**FULL/LONG TITLE OF THE STUDY**

Identifying the facilitators and barriers to implementation of tumour biopsy in the diagnostic pathway for small renal masses

**SHORT STUDY TITLE / ACRONYM**

Short title: Facilitators and barriers to renal tumour biopsy

Acronym: IFIT-B (**I**dentifying the **F**acilitators and barriers to **I**mplementation of **T**umour **B**iopsy in the diagnostic pathway for small renal masses)

**PROTOCOL VERSION NUMBER AND DATE**

Version 1.0, date: 17 February 2020

**RESEARCH REFERENCE NUMBERS**

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**CHIEF INVESTIGATOR (CI):**

Ms Maxine Tran

UCL Department of Surgical Biotechnology,

Division of Surgery and Interventional Science,

9th Floor Royal Free Hospital

Pond Street, London NW3 2QG

Email: m.tran@ucl.ac.uk

**SPONSOR: Royal Free London NHS Foundation Trust**

**Representative of the Sponsor:**

**Royal Free London NHS Foundation Trust**

**Pond St**

**London**

**NW3 2QG**

Phone:

Email:

**Funding Source**:

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Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorisation from Royal Free London’s R&D Office or its affiliates.

**SIGNATURE PAGE**

**Chief Investigator Declaration**

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the approved protocol, GCP, the Data Protection Act (1998), the Trust’s Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition), the Sponsor’s SOPs, and other regulatory requirements as appropriate.

This protocol has been written in accordance to the Sponsor’s procedure identified as: SOP029 ‘Applying for Royal Free Sponsorship’ and is intended for use at UK sites **only.**

|  |  |  |  |
| --- | --- | --- | --- |
| **For and on behalf of the Study Sponsor:** | | | |
| Signature:  ...................................................................................................... | |  | Date: ....../....../...... |
| Name (please print):  ...................................................................................................... | |  |  |
| Position: ...................................................................................................... | |  |  |
| **Chief Investigator:** *Please insert the Chief Investigator’s name.* | | | |
| Chief Investigator Site: *Please insert the Chief Investigator Site.*  Signature: ...................................................................................................... |  | | Date: ....../....../...... |
| Name: (please print):  Miss Maxine Tran.................................................................................... |  | |  |

**Acknowledgements and Protocol contributories**

|  |  |
| --- | --- |
| Chief Investigator | Ms Maxine Tran UCL Department of Surgical Biotechnology, Division of Surgery and Interventional Science, 9th Floor Royal Free Hospital Pond Street, London NW3 2QG Email: [m.tran@ucl.ac.uk](mailto:m.tran@ucl.ac.uk) |
| Study Co-ordinator | To be appointed |
| Sponsor | Royal Free London NHS Foundation Trust Pond St London  NW3 2QG |
| Joint-sponsor(s)/co-sponsor(s) | Not applicable |
| Funder(s) | National Institute for Health Research (NIHR)  Research for Patient Benefit (RfPB) scheme  NIHR Central Commissioning Facility Grange House 15 Church Street Twickenham TW1 3NL Tel: 020 8843 8057 Email: [rfpb@nihr.ac.uk](mailto:rfpb@nihr.ac.uk) |
| Key Protocol Contributors | Miss Maxine Tran University College London Email: [m.tran@ucl.ac.uk](mailto:m.tran@ucl.ac.uk)  Dr Veronica Ranieri University College London Email: [v.ranieri@ucl.ac.uk](mailto:v.ranieri@ucl.ac.uk)  Professor Kurinchi Gurusamy University College London Email: k.gurusamy@ucl.ac.uk  Mr William Wildgoose Patient representative Email: whwildgoose@aol.com  Dr Antony Goode Royal Free Hospital Email: antonygoode1@nhs.net  Dr Elena Pizzo University College London Email: e.pizzo@ucl.ac.uk  Dr Soha El-Sheikh Royal Free Hospital Email: s.elsheikh@nhs.net  Mr Grant Stewart University of Cambridge Email: gds35@cam.ac.uk  Mrs Netty Kinsella The Royal Marsden NHS Foundation Trust Email: netty.kinsella@rmh.nhs.uk  Mr Ravi Barod Royal Free Hospital Email: r.barod@nhs.net  Mr Axel Bex Royal Free Hospital Email: [axel.bex@nhs.net](mailto:axel.bex@nhs.net) |
| Committees | **Study management committee** Miss Maxine Tran University College London Email: [m.tran@ucl.ac.uk](mailto:m.tran@ucl.ac.uk)  Dr Veronica Ranieri University College London Email: v.ranieri@ucl.ac.uk  Professor Kurinchi Gurusamy University College London Email: k.gurusamy@ucl.ac.uk  Mr William Wildgoose Patient representative Email: whwildgoose@aol.com  Dr Antony Goode Royal Free Hospital Email: antonygoode1@nhs.net  Dr Elena Pizzo University College London Email: e.pizzo@ucl.ac.uk  Dr Soha El-Sheikh Royal Free Hospital Email: s.elsheikh@nhs.net  Mr Grant Stewart University of Cambridge Email: gds35@cam.ac.uk  Mrs Netty Kinsella The Royal Marsden NHS Foundation Trust Email: netty.kinsella@rmh.nhs.uk  Mr Ravi Barod Royal Free Hospital Email: r.barod@nhs.net  Dr Axel Bex Royal Free Hospital Email: [axel.bex@nhs.net](mailto:axel.bex@nhs.net)  **Oversight committee**  To be appointed |

