Full title of trial	A two site pilot study of functional and microstructural imaging using magnetic resonance imaging in patients with renal tumours
Short title	Renal tumour Imaging using MRI.
Version and date of protocol	V1.1 21/03/2024
Sponsor:	University College London (UCL)
Sponsor reference number:	162190
Funder (s):	UCL/UCLH Biomedical Research Centre (NIHR)
IRAS Number:	323984
UCL Data Protection Number:	Z6364106/2023/11/12
Intervention:	MRI of renal tumours

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PROTOCOL VERSION HISTORY

Version Stage	Versions Number	Version Date	Protocol updated & finalised by;	Reasons for Update
Former	1.0	24/11/2023	Richard Hesketh	
Current	1.1	21/03/2024	Richard Hesketh	

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the U.K. Policy Framework for Health and Social Care Research 2017 (3rd edition) (as amended thereafter), the EU General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018), Sponsor SOPs and applicable Trust policies and legal frameworks.

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

I (investigator) agree to ensure that no research activity or recruitment will commence at participating research sites until the appropriate regulatory approvals and NHS confirmations of Capacity and Capability have been issued, and Sponsor green light confirmed.

I (investigator) 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. Any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature: ..... Date 21/03/2024

Print Name (in full): Richard Hesketh

Position: UCL Clinical Lecturer

On behalf of the Study Sponsor:

Signature: Date.22./.03./.2024

Print Name (in full): .....Pushpsen Joshi.....

Position: .....Research Governance Manager .....

IDENTIFIERS	
IRAS Number	323984
REC Reference No.	
Sponsor Reference No.	162190
Other research reference number(s) (if applicable)	UCL Data protection: Z6364106/2023/11/12
Full (Scientific) title	A two site pilot study of functional and microstructural imaging using magnetic resonance imaging in patients with renal tumours
Health condition(s) or problem(s) studied	Cancer
Study Type i.e. Cohort etc	Interventional study
Type of trial:	Prospective pilot study
Trial design and methods:	Patients with known renal tumours will be identified from clinic and MDTs at the Royal Free. Study 1: 20 patients - histological analysis of renal tumours retrieved from the RFH tissue biobank. Study 2: 10 patients – Comparison between MRI and co-registered tumour histology in patients undergoing nephrectomy. Patients undergo a single MRI scan prior to standard of care surgery. Study 3: 10 patients – Repeatability study of microstructural renal MRI. Patients undergo two MRI's within 14 days.
Trial duration per participant:	Single visit (study 2), two visits (study 3)
Key Study milestones	3 months: ethics and R&D approvals completed 4 months: CRF training completed and first patient recruited 12 months: Last prospective patient recruited 18 months: Data analysis complete
Planned trial sites:	Two sites: Royal Free London Hospital and University College London Hospital
Total number of participants planned:	20 participants: Study 1. 10 participants: Study 2. 10 participants: Study 3.

Main inclusion/exclusion criteria:	Inclusion criteria: 1) Aged 18 and over 2) Confirmed renal tumour $\leq$ 7 cm planned for surgical resection 3) Willing and able to provide written informed consent 4) Able to lie supine for the duration of an MRI Exclusion criteria: 1) Contraindication to MRI e.g., cardiac pacemaker 2) Contraindication to MR contrast agents 3) Pregnancy 4) Breastfeeding 5) Deranged renal function (eGFR <30) in the last three months. 6) Previous treatment of the renal tumour e.g., ablation, radiotherapy
Statistical methodology and analysis:	Prospective pilot study, no specific statistical methodology
FUNDING & OTHER	
Funding	NIHR UCLH BRC: BRC1125/HEI/RH/110410: £48,712
Other support	.
STORAGE of SAMPLES / DATA (if applicable)	
Human tissue samples	All human tissue samples will remain stored in NHS hospitals as per clinical practice. Only pseudo-anonymised digital scans will be stored in UCL computers.
KEY STUDY CONTACTS Full contact details including phone, email and fax numbers	
Chief Investigator	Dr Richard Hesketh, r.hesketh@ucl.ac.uk, 07979510466
Co-investigators	Professor Maxine Tran, m.tran@ucl.ac.uk (PI: Royal Free Hospital) Professor Shonit Punwani s.punwani@ucl.ac.uk Dr Eleftheria Panagiotaki e.panagiotaki@.ucl.ac.uk Dr Timothy Bray, t.bray@ucl.ac.uk Dr Soha El- Sheikh, s.elsheikh@nhs.net

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KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also must be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals and confirmations of NHS Capacity and Capability are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC and JRO of the end of the study (including the reasons for premature termination, where applicable). Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC and JRO.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

KEY WORDS

MRI, magnetic resonance imaging, renal cancer

LIST OF ABBREVIATIONS

AE	Adverse event
CI	Chief investigator
CRF	Case report form
CRO	Contract research organisation
DCE	Dynamic contrast enhanced
DWI	Diffusion weighted imaging
GCP	Good Clinical Practice
ICF	Informed consent form
ISF	Investigator Site File
IVIM	Intravoxel incoherent motion
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
PIS	Patient information sheet
RCC	Renal cell carcinoma
REC	Research ethics committee
RFH	Royal Free Hospital
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedure
UCL	University College London
UCLH	University College London Hospital
VERDICT	Vascular, extracellular and restricted diffusion for cytometry in tumours

Contents

1. SUMMARY

Renal cancer has the highest mortality rate of any urological cancer. Despite the overall mortality rate renal tumours are diverse, presenting with a range of different histological subtypes and nuclear grade, ranging from the benign to the highly malignant. Current clinical imaging of renal tumours is heavily reliant on computed tomography (CT) which is an accurate technique for tumour detection and staging but cannot reliably differentiate tumour types or grade. Percutaneous biopsy is not routinely adopted due to concerns of tumour seeding, diagnostic uncertainty and sampling error due to intra-tumoral heterogeneity.

