sample size is recruited and last patient on the study completed all follow-ups.

Molecular data analysis

Detailed description of the molecular analysis methodology is beyond the scope of this protocol.

12.5 Safety Considerations

There are no immediate safety implications anticipated due to the observational and non-interventional nature of the study.

There is potential for primary cancers to be identified in some tissue specimens where it had been missed at the local site when undergoing conventional histology. These updated results from the pseudonymised specimens will not be available in a timeframe that could influence patient treatment.

12.6 Follow-Up

The final patient questionnaires are completed at 60 months post-operatively. Outcome data is derived from the tissue specimens. As above, results from SSS of the tissue specimens will not be fed back to the individual MDT as it will have no potential to influence management which will already have been enacted.

12.7 Quality Assurance

The core MOSES team handling the pseudonymised data have all undergone GCP training with valid contemporary certification.

12.8 Expected Outcomes of the Study

TBM is a relatively new surgical procedure with little data relating to patients experience and recovery from this operation. The pain and MDADI questions will go some way to showing the acceptability of this procedure to patients. It is expected that by 6 weeks the pain and MDADI scores will have returned to near baseline. Most patients will go on to receive radiotherapy to their pharyngeal mucosa, which is known to worsen swallowing function. This data will go some way to clarifying that any subsequent difficulties may not be attributable to the TBM procedure.

Any increased pick up rate resulting from SSS could lead to wider adoption of this process in the management of HNSCCUP. The size of any primary sites identified through SSS over conventional histology will also be recorded and could influence the size of histological levels employed for future TBM and tonsillectomy specimens in the future management of HNSCCUP.

Data from the patient interviews and thematic analysis should help to guide patient goals for any further research in HNSCCUP. Of particular note will be the patients' wishes regarding timing of the tonsillectomy and TBM procedures, which can occur separately, particularly if initial investigation is performed in a peripheral hospital that does not offer TBM. The potential changes in management from identification of primary sites using SSS, and potential for escalation of treatment through the addition of concomitant chemotherapy will also be novel.

Results from the exploratory molecular analysis are expected to give us greater understanding of the molecular make-up of suspected HNSCCUP. Including, but not limited to, how cancers where the primary is identified differ from those primaries that remain occult, and how the cervical disease differs from primary site tissues in the oropharynx.

Results from this prospective observational study will form the foundation of a potential phase III trial investigating the roles of TBM and SSS in management of suspected HNSCCUP. The precise research question is yet to be established.

12.9 Dissemination of Results and Publication Policy

Findings from the study will be submitted for publication in relevant H&N peer reviewed journals. JH will be lead author and VP will be last author on papers, with MR and KH also included as senior authors. The Principal Investigators at each site will be included as authors, as per journal policy and following review and approval of the final manuscripts.

BOL will lead on analysis, dissemination and publication of work related to the exploratory molecular analysis.

Following completion of the study, we plan to run a consensus day for management of HNC of unknown primary. The published and unpublished data from this study is intended to contribute.

13 Problems Anticipated

13.1 Slow recruitment of TBM centres

Early contact with the TBM centres across the UK should improve timely recruitment.

13.2 Slow recruitment of TBM patients

It is very unlikely that any eligible patients will be missed by the MDTs and clinicians involved in recruitment. It is also felt to be unlikely that patients will not consent to being involved in the study as, by design, there has intended to be minimal burden from the questionnaires.

14 Project Management

Name	Vinidh Paleri
Role(s)	Chief investigator
Responsibilities	Oversight of project design, conduct and reporting. Liaison with Research Ethics Committee (REC), and other review bodies, during the application process, and where necessary during, the conduct of the research. Ensure adherence to protocol. Analysis and write up of MOSES findings

Name	Max Robinson
Role(s)	Co-investigator Chief pathologist
Responsibilities	Coordination of processing of pathology specimens once received at Newcastle laboratories and reviewing of slides for diagnosis of primary outcome of MOSES trial. Analysis and write up of MOSES findings

Name	John Hardman
Role(s)	Co-investigator Clinical research fellow
Responsibilities	Recruitment of contributing centres. Coordination of centralising pathology specimens to Newcastle laboratories Coordination of data governance and control of the MOSES database. Tabulation of data from questionnaires. Analysis and write up of MOSES findings and MOSES Qualitative findings

Name	Kevin Harrington
Role(s)	Co-investigator Professor of oncology
Responsibilities	Academic supervision of JH Analysis and write up of MOSES findings