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# LIST OF ABBREVIATIONS/GLOSSARY OF TERMS

AE Adverse Event

AR Adverse Reaction

CI Chief Investigator

CRF Case Report Form

GCP Good Clinical Practice

ICF Informed Consent Form

ISF Investigator Site File

NHS R&D National Health Service Research & Development

PI Principal Investigator

PIS Participant Information Sheet

QA Quality Assurance

QC Quality Control

RCT Randomised Control Trial

REC Research Ethics Committee

RFL Royal Free London

SDV Source Document Verification

SOP Standard Operating Procedure

SSA Site Specific Assessment

# ROLES AND RESPONSIBILITIES

**Chief Investigator (CI):**

Ms Maxine Tran  
UCL Department of Surgical Biotechnology,  
Division of Surgery and Interventional Science,  
9th Floor Royal Free Hospital  
Pond Street, London NW3 2QG  
Email: [m.tran@ucl.ac.uk](mailto:m.tran@ucl.ac.uk)

**Study management committee**

Miss Maxine Tran  
University College London  
Email: [m.tran@ucl.ac.uk](mailto:m.tran@ucl.ac.uk)

Dr Veronica Ranieri  
University College London  
Email: v.ranieri@ucl.ac.uk

Professor Kurinchi Gurusamy  
University College London  
Email: k.gurusamy@ucl.ac.uk

Mr William Wildgoose  
Patient representative  
Email: whwildgoose@aol.com

Dr Antony Goode  
Royal Free Hospital  
Email: antonygoode1@nhs.net

Dr Elena Pizzo  
University College London  
Email: e.pizzo@ucl.ac.uk

Dr Soha El-Sheikh  
Royal Free Hospital  
Email: s.elsheikh@nhs.net

Mr Grant Stewart  
University of Cambridge  
Email: gds35@cam.ac.uk

Mrs Netty Kinsella  
The Royal Marsden NHS Foundation Trust  
Email: netty.kinsella@rmh.nhs.uk

Mr Ravi Barod  
Royal Free Hospital  
Email: r.barod@nhs.net

Dr Axel Bex  
Royal Free Hospital  
Email: [axel.bex@nhs.net](mailto:axel.bex@nhs.net)