An imaging test that can reliably differentiate between different tumour types and grades would result in improved personalised treatment decisions, benefiting patients with renal tumours and potentially delivering a considerable saving to the NHS by reducing unnecessary treatment of benign or indolent tumours.

Magnetic resonance imaging (MRI) delivers unique soft tissue contrast and sequences can be designed to be sensitive to a wide range of microstructural tissue features. This project aims to develop magnetic resonance imaging (MRI) sequences and relate the imaging findings with the underlying histology of the tumour. In the future we aim that this will be the foundation of incorporating MRI into the clinical management algorithm of renal tumours.

2. BACKGROUND AND RATIONALE

Globally there are over 430,000 new cases of renal cancer each year and renal cancer has the highest mortality rate of any urological cancer. However, survival is dependent on stage – localised disease has a 5-year survival rate of 93% which falls to 12% for metastatic disease. The requirement to treat tumours early to maximise the chances of curative treatment meant radical nephrectomy was recommended for all solid renal tumours until relatively recently. However, though the increased the incidence of small renal tumours, largely as incidental findings on imaging, it has been recognised that only ~2% of these have metastatic potential(1). Thus, treatment algorithms have been refined and T1a stage renal tumours (≤4 cm) management options now include active surveillance and ablation as well as surgical resection. Management is currently decided by shared decision making between clinician and patient, informed by population rather than personalised risk of progression. With this approach ~4% of nephrectomies are being performed with subsequent benign tumour pathology, with significant associated mortality, morbidity and expense(2).

Surgical histology remains the gold standard diagnostic test for renal tumours(3) but imaging is the only way to non-invasively sample whole tumours, which is highly desirable in renal tumours which demonstrate considerable intra-lesional genetic, metabolic and morphological heterogeneity(4). This study aims to develop and apply novel MR methods that permit detailed characterisation of tissue function and microstructure to non-invasively characterise tumours.

VERDICT (Vascular, Extracellular, Restricted Diffusion for Cytometry in Tumours)

The signal in diffusion-weighted MRI (DW-MRI) is generated by detection of the bulk movement of water molecules which is influenced by numerous factors including cell size and shape, cell density, extracellular volume and vascularity. Many of these tissue features are altered in tumours, particularly an increase in cellular density and reduction in the extracellular volume, therefore DW-MRI and a calculated apparent diffusion coefficient (ADC) have been used for tumour detection in many different organs. Renal tumours, along with most tumours in other organs, typically demonstrate a reduced apparent diffusion coefficient (ADC) indicating that water movement is more restricted compared to normal tissue and there is limited evidence that this can be useful to differentiate between tumour types and grade(5). However, the ADC is an over-simplification of the DWI signal and fails to discrimate between the underlying histological changes. The Vascular, Extracellular, Restricted Diffusion for Cytometry in Tumours model uses a 3-compartment tissue model designed to account of the main histological features of tumours that influence the DWI signal and can estimate specific tissue properties such as cell size, intracellular, extracellular – extravascular and intravascular space fractions.

The VERDICT model was developed in colorectal xenograft models where it demonstrated superiority to ADC and the intravoxel incoherent motion (IVIM) models. It has since been translated to clinical studies of prostate cancer, where a high level of repeatability and particular usefulness in differentiating benign and clinically significant but low grade tumours(6, 7).

Renal tumours are a diverse range of histological subtypes tumour type is important as well as grading. DW-MRI and ADC have demonstrated the ability to differentiate between many different types. However, one of the critical differentiations, distinguishing clear cell carcinomas from benign oncocytomas, is particularly challenging(8). We hypothesise that the improved characterisation of the tumour microstructure that VERDICT offers will be be able to differentiate between these two entities.

Fat fraction and quantitative susceptibility mapping

Imaging of fat is commonplace in clinical MRI studies, usually using in and out of phase Dixon imaging. This allows visual assessment of a loss of signal but inaccurate fat quantification. The modelling based on the Dixon method has evolved to account for some of the major confounders including B_0 inhomogeneity, T_2* decay and the spectral complexity of the fat signal permitting accurate and reproducible fat quantification(9).

The quantification of fat is an important diagnostic tool for the characterisation of renal tumours. Macroscopic fat, visible on CT or fat suppression MRI, is most frequently seen in angiomyolipomas, but occasionally RCCs may contain macroscopic fat. Different histological subtypes of RCC demonstrate different quantities of triglyceride, cholesterol and glycogen accumulation, for example clear cell RCCs are associated with a large lipid rich cytoplasm, which reduces at the higher tumour grades(10, 11).