Name	Ben O'Leary
Role(s)	Co-investigator Oncologist
Responsibilities	Exploratory molecular analysis

Name	Grainne Brady
Role(s)	Co-investigator Speech and Language Therapist
Responsibilities	Qualitative researcher Analysis and write up of MOSES Qualitative findings

Name	Mary Wells
Role(s)	Co-investigator Professor of Nursing
Responsibilities	Qualitative researcher Analysis and write up of MOSES Qualitative findings

15 Ethical considerations

The protocol will be submitted for ethical review to the Human Research Authority's 'Integrated Research Application System' (IRAS). It is believed the application will be suitable for a 'proportionate review' which allows fast tracking of the process.

Having undergone SSS, the tissue specimens may have new or additional carcinomas identified. This information will not be available to the treating MDT in a timeframe that could influence patient care. Their treatment plans will have been enacted. The results of the pathological processing will not be fed back to the contributing centres but will only be held in a pseudonymised central MOSES database.

Patients will be asked to complete pain score questionnaires and swallowing function questionnaires. Many centres collect swallow function scores for head and neck cancer patients routinely. These questionnaires will be an additional burden to these patients. However, it is also acknowledged that by asking for these data it may prompt closer attention and better care for these patients.

Patients approached to take part in one-to-one interviews have potential to discuss their perceptions regarding their cancer and cancer management. This could be potentially distressing for some patients. They will be provided with appropriate contact information for Clinical Nurse Specialists throughout the process. They are also eligible to withdraw from the process at any stage without any impact on their care. It is likely that the majority of the patients will have completed their treatment and be in surveillance by the time they are approached to be involved in the interviews.

16 Informed consent process

16.1 Informed Consent Forms

Please see appendix for PISs and ICFs.

Consent for the qualitative interviews is distinct from consent to the main study.

See 'consent' in Section 'Study procedures and methodology' for further information on the consent process.

17 Budget

17.1 Approved funding

This study has been funded by a grant from Oracle Cancer Trust. The following is a summary of the costings for the grant application that were revised and approved on 3rd December 2018:

	Item	Total	Comment
TOTAL COST OF PROJECT	Pathological processing	£ 30,937.50	(£475.96/case)
	Clinical research fellow	£ 50,538.09	Total for 2 yrs
	MD registration fees (ICR)	£ 9,220.00	(£4,610 /yr)
	Qualitative Research Methods Course	£ 1,525.00	https://bit.ly/2DXIbxY
	Supervising PI (Prof Vin Paleri)	£ 11,567.00	(2hrs/wk)
	Dr Max Robinson (pathology lead)	£ 9,203.80	(2hrs/wk)
	Consensus meeting	£ 5,000.00	
ORACLE GRANT REQUESTED	TOTAL	£ 117,991.39	
	Per Annum	£ 58,995.70	over 2 yrs

This study received a further grant from the Biomedical Research Centre TPT Pump Priming fund. This award of £20,000 will cover Human Tissue Bank costs at RMH and the receipt and transfer of tissue from the contributing units to the laboratory at the RVI in Newcastle. It will also cover reimbursement of patient travel costs, room hire, basic catering/tea/coffee, interview transcription and a licence for the NVIVO coding analysis software for the qualitative interviews.

Statistics and database costs were expected to be around £10,000. However, these costs are no longer applicable, following the award of the TPT Pump Priming grant above.

17.2 Outstanding funding

An application has been made to the Get A-Head charity for continued funding to cover extended recruitment, follow-up and to obtain tissue samples for the exploratory molecular analysis.

17.3 Other support for the Project

We are grateful for the support from Oracle Cancer Trust, the Royal Marsden Hospital, the Institute for Cancer Research and Newcastle upon Tyne Hospitals NHS Foundation Trust.

The salary for the Clinical Research Fellow has also received contributions from the Royal College of Surgeons of England and ENT UK.

18 Collaboration with other scientists or research institutions

18.1 Curriculum Vitae of investigators

The CV of the Principal investigator will be provided.

18.2 Other research activities of the investigators

Current research projects that the principal investigator is involved in are listed in the appended CVs, including the source of funding of these projects, the duration of those projects and the percentage of time spent on each.

19 Financing and Insurance

Financing has been outlined in the 'Budget' section above.

Insurance is as per Sponsors arrangements.

20 References

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