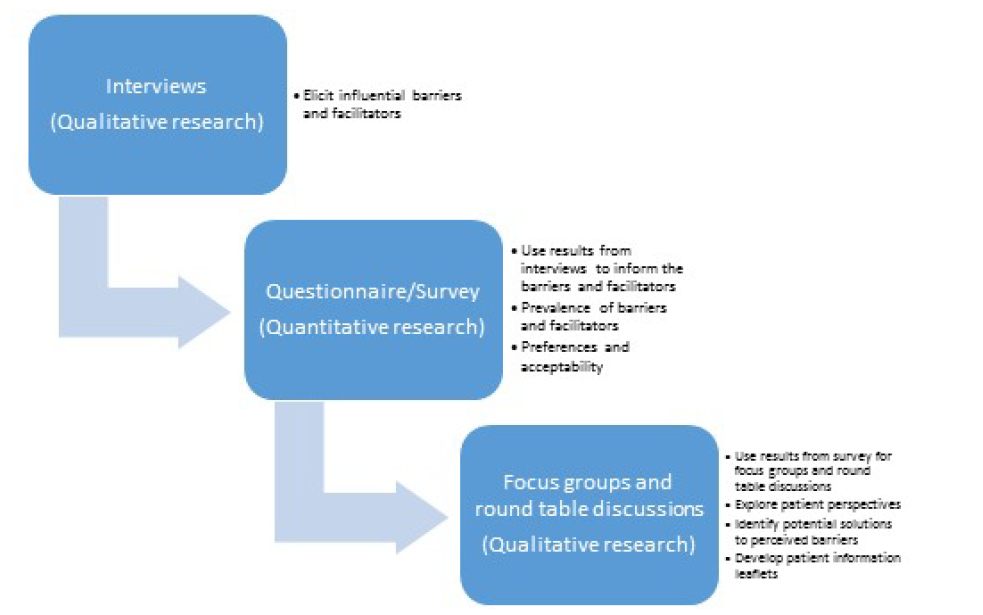
**Oversight committee**

To be appointed

# STUDY SUMMARY

|  |  |
| --- | --- |
| **Official title:** | Identifying the facilitators and barriers to implementation of tumour biopsy in the diagnostic pathway for small renal masses |
| **Brief title /Acronym:** | Facilitators and barriers to renal tumour biopsy (IFIT-B) |
| **Sponsor reference number:** |  |
| **Public database trial ID:** |  |
| **Research Question** | The overarching research question is ‘what are the current facilitators and barriers to the adoption of a renal tumour biopsy service?’ |
| **Study design** | Mixed-methods approach |
| **Eligibility criteria:** | ***Inclusion criteria:***  Urologists, radiologists, uro-pathologists, patients, clinical/management leads and service commissioners. In both the qualitative and quantitative aspects of the study, we will employ purposive sampling of patients to enable the sample to be representative of different demographic characteristics including age, gender, ethnicity, work and social commitments, to ensure we collect a wide range of experiences. |
| ***Exclusion criteria:***  None applicable |
| **Anticipated start date** | 01/02/2020 |
| **Anticipated end date** | 31/01/2022 |
| **Target number of participants** | Interviews: until saturation is reached (though anticipated following 32-39 interviews)  Questionnaire: healthcare professionals, and patients and members of the public from 5 hospitals (anticipated sample size: 100)  Focus group: until saturation is reached (groups will be composed of 4 to 6 individuals per group) |
| **Primary aim** | The objectives of this research are to find out the following  • What are the patient, public and professional preferences and views in relation to the usefulness of tumour biopsy in the management of small renal masses?  • What is the impact of RTB (renal tumour biopsy) on provision of care, in terms of clinical processes and outcomes?  • What is the impact of RTB on patient experience, including choice and treatment decision making process?  • What is the cost and cost-effectiveness of a RTB service?  • What interventions (professional or organisational) would be required to enable implementation of RTB in the diagnostic pathway of small renal masses? |
| **Secondary aim(s)** | None applicable. |
| **Sources of funding** | National Institute for Health Research (NIHR)  Research for Patient Benefit (RfPB) scheme |
| **Sponsor** | **Royal Free London NHS Foundation Trust** |
| **Contact name** | ***Sponsor representative :***  ***Email***  ***Tel***  ***Fax***  ***Chief Investigator:***  Miss Maxine Tran  Email: m.tran@ucl.ac.uk |

# 4.0 STUDY FLOW CHART

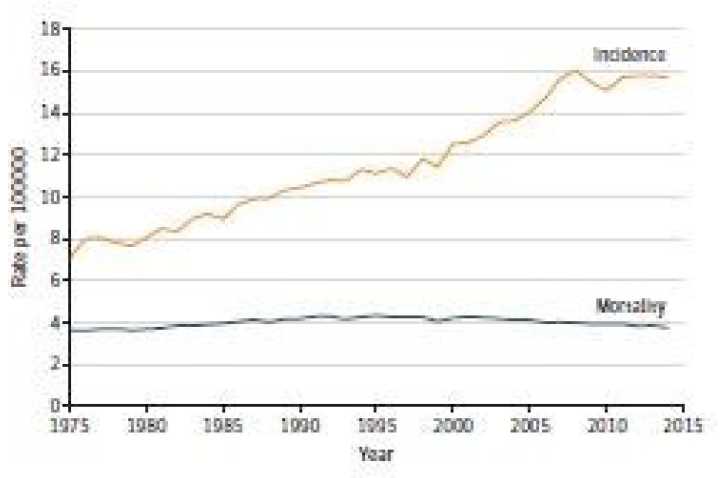


# INTRODUCTION

## BACKGROUND

**(i) What is the problem being addressed?**

**Incidental small renal masses and their overtreatment**

The diagnosis of incidental small renal masses has been increasing steadily since the 1970s, fuelled by the uptake of imaging methods, but surprisingly, earlier diagnosis and surgical treatment has had no impact on kidney cancer mortality[1], Figure 1. The combination of rising incidence but yet stable mortality is probably indicative of overdiagnosis and over-treatment[2]. Over-diagnosis and over-treatment is defined as the diagnosis and management of a disease process that would otherwise not have gone on to cause symptoms or death[2]. Further, a recent study in the United States has now provided evidence that increased use of CT imaging is associated with increased diagnosis of kidney masses, leading to over-treatment and harm[1, 3, 4].

**Figure 1**. Kidney cancer incidence and mortality in the United States 1975-2014.

The observed incidence of kidney cancer has roughly doubled since the advent of the CTs, while mortality has remained stable[1].