Fat fraction mapping is calculated using data from a gradient echo sequence. The same acquisition can also be used as the raw data for susceptibility mapping. Quantitative susceptibility mapping (QSM) is a post processing technique that uses the phase data of the gradient echo acquisition to generate maps of tissue magnetic susceptibility. This has the ability to quantitatively differentiate between

diamagnetic calcifications and paramagnetic haemorrhage. The majority of QSM studies have been performed in the brain, but the feasibility of renal QSM has recently been demonstrated(12). Microhaemorrhage are common in papillary and clear cell RCC whilst calcification is most commonly associated with clear cell RCC(13).

Perfusion MRI

Vascularity is another important differentiator of renal tumour subtypes. Clear cell RCCs are usually hypervascular, enhance avidly in the corticomedullary phase before washing out on delayed images. Conversely, papillary RCCs are hypovascular and iso- or hypo-enhacing relative to normal renal parenchyma.

Two methods are proposed to examine renal tumours. Dynamic contrast enhanced (DCE) MRI involves imaging before and after the injection of gadolinium contrast - gadoteridol (ProHance) or gadoterate meglumine (Dotarem) - at a dose of 0.1 mmol/kg. DCE MRI is used to identify and classify multiple different tumours, perhaps most notably in breast tumours where signal intensity curves are routinely used in clinical practice. Multi-timepoint pre- and post-contrast imaging of renal tumours is already standard-of-care. Small studies have demonstrated that analysis of the enhancement and washout characteristics can differentiate between RCC subtypes and that semi-quantitative measurements can be performed reproducibly(14, 15).

Arterial spin labelling (ASL) is an alternative to DCE-MRI in which blood is magnetically labelled prior to entering the kidneys and provides endogenous contrast. It has several advantages in that it doesn't require gadolinium injection and is a quantitative measure of tissue perfusion whereas DCE-MRI measurements are dependent on both blood flow and vascular permeability. However, labelling efficiency can be variable and the lower signal-to-noise ratio with ASL limits spatial resolution and makes detection of low levels of perfusion challenging.

RCC subtype differentiation has been demonstrated with ASL, both were able to differentiate papillary cell RCCs from other subtypes(16). Furthermore, the volume transfer constant (K^{trans}) and rate constant (*Kep*) positively correlate with perfusion (P_{ASL}) derived from ASL(17).

The described imaging sequences have all been applied to renal imaging previously. However, with the aim being to differentiate between both tumour subtypes and grade, relying on a single sequence has produced limited results. For example, perfusion imaging (DCE and ASL MRI) are able to differentiate between hypervascular and hypovascular tumours, but can't reliably subclassify these groups or differentiate between tumour grade(16). This is hardly surprising as tumours aren't classified histologically based on a single feature but from a combination of features. For this reason this study aims to develop a multi-parametric imaging protocol that is able to identify multiple microstructural features of renal tumours.

Co-registration of histology to *in vivo* imaging

A vital component of validation of functional and microstructural imaging findings is relating them to the underlying histological features. Renal tumours are often large and heterogeneous. Complex

methods of co-registration have been described(18). For this pilot study we will perform imaging sequences in the same plane as the histological sectioning plane and provide coordinates from the MRI for targeted sampling of the tumour.

OUTCOME MEASURES/ENDPOINTS

2.1Primary Objectives

1. To develop novel MRI sequences and techniques for functional and microstructural characterisation of renal tumours.

2.2 Secondary Objective(s)

1. The biological validation of MR imaging biomarkers by correlation with histology.
2. To demonstrate the repeatability of quantitative and qualitative MR imaging biomarkers of renal tumours.
3. To use the pilot combined imaging and histological dataset to plan and power a subsequent clinical validation study.

3. TRIAL DESIGN

The study is a prospective cohort study in which participants will be scanned prior to surgery. Where possible scans will be performed as part of the patient's routine clinical care to minimise the burden on participants in terms of additional hospital visits.

The study duration will be 24 months.

Imaging in this study will take place at University College London Hospital. Patients may be referred from MDTs and urology clinics from The Royal Free Hospital and all surgery and histopathology will be performed at Royal Free Hospital.

4. SAMPLING METHODS

4.1 Inclusion criteria

Patient volunteers will be recruited if they meet the following inclusion criteria:

1) Aged 18 and over
2) Confirmed renal tumour $\leq$ 7 cm planned for surgical resection
3) Willing and able to provide written informed consent
4) Able to lie supine for the duration of an MRI

4.2 Exclusion criteria

1) Contraindication to MRI e.g., cardiac pacemaker
2) Contraindication to MR contrast agents
3) Pregnancy
4) Breastfeeding
5) Deranged renal function (eGFR <30) in the last three months.
6) Previous treatment of the renal tumour e.g., ablation, radiotherapy

4.3 Recruitment

Patient volunteers will be recruited in one of the following ways:

a. Identification at the relevant multidisciplinary team meeting
    i. Patients eligible for the study may be identified at the multidisciplinary meetings involving clinicians and radiology members of the research team.
b. Direct referral from clinical colleagues
    i. Patients may be identified at outpatient clinics or as inpatients at Royal Free Hospital. A discussion between the research team and the clinical team will be held and the eligible patients' suitability will be assessed. The MRI scan will only be booked after the patient has given his or her consent to participate in the study.