Not all renal tumours are cancers. Imaging alone is not able to distinguish benign from cancerous lesions and up to 30% of renal masses are, in fact, benign[5, 6]. The proportion of non-malignant disease is higher in patients <40 years old, where up to 36% of excised renal masses have been found to be benign[7]. Currently, the only available method of diagnosing a benign tumour prior to surgery is to have a percutaneous renal tumour biopsy (RTB)[6].

However, the management of renal masses is generally still very much dominated by imaging followed by surgery. Surgical approaches include:

* partial nephrectomy (removal of tumour whilst leaving rest of the normal kidney) which is indicated for small tumours whenever feasible and is usually performed with the assistance of a Da Vinci robot surgical system;
* radical nephrectomy (removal of the tumour including the rest of the kidney) is indicated for larger tumours or when partial nephrectomy is technically not possible, for example if the small lesion is located deep within the centre of the kidney. Radical nephrectomy can be performed laparoscopically, or with the assistance of a Da Vinci robot, or by traditional open surgical approach.

British urological surgeons are mandated to enter surgical (nephrectomy and partial nephrectomy) outcomes onto a national audit database hosted by the British Association of Urological Surgeons (BAUS) [https://www.baus.org.uk/patinets/surgical\_outcomes/nephrectomy/]. An audit of the BAUS data showed that over a 4 year period (2013-2016), there were 32130 surgical cases (all tumour sizes), of which only 7% had had a presurgical biopsy. Sub-analysis showed that 1202 cases had a final pathology of oncocytoma (a benign tumour) and of these, only 2.9% had had a pre-surgical RTB [8,9]. Of particular significance, there was an overall complication risk of 20%, a 4% risk of major complication, classified as Clavien Dindo Grade 3 or above (i.e. a complication requiring surgical/radiological or endoscopic intervention [grade 3] or a life threatening complication requiring ITU admission [grade 4]), and a 0.5% mortality rate. Of the patients who had had surgery and were subsequently found to have had an oncocytoma, there were 5 deaths within 60 days of surgery [9]. It is important to note, that the major limitation of the BAUS data is that it is a surgical audit, and as such, does not provide information on the number of patients with renal masses that had RTB and elected not to have surgery.

Also of relevance is that this study only looked at oncocytomas (up to 60% of benign renal lesions), and therefore is likely an under-representation as complications and mortality attributed to surgery for other benign renal lesions (such as angiomyolipomas and cystic nephromas) were not included in this analysis.

Surgical excision of benign renal masses can still be recommended for symptomatic cases, for example for tumours that are very large and cause pain or haematuria, or general anxiety. However, the great majority of incidentally diagnosed renal masses are small (less than 4cm, termed small renal masses [SRM]) and do not cause any symptoms[10]. Moreover, longitudinal studies have shown that up to two thirds of SRMs grow very slowly or not at all, with an average growth of 0.13cm/year, and a very low risk of metastasis[10,11]. So, while the mortality and morbidity risks of surgery may be acceptable in the context of high grade/large kidney cancers or symptomatic disease, they may be considered rather significant for an asymptomatic, indolent small tumour that may be of little clinical relevance.

A recent study in the United States highlighted the overtreatment of the SRM [12,13]. These authors analysed data from the National Cancer Database from 2010 to 2014 on the contemporary management of 52804 patients with SRM. Over the four years studied, active surveillance as a treatment option increased by 25% compared to 82% increase in robot-assisted surgeries. Significantly, surgery for SRM increased in older patients and those with more co-morbidities by 98% and 92% respectively.

We have also reviewed the BAUS national nephrectomy audit data (2012-2016) in the context of surgical management of SRMs. Overall, 6417 surgeries were performed for SRMs (4220 partial nephrectomies and 2197 nephrectomies) during this period. There were a total of 234 serious complications (Clavien Dindo grade 3 or higher) and 6 post-operative deaths. Of 5882 patients where the histology was recorded, 623 were benign (10.6%) and 2827 were low grade or had low malignant potential (48%). This indicates that surgery and its complications (which included 5 deaths) could have been avoided in this group of patients (58.6%), and in particular in the 24% of patients who were aged 70 years or over, or had significant co-morbidities (American Society of Anesthesiologists score 3 and above).

These analyses demonstrate that the overtreatment of SRM is manifest, at least among the elderly and patients with co-morbidities.

Surgical management of renal masses also has implications on the mental health of patients. A recent study analysing the psychosocial stress factors in patients undergoing renal cancer treatment identified that a significant number of patients were in need of psychosocial care; with the main stressors being anxiety, nervousness, worry and sleeping difficulties[14].

Recognised alternative treatment strategies for benign tumours or low grade cancers include active surveillance or percutaneous ablation by either heating (radio-frequency ablation) or freezing (cryoablation) tumour cells[15]. Active surveillance and ablation therapy are currently mainly offered to patients who are elderly, high surgical risk candidates, or those wishing to avoid surgery. However, there is an increasing body of evidence that these options provide equivalent oncological control to traditional surgery and could benefit more patients, especially with small renal masses[16-21]. Indeed, the NIHR is funding a feasibility study comparing cryoablation and partial nephrectomy in the management of SRM (Nephron Sparing Treatment for small renal masses [NEST]: PB-PG- 0817-20013; PI M Tran).

**Renal tumour biopsy and its potential role in managing small renal masses**

Renal tumour biopsy (RTB) can impact on treatment decision making by distinguishing benign or low-grade tumours from high-grade cancers. A recent systematic review and meta-analysis of 57 studies and 5228 patients has shown a diagnostic yield of 925, with excellent sensitivity (99.1%) and specificity (99.7%) for RTB, particularly when core biopsy is used rather than fine needle aspiration[22]. There was an overall complication rate of 8.1%, with only two major (defined as Clavien-Dindo 3 or above) complications (0.04%) reported. These were: one case of gross haematuria requiring admission for clot induced urinary retention, and one case of pseudoaneurysm requiring percutaneous embolization[22]. Concordance between RTB and final surgical histology is also high at 87-94% when stratifying to low and high grades[6, 22], providing reassurance at point of diagnosis.

An absolute contraindication to RTB would be in patients when the result will not change management, for example in patients with shortened life expectancy or in patients requesting surgical removal regardless of the outcome of the RTB. Relative contraindications would include uncorrected coagulopathies, or very cystic lesions in which diagnostic yield would be low[20].

We have audited our own experience as a high surgical volume centre in the UK that has adopted RTB in the routine diagnostic pathway of small renal masses. We have performed 596 biopsies (556 patients) over a 3-year period, with a diagnostic rate of 89%, and a low complication rate of 2.5% (all minor, classified as Clavien-Dindo grade 2 or less). In our series (largest reported in Europe), 26% (n=143) of patients had benign or low grade cancer on histology, of which only 2 patients decided to proceed with surgical excision of their renal tumour and 3 patients chose percutaneous cryoablation (freezing of the tumour). Final surgical histology in the two patients that chose to undergo surgery was concordant with the RTB and confirmed benign disease (100% concordance). Thus, in our audited experience, utilisation of RTB has enabled 99% (n=141) of patients with benign or low grade histology to avoid surgery in favour of less morbid options such as active surveillance or tumour ablation[23].

The increased use of imaging is likely to continue; therefore, the diagnosis of small renal masses is likely to increase on its current trajectory. Thus, improving risk stratification with tumour biopsy prior to treatment decision making is essential to reduced harm for patients diagnosed with an incidental renal lesion.

**(ii) Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health care services?**

The role of biopsy in the management of kidney cancer has been identified as one of the top 10 priority areas for research by the James Lind Alliance (JLA) Priority Setting Partnership (PSP) for kidney cancer[24]. The JLA initiative brings together patients, carers and clinicians to identify and prioritise areas for research so that funders are aware of the issues that matter most to patients and clinicians. The role of RTB has also been identified as a priority by the European Association of Urology Renal Cell Cancer Guideline Panel[22].

Our research will examine current RTB service provision in independent secondary and tertiary care practices to enable the identification of facilitators and barriers at the provider, interpersonal and practice level. This insight is required to develop implementation strategies to improve access to RTB. This will not only improve patient outcomes in terms of avoidance of over-treatment and the accompanying complication and mortality risk, but may also reduce the psychosocial impact associated with surgery. Additional benefits of RTB may include more rapid diagnosis, rather than having to wait until after surgery, and potentially less psychological distress to patients compared to surgery. This may also generate health cost savings both to the patient and to the health service, where savings can be diverted for patient benefit elsewhere in the NHS.

This research is particularly timely, given the recent well publicised Government new cancer strategy for the NHS which is a drive for earlier diagnosis[25] and CRUK’s manifesto of early detection of cancer (https://www.cancerresearchuk.org/early-diagnosis-0). These broad goals, while unquestionably laudable, will also compound the increased detection of ‘incidentalomas’ (incidental tumours) such as the small renal mass. Appropriate strategies to mitigate potential over-treatment of SRM need to be developed. The proposed study (IFITB) will provide significant useful and actionable insights to address this.

Members of the public and patients have also confirmed that this is an important issue that they would like to be addressed. We have conducted a pre-study online survey with the Kidney Cancer UK (KCUK) charity.