Patient information sheet (PIS)

Eligible participants would be identified by a trained member of the research team, clinical team from clinic or at relevant MDTs. Prospective study team members would be trained on the RIM study and would sign the study delegation log. They would then be able to approach participants and enrol them for the study. These study members would also be GCP trained and able to consent trial participants. Participants will be contacted by a member of the clinical team in person or on the telephone, or sent a letter inviting them to take part. The patient information sheet (appendix) will be sent to them by post or email. If agreeable, MRI appointment will be made by the research team (if not already been made as part of their routine investigation or standard of care). For new MRI bookings, patient consent would be sought before arranging this booking. When attending for the MRI, a member of the clinical team (radiographer, nurse, doctor or medial physicist) will confirm the desire of the patient to join the study and if agreeable, together they will sign the informed consent document. Participants may be asked to fast (for at least 8 h) before their scan. This information is already provided in the PIS and they would be given at least 24 h to decide before their enrolment in the study. Patient will usually be consented on the morning of the scan.

Participant recruitment at a site will only commence when the trial has:

1. Been confirmed by the Sponsor (or it's delegated representative), and
2. Been issued with Confirmation of Capacity and Capability from each participating site (where applicable).

4.4 Informed Consent

All participants will receive information more than 24 hours prior to inclusion in the study and signing the informed consent documents. Consent would be obtained by a member of the research team who has been trained in obtaining informed consent. He/she will go through the patient information sheet with the patient and provide an opportunity to ask questions and to opt in/out of the study.

The Investigator or designee 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 and without prejudicing his/her further treatment. Data and samples collected up to the point of withdrawal can only be used after withdrawal if the participant has consented for this.

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 records.

The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g., where new safety information becomes available) and participants will be re-consented as appropriate.

5. TRIAL PROCEDURES

5.1 Pre-MRI renal function testing

Renal impairment with an eGFR <30 ml/min is a relative contraindication to many imaging contrast agents. Renal tests performed in the last 3 months as part of routine standard of care will be used to check renal function.

5.1.1 Intervention Procedures

Patients with renal tumours will undergo an MRI study which will last a maximum of one hour.

5.1.2 Study 1: Histopathological validation of a renal VERDICT model

5.1.2.1 Primary objective:

To define the histopathological tissue characteristics of renal tumours to adapt and optimise the VERDICT model.

5.1.2.2 Method

Histology from a range of tumours from the major subtypes e.g., clear cell, papillary, chromophobe and oncocytoma, will be analysed to estimate the common differential tissue patterns. Key components to understand include determining mean cell diameter and shape, extracellular space area and anisotropy and vascular area. The VERDICT model is highly adaptable and adaptation to reflect the underlying histopathology is an important step of validation and improving its

performance. Histopathological samples from 20 patients who have had renal tumours resected with known histopathology results will be accessed from the Royal Free Hospital Histology Biobank (Characterisation of the immunological and biological markers of Renal cancer progression REC reference: 16/WS/0039). New sections will be cut, and undergo staining ± immunohistochemistry e.g., haemotoxylin and eosin (H&E) staining and IHC with a vascular marker e.g., CD34.

Slides will be pseudo-anonymised, digitised and the data analysed and stored on UCL computers.

5.1.3 Study 2: Multi-parametric renal microstructural imaging

5.1.3.1 Primary objective

- To develop and optimise multi-parametric microstructural and functional MRI to characterise renal tumours.

5.1.3.2 Secondary objectives

- Spatial comparison of MRI and histology to pilot biological validation of quantitative and qualitative MRI biomarkers.

5.1.3.3 Method

10 participants will be identified according to the study criteria and whom are planned for surgery at the Royal Free Hospital will be identified from weekly MDT meetings and urology clinics at Royal Free Hospital. Eligible participants will be contacted in person or by telephone and entered into a screening log kept on a secure NHS OneDrive account. Patients who satisfy the inclusion and exclusion criteria will be invited to have an MRI scan at University College Hospital University College London Hospital prior to their surgery and provided with an invitation letter, participant information sheet (PIS) and copy of the consent form a minimum of 24 h in advance by email or in person.

Consent will be obtained for scans at the time of attendance for the MRI scan by the investigator or a designee. They will explain that participants are under no obligation to partake or provide a reason for declining to partake in the study. A copy of the signed consent form will be provided to the patient.

MRI will be performed in a 3T MRI scanner at UCLH and routine clinical safety procedures followed. 3D multi-parametric MRI of the kidney(s) will include the following sequences:

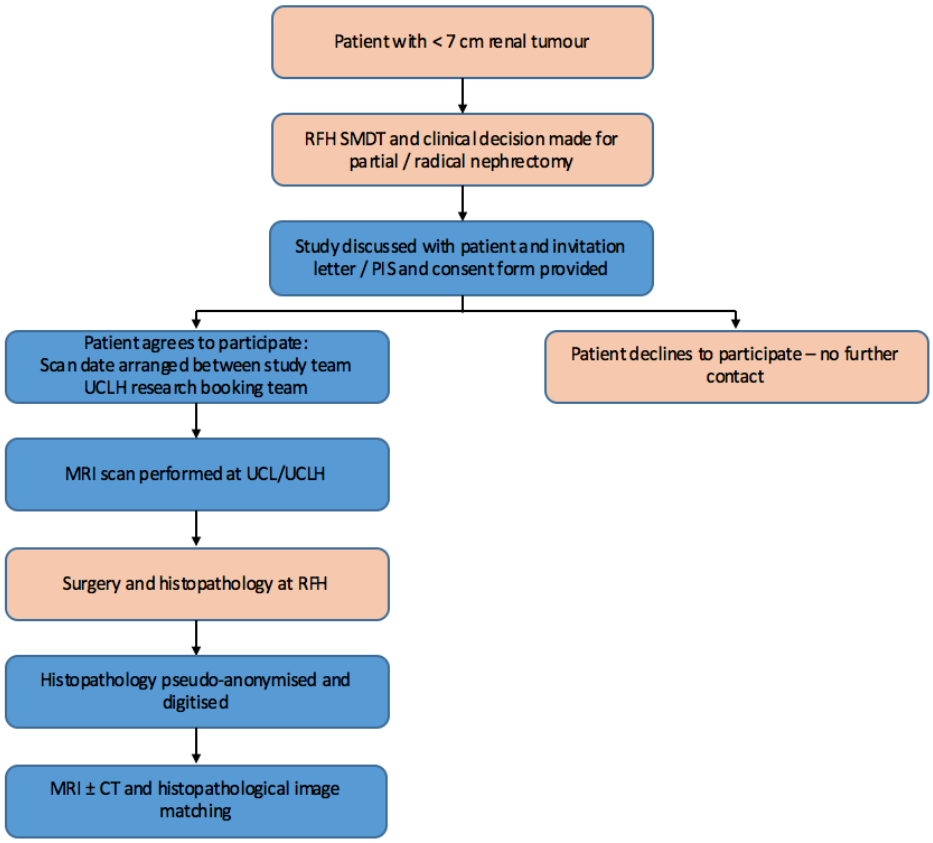
- Localisation imaging
- Anatomical T2-weighted imaging
- Diffusion imaging with multiple b-values for VERDICT modelling.
- 3D gradient echo imaging (fat fraction, T2* and quantitative susceptibility mapping)
- Perfusion imaging using dynamic contrast enhanced (DCE) MRI and/or arterial spin labelling (ASL).

Patients will receive an intravenous injection of gadolinium contrast at a dose of 0.1 mmol/kg via an intravenous cannula for DCE-MRI. This is standard-of-care for clinical MRI of the kidneys (and many other body parts).

MRI images will be pseudo-anonymised and analysed offline. CT scans performed as part of the patients routine clinical care will be obtained from the local PACS (UCLH / RFH), pseudo-anonymised and analysed in conjunction with the MRI scans offline.

Partial or radical nephrectomy will be performed as part of the patient's clinical care. The sample will be bi-valved as part of routine histopathological procedure. From the MRI imaging the tumour position will be coordinated and sections taken of the tumour in the coronal plane. Where possible a coronal sections of the whole tumour will be taken. Where tumour size makes this impossible, blocks from a defined location will be taken. A fresh frozen tissue sample will be cryosectioned and stained with oil red O for lipid quantification. Haematoxylin and eosin (H&E) staining and CD34 immunohistochemistry for vascular endothelial cells will be performed on fixed tissue sections.

5.1.3.4 Patient pathway



5.1.4 Study 3: Repeatability of microstructural imaging

5.1.4.1 Primary objective:

To determine the repeatability of microstructural imaging sequences.

5.1.4.2 Method

10 patients who meet the study criteria will be identified from weekly MDT meetings and urology clinics at Royal Free and University College Hospitals. Eligible participants will be contacted in person or by telephone and entered into a screening log kept on a secure NHS computer within the NHS firewall. Patients will be invited to have two MRI scans repeated ≤ 14 d apart. All patients will be provided with a participant information sheet (PIS) and copy of the consent form a minimum of 24 h in advance.

Consent will be obtained for scans at the time of attendance for the MRI scan by the investigator or a designee. They will explain that participants are under no obligation to partake or provide a reason for declining to partake in the study and are able to withdraw at any time. A copy of the signed consent form will be provided to the patient.

MRI will be performed in a 3T MRI scanner at UCL/UCLH and routine clinical safety procedures followed. 3D multi-parametric MRI of the kidney(s) will include the following sequences:

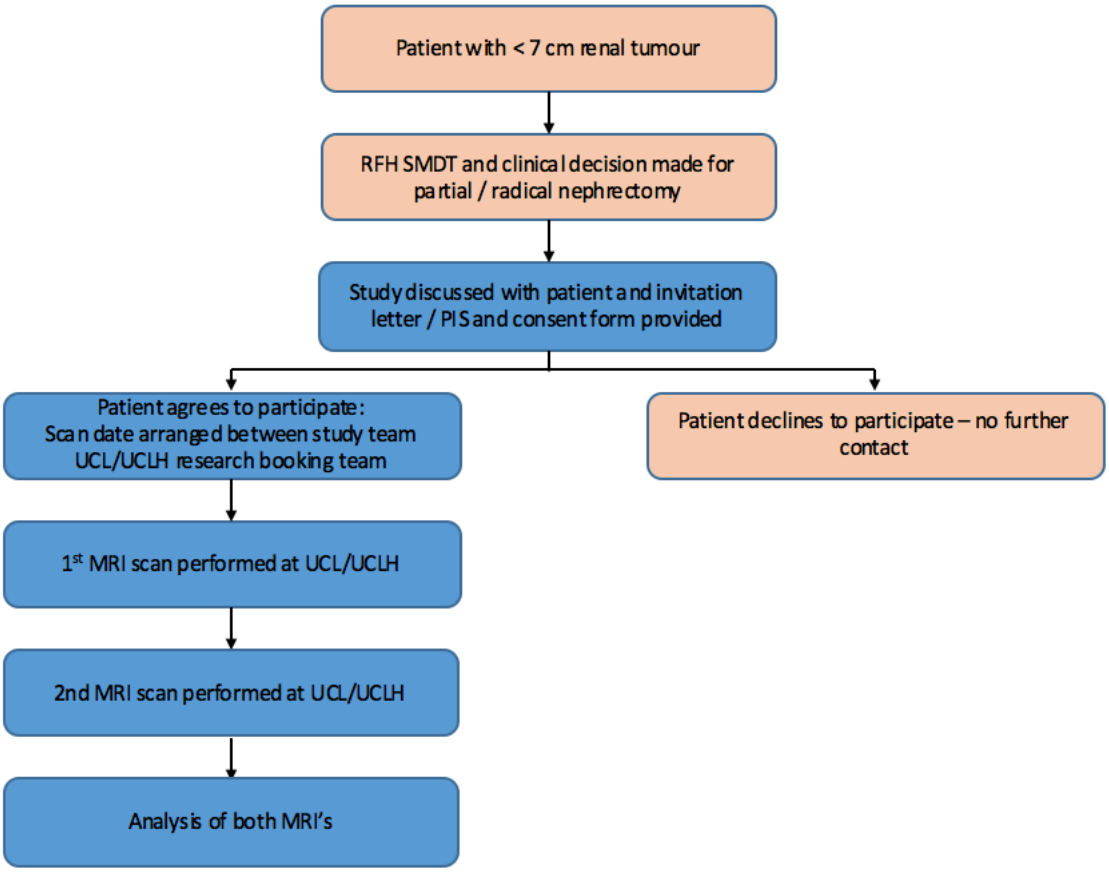
- Localisation imaging
- Anatomical T2-weighted imaging
- Diffusion imaging with multiple b-values for VERDICT modelling.
- 3D gradient echo imaging (fat fraction, T2* and quantitative susceptibility mapping)
- Perfusion imaging using dynamic contrast enhanced (DCE) MRI and/or arterial spin labelling (ASL).

Patients will receive an intravenous injection of gadolinium contrast at a dose of 0.1 mmol/kg via an intravenous cannula for DCE-MRI. Gadolinium is standard-of-care for clinical MRI of the kidneys (and many other body parts).

Each patient will have a repeat scan performed with the same protocol ≤ 14 days.

MRI images will be pseudo-anonymised and analysed offline.

5.1.4.3 **Patient pathway**



5.2 Material / Samples

Pseudo-anonymised data (MRIs, CTs, digitalised histopathology sections and patient information such as tumour type and grade) will be stored in university (UCL) computers.

The Royal Free Hospital NHS Trust will process, store and dispose of histopathological sections from nephrectomy specimens as part of routine clinical practice in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereto.

5.3Discontinuation/withdrawal of participants

Reasonable travel expenses will be covered and participants given a £10 Amazon voucher as a token of appreciation. Participants may withdraw from the study at any time and without giving a reason without this affecting their clinical care or legal rights.

5.4 Definition of End of Trial

For the prospective dataset collection we will consider the end of the study as the recruitment of the last patient. UCL BRC project funding ends 24 months after the project begins. Linked anonymised

data will be securely stored on University computers for 20 years to enable potential long-term predictions of survival and tumour recurrence.

6. FINANCE AND SUPPLY OF EQUIPMENT

The research costs for the study have been supported by NIHR University College London Hospitals Biomedical Research Centre (BRC1125/HEI/RH/110410). Value: £48, 712.

7. DATA MANAGEMENT

7.1 Confidentiality

The study is compliant with the requirements of the General Data Protection Regulation (2016/679) and the UK 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 - data-protection@ucl.ac.uk The data processors are Richard Hesketh.

Only clinicians involved in the direct care of the patient will have access to personal information. The clinician will enter pseudo-anonymised data on to a database which will only be accessible by researchers in the research team. The 'key' which will have study numbers associated with the patient's hospital number will be stored on secure NHS computers at UCLH, only accessible by clinical fellows and the chief investigator using a password.

Patient consent forms will be held in locked desks at UCLH. Only the Principal Investigator and the nominated Clinical Research Fellow(s) working on the project at RFH / UCLH will have access to this information. Patients on the pseudo-anonymised database will have a study number and relevant clinical information about their renal tumour. This information will include the patient's age, clinical details about renal cancer (location, histopathology results, blood tests). The pseudo-anonymised database will be stored on UCL computers, which will also be password protected. Similarly, all data stored in UCL computers will be anonymised.