* 140 responses were received, from patients (n=86), members of their family (n=30) and the general public (n=24)
* 89% said that knowing whether a tumour was benign or cancerous would help a patient decide whether or not to have surgery
* 93% thought it was important to find out why some hospitals didn’t offer kidney tumour biopsies
* 94% thought it was important to find out how a tumour biopsy service could be implemented so that every patient had access to it if they wanted
* Only 22% of patients reported having been offered a biopsy of their tumour
* 72% of patients when offered a biopsy, chose to have one

**(iii) Review of existing evidence – How does the existing literature support this proposal?**

Current evidence supports the concern that increased use of imaging is associated with increased risk of nephrectomy or partial nephrectomy, while having no effect on overall mortality rates from kidney cancer[1, 3, 4]. A significant proportion of SRMs are benign or have low-grade non-aggressive features and diagnostic tumour biopsy should be considered to avoid unnecessary surgery and personalise treatment decision making[4, 6]. Historical concerns regarding RTB accuracy, causing tumour seeding and other major complications, have now been confirmed to be unfounded[6, 22].

Yet despite the benefits, it is clear that RTB is still underutilised and not adopted into the diagnostic armamentarium of the mainstream practising urologist[9, 26]. A recent study in Canada using a web- based survey of members of the Canadian and Quebec Urologic Associations found that only 12% of urologists routinely used RTB, while 53% never performed RTB. The most frequent reasons offered for not using RTB was a belief that biopsy would not alter management and the risk of obtaining a false-negative or non-diagnostic biopsy[26].

Utilisation of RTB in the United States is also modest at 20.7%, with evidence of disparity in patient sex and race, which persisted after adjustment for age, comorbidity and tumour size[27]. A retrospective analysis using a decision algorithm on 1175 SRM treated with surgery in 5 academic centres in the United States, found that 52% were either benign (23%)[9] or amendable to active surveillance (29%), and thus, if a pre-operative biopsy had been performed, over half of the cases could have avoided surgery, at least initially[28]. Similarly, studies in Canada show that around 40% of patients avoid surgery based on the result of RTB[6, 29].

British urological surgeons are mandated to enter surgical (nephrectomy and partial nephrectomy) outcomes onto a national audit database hosted by the British Association of Urological Surgeons (BAUS). The BAUS audit showed that over a 4-year period (2013-16), there were 32130 surgical cases, of which only 7% had had a presurgical biopsy[9].

## RATIONALE

Our research will examine current RTB service provision in independent secondary and tertiary care practices to enable the identification of facilitators and barriers at the provider, interpersonal and practice level. This insight is required to develop implementation strategies to improve access to RTB. This will not only improve patient outcomes in terms of avoidance of over-treatment and the accompanying complication and mortality risk, but may also reduce the psychosocial impact associated with surgery. Additional benefits of RTB may include more rapid diagnosis, rather than having to wait until after surgery, and potentially less psychological distress to patients compared to surgery. This may also generate health cost savings both to the patient and to the health service, where savings can be diverted for patient benefit elsewhere in the NHS.

This research is particularly timely, given the recent well publicised Government new cancer strategy for the NHS which is a drive for earlier diagnosis[25] and CRUK’s manifesto of early detection of cancer (https://www.cancerresearchuk.org/early-diagnosis-0). These broad goals, while unquestionably laudable, will also compound the increased detection of ‘incidentalomas’ (incidental tumours) such as the small renal mass. Appropriate strategies to mitigate potential over-treatment of SRM need to be developed. The proposed study (IFITB) will provide significant useful and actionable insights to address this.

All interviews will follow the structure set out in a topic guide, which will draw on both a theoretical domains framework (TDF)[30] and the published empirical literature. The TDF was developed by implementation scientists and selected as a comprehensive, validated framework for determining barriers and facilitators to the implementation of best practice. Interviews will be transcribed verbatim and coded using Computer Assisted Qualitative Data Analysis Software (i.e. NVivo). Braun and Clarke’s model of thematic analysis with a six-phase approach will be used to generate, review, and define themes within the interview transcripts.

# 6.0 RESEARCH QUESTION

The overarching research question is ‘what are the current facilitators and barriers to the adoption of a renal tumour biopsy service?’

## PRIMARY AIM

The objectives of this research are to find out the following

* What are the patient, public and professional preferences and views in relation to the usefulness of tumour biopsy in the management of small renal masses?
* What is the impact of RTB on provision of care, in terms of clinical processes and outcomes?
* What is the impact of RTB on patient experience, including choice and treatment decision making process?
* What is the cost and cost-effectiveness of a RTB service?
* What interventions (professional or organisational) would be required to enable implementation of RTB in the diagnostic pathway of small renal masses?

## SECONDARY AIM (s)

None applicable.

# TRIAL DESIGN

This study will employ an exploratory mixed-methods approach (Figure 2). Potential participants will be firstly invited to partake in individual interviews, from which we will extract the key factors that influence decision-making in relation to adopting RTB. Once such factors are identified, a larger sample of potential participants will be asked to partake in a short questionnaire evaluating the wider prevalence of such factors, and the applicability and preferences for a range of potential solutions. The topic guides for the interviews are available in the Appendices.