7.2 Personal Data breaches

Personal data breaches will be immediately reported to the UCL Information Security Group (ISG) and the UCL Data Protection Officer, and to the Sponsor via the UCL JRO research incident reporting form (as per form and guidance: https://www.ucl.ac.uk/legal-services/guidance/reporting-loss-personal-data). The following information will be provided: full details as to the nature of the breach, an indication as to the volume of material involved, and the sensitivity of the breach (and any timeframes that apply). Sites will additionally follow their Trust incident reporting mechanisms, and will document this within their TMF/ISFs.

8. STATISTICAL CONSIDERATIONS

This study is developing novel imaging techniques at a pilot / proof of concept stage. At this stage there isn't a significant statistical requirement and any statistical analysis required will be performed in house.

As many of the imaging techniques have had limited use in renal imaging there are no data from which to reliably calculate a sample size. However, we will be developing the technology iteratively and will use the findings from this study to inform and power future studies.

9. Planned recruitment rate

We anticipate to be able to recruit two patients per month.

10. ASSESSMENT AND MANAGEMENT OF RISK

We do not anticipate significant risks for the participants associated to the study. The main risks are associated with the additional MRI acquired.

MRI is a safe technique and the scans performed in this study will follow routine clinical procedures and using clinical equipment. Patients will be screened by a trained radiographer to ensure that no risks are introduced e.g., metallic objects being brought into the magnetic field of the scanner. Patients will wear earplugs and headphones during the MRI scan to protect from the loud noises generated.

Patients may receive a gadolinium contrast injection which is routinely used in clinical MRI scans of multiple body sites including the kidneys. It is associated with a very low rate of immediate adverse events (0.06-0.09%) and most adverse events are mild e.g., nausea and vomiting. The incidence of acute, severe allergic reactions is estimated to be 0.0025-0.005%(19). Trained medical personnel will always be present to manage this situation. While the patient is in the MRI scanner regular contact will be made between the research team in the control room and the patient. Patients will hold an emergency call button to raise attention or terminate the scan if required.

The scanner software employs a series of safety checks to ensure that any specific set of scan parameters are safe to use. A local institutional quality control procedure is in place locally and will be used to approve any modifications to the pulse sequence software. Specifically, all code modifications are independently checked by two experienced physicists to ensure that:

- All code modifications are fully documented
- All software safety checks are still carried out
- Code modifications do not affect the validity of these software checks
- A risk assessment is produced for each approved set of code modifications to show that the manufacturer's calculations of physiological effects remain valid.

All RFH, UCLH and UCL individuals involved in this study will have received the adequate health and safety training regarding MRI and tissue handling. Therefore, we do not foresee any potential risk given that all protocols are followed accurately. Well established procedures are in place at RFH, UCLH and UCL to cope with the unlikely event of a breach of health and safety protocols.

11.RECORDING AND REPORTING OF ADVERSE EVENTS

11.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention 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. • Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences
* 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.	

11.2 Assessments of Adverse Events

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

Category	Definition

Mild	The adverse event does not interfere with the participant's daily routine, and does not require further intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

11.2.1 Causality

The assessment of relationship of adverse events to the intervention is a clinical decision made by the Investigator (or delegated medically qualified person) based on all available information at the time of the completion of the case report form.

If a differentiated causality assessment which includes other factors in the trial is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this trial to capture events related to the MRI scan. The assessment of relationship of an adverse event to this/these additional safety issue(s) will also be carried out as part of the trial.

The differentiated causality assessments will be captured in the study specific SAE form.

The following categories will be used to define the 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).
Related	A causal relationship between the intervention and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Not related	There is no reasonable possibility of a causal relationship between the intervention and an adverse event.
Not Assessable	Unable to assess on information available.

11.2.2 Expectedness

All SAEs assigned by the Investigator or delegate as suspected to be related to the intervention will be assessed for expectedness against the current SmPC or clearly defined in this protocol.

Category	Definition
Expected	An adverse event which is consistent with the information about the intervention listed in the section 10 of this protocol.
Unexpected	An adverse event which is not consistent with the information about the intervention listed in the MRI instruction manual or clearly defined in this protocol**.**

** This includes listed events that are more frequently reported or more severe than previously reported.*

11.2.3 Recording of Adverse Events

All adverse events within the first 24 h following an MRI scan will be recorded in the CRF following consent.

Procedures for recording and reporting Serious Adverse Events (SAEs)

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's SAE log. The CI/PI or designated individual will complete an SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible. Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

All SAEs will be reported to the Sponsor within 24 hours of becoming aware. The CI/PI or designated individual will complete the Sponsor's online Research Incident Reporting Form (https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo) within 24 hours of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible.

Where the SAE is unexpected and thought to be related to the intervention, this must be reported by the Investigator to the main REC that approved the study within 15 days of the Investigator becoming aware of the event, using the non-CTIMP safety report to REC form. This form can be found on the HRA website: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/. The Sponsor should be copied into this, so they are aware. Discuss with the JRO Quality Assurance team in the first instance.

Follow-up SAE reports (clearly marked as follow-up) will be completed via https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo and submitted to the JRO as further information becomes available.