## Interviews

Qualitative interviewing will be used due to its ability to extract rich and meaningful narratives from healthcare professionals, service designers, commissioners, patients and members of the public. Semi-structured interviews will be conducted to enable the researcher to capture detailed insights about each individual’s personal experiences and/or perceptions regarding the facilitators and barriers to RTB. Patients will be specifically asked about their perceptions and potential acceptability of renal tumour biopsy in the diagnostic pathway of small renal masses.

Participants will consist of healthcare professionals involved in conducting RTBs, clinical service designers and commissioners, and kidney tumour patients. Participants will be recruited from 5 hospitals (to include teaching and district general hospitals) ranging from low to high procedural volume. The aim is to reach saturation, so we plan to interview 3-4 individuals per professional grouping (subject to revision as the interviews are being carried out), at least 1 per professional grouping per hospital surgical nephrectomy volume (high, medium and low). We will also interview 2-3 clinical commissioning leads (from within and outside of London) and have already established collaborative support from Professor Kathy Pritchard-Jones (Chief Medical Officer for London Cancer) who has extensive experience in service design and delivery, having led the development of the London Cancer integrated cancer system and re-organisation of specialist cancer services in London and Manchester; and Caroline Blair (Programme director for Renal Cancer, NHS England).

Maximum variation sampling will be employed to obtain as wide a range of perspectives as available to us. Using this sampling technique will permit us to describe the range of factors that influence participants’ experiences and/or perceptions regarding RTB and the extent to which these are shared between participants. Healthcare professionals will be selected purposively according to their experience and familiarity of RTB, including surgical/radiological and pathology trainees. Patients and members of the public will also be purposively selected according to whether they have undergone a RTB, and demographic factors such as gender, age, ethnicity and co-morbidity. It is anticipated that saturation will be reached with between 10-16 patients. This focused approach will give a total of between 32-39 interviews.

All interviews will follow the structure set out in a topic guide, which will draw on both a theoretical domains framework (TDF)[30] and the published empirical literature. The TDF was developed by implementation scientists and selected as a comprehensive, validated framework for determining barriers and facilitators to the implementation of best practice. Interviews will be transcribed verbatim and coded using Computer Assisted Qualitative Data Analysis Software (i.e. NVivo). Braun and Clarke’s model of thematic analysis with a six-phase approach will be used to generate, review, and define themes within the interview transcripts[31].

## Questionnaire

A questionnaire will be constructed based on the influential facilitators and barriers elicited in the individual interviews. It will seek to assess the prevalence of such influences, and the preferences and acceptability of potential solutions. Similar to the qualitative interviews, participants will consist of both healthcare professionals, and patients and members of the public. All surgeons (including trainees), radiologists, pathologists and clinical leads involved in the administration of RTBs, as well as patients and members of the public across the 5 hospitals will be invited to complete an online questionnaire. We will also request BAUS for support to extend our questionnaire (online) to all urological surgeons currently entering data onto the BAUS audit, although we anticipate this to be ambitious. It has to be highlighted however, that although this information is desirable, further steps of the research are not solely dependent on achieving this. To maximise recruitment and response rate, we will also distribute the questionnaire (printed version) at the Renal Oncology section meeting at the annual BAUS conference and BAUS oncology sub-section meeting.

We anticipate that the constructed online (and paper) questionnaire will consist of between 6-8, and no more than 10 items. On average, respondents take about 5 minutes to answer a 10-question survey. We will use a GDPR-compliant online survey tool.