11.3 Incidental Findings in Research

In the event that a clinically significant and unexpected finding is found on MRI e.g., unexpected cancer or suspicious lesion, the clinical team will be directly informed by the investigator. In addition, any such findings will be recorded on the standard clinical MRI report on the trust's radiology reporting system.

11.4 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice in the form of a substantial amendment to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

11.5 NHS Serious Incidents and Near Misses

A serious incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Serious Incidents and near misses will be reported to the Sponsor and Trust Quality & Safety department as soon as the study team becomes aware of them.

11.6 Complaints from research participants

In the first instance, research participant complaints (patients or health volunteers) will be reported to the CI/PI to investigate, as documented in the patient information sheet(s), and to the Sponsor via research-incidents@ucl.ac.uk, following the *UCL Complaints from Research Subjects about UCL Sponsored Studies and Trials* policy. For participants who are NHS patients, complaints will be reported to the NHS Complaints Manager at the Trust where the recruitment and study procedures were undertaken. Complaints from NHS patients are handled under NHS complaints policies and procedures, with involvement from PALS and the Sponsor where necessary.

12.REGULATORY REVIEW AND PATIENT AND PUBLIC INVOLVEMENT

12.1 Regulatory Review

The Sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed 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).

The study was deemed to require regulatory approval from the following bodies NHS REC Favourable Opinion and HRA Approval). **Before any site can enrol patients into the study,** the Chief Investigator/Principal Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place.

For any amendments to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments as well as the study delivery team) to confirm ongoing Capacity and Capability for the study.

All correspondence with the Sponsor, REC and HRA will be retained. The Chief Investigator will notify the Sponsor and REC of the end of the study.

It is the Chief Investigator's responsibility to produce the annual progress reports when required; an annual progress report (APR) will be submitted to the Sponsor and REC within 30 days of the anniversary date on which the favourable opinion was issued, and annually until the study is declared ended.

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

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the Sponsor and to the REC and HRA.

12.2 Peer Review

The study has been independently peer reviewed as part of the procedure for obtaining funding from (NIHR UCLH/UCL Biomedical Research Centre).

13.MONITORING AND AUDITING

A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan. The degree of monitoring will be proportionate to the risks associated with the trial. Risk will be assessed on an ongoing basis by the Chief Investigator, and adjustments made accordingly (in conjunction with the Sponsor).

The Chief Investigator will be responsible for the day to day monitoring and management of the study. The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the Sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

The UCLH/UCL Joint Research Office, on behalf of UCL as Sponsor, will conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, and in accordance with the Sponsor's monitoring and audit policies and procedures.

14.TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files.

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up-to-date, signed and dated copies held in the Investigator Site File (ISF).

15.INSURANCE AND INDEMNITY

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical 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 clinical 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 be advised to 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 clinical study shall provide clinical 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.

Additionally, UCL does not accept liability for sites such as GP surgeries in primary care; investigators/collaborators based in these types of sites must ensure that their activity on the study is covered under their own professional indemnity.

16.RECORD KEEPING AND 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 Trial Master File at University College London 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 in line with all relevant legal and statutory requirements. Study documents will be archived for a minimum of 5 years from the study end, and no longer than 20 years from the study end.

The Trial Master File will be archived at UCL, in accordance with the UCL Retentions Schedule. It will be archived for a minimum of 5 years from the study end, and no longer than 20 years from study end.

17.INTELLECTUAL PROPERTY

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol, the study data and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used independently of the study by each participating site, shall belong to UCL. All intellectual property rights deriving or arising from the material or any derivations of the material provided to UCL by the participating site shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it agrees hereby to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL or its funder. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

18.PUBLICATION AND DISSEMINATION

The analysis of results and dissemination of findings will be performed via:

a) Technical conference presentations. Scientific developments and validation results will be presented regularly throughout the project at international conferences directed at the imaging and oncology scientific communities e.g., ISMRM, RSNA, ASCO and ECR.
b) Technical journal publications. Major methodological developments will be published in technical journals e.g., Magnetic Resonance in Medicine.
c) Public engagement (as detailed in section 12.3).

19.APPENDICES

19.1 APPENDIX 1: Schedule of Assessments

Study schedule for RIM - Substudy 2			
	Visit 1	EoT	
Informed Consent	x		

Inclusion/Exclusion Criteria	x		
Medical History	x		
Concomitant Medications review	x		
mpMRI	x		
Adverse Event assessment	x	x	
Study Data Collection	x	x	
Study schedule for RIM - Substudy 3			
	Visit 1 (day 0)	Visit 2 (day ≤14)	EoT
Informed Consent	x		
Inclusion/Exclusion Criteria	x		
Medical History	x	x	
Concomitant Medications review	x	x	
mpMRI	x	x	
Adverse Event assessment	x	x	x
Study Data Collection	x	x	x
Abbreviations			
D - Day			
SoC - Standard of care			
EoT - End of Trial			
W - week			
t - Telephone call			

19.2 APPENDIX 2: Associated Documents

Document Name	Document Version	Document Date
ICF	Draft	03/10/2023
PIS	Draft	03/10/2023
GP Letter	Draft	03/10/2023
Incidental findings letter	Draft	03/10/2023
Schedule of Events	Draft	25/10/2023
SOECAT	Draft	25/10/2023

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