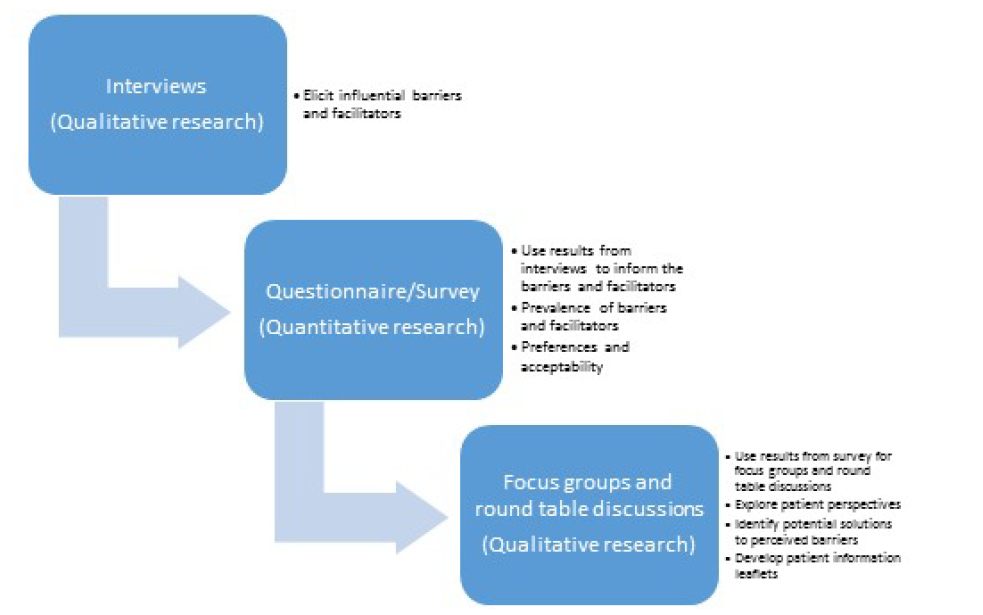
Data will be extracted from the online and paper questionnaires and entered into statistical analysis software (i.e. SPSS). The analysis will comprise of both descriptive data (mean and standard deviation/median and interquartile range as appropriate) and inferential statistics, where we will examine whether the prevalence of influences and preference for potential solutions differ between participant groups and according to demographic variables.

## Patient and public focus groups and roundtable discussions

Patients, members of their family and the public will be invited from all the hospitals, KCUK website and the UCL Biomedical research PPI network, to take part in focus group discussions hosted locally (4-6 patients per group). Focus groups discussions provide a different important dimension to the study as they may elicit different ‘themes’ by identifying common trends, perceptions and assumptions while also providing diversity among participants.

These meetings will have three goals:

1. Explore patient and public perspectives on the role of RTB in the diagnostic pathway of small renal masses
2. Identify potential solutions and next steps to address perceived barriers
3. Help in developing patient information leaflets regarding RTB and in the dissemination of findings from the study via social media, and local hospital events

****We will also hold roundtable workshops where findings from the study will be presented to both patients and clinicians, to stimulate discussion and to construct intervention strategies incorporating both viewpoints.

**Figure 2.** A schematic flow diagram illustrating the integration of the qualitative and quantitative components of the study.

Qualitative interviewing will be completed prior to commencing quantitative data collection. Figure 2 is a schematic flow diagram illustrating the integration of the qualitative and quantitative components of this part of the study (1, 2 and 3).

## Health Economic analysis

We will conduct an exploratory preliminary economic analysis to estimate the cost of Renal Tumour Biopsy (RTB) intervention adoption in the NHS. To this aim we will gather data from available evidence and from expert opinion (e.g. using the interviews with clinicians in the qualitative component of the study). The cost-utility measures will be the incremental cost per unit of change in the Quality Adjusted Life Years (QALY) gained.

We will develop a decision-analytic model (Markov model) to estimate the cost-effectiveness of performing RTB prior to surgery versus current common pathway (no RTB) to diagnose and manage SRMs. The model will estimate the lifetime costs (including active surveillance and robotic/laparoscopic/open surgery costs) and life expectancy of an average patient in both options. We will populate the model using data from published evidence on incidence, probabilities (e.g. false positive or negative tests, complications), NHS reference costs (e.g. the cost of the diagnostic test, surgery, follow up, complications, treatments for cancer), life expectancy and outcomes (e.g. utilities to calculate QALYs). Unit costs will be collected and assessed from the perspective of the NHS and personal social services via standard sources.

Where possible we will use real data from two representative hospitals where patients undergo the RTB procedure and the current pathway. Cost-utility will be calculated as the mean cost difference between the intervention (RTB prior to surgery) and control group (no RTB prior to surgery) divided by the mean difference in outcomes to give the incremental cost effectiveness ratio (ICER).

We will perform sensitivity analysis to control for uncertainty in the data parameters. Cost effectiveness acceptability curves will be constructed to show the likelihood that the intervention is cost-effective.

The results of the analysis will inform on whether performing RTB prior to offering surgery represents good value and provides a better, improved diagnostic pathway to benefit patients and the NHS.

# 8.0 PARTICIPANT SELECTION CRITERIA

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standards used to ensure the trial results can be appropriately used to make future treatment decisions for other people with similar disease or medical condition. It is therefore vital exceptions are not made to the following detailed selection criteria.

All participants that are screened for inclusion into the study must be entered onto the sponsor screening log RFLRDLOG0001 and will be assigned a sequential number. Participants will be considered eligible for enrolment into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be entered onto the sponsors Subject ID log RFLRDLOG0002 and assigned a Trial specific Identification number in a pre-agreed format in accordance with Site identifier and next sequential numerical value e.g. RF001

## INCLUSION CRITERIA

Urologists, radiologists, uro-pathologists, patients, clinical/management leads and service commissioners. In both the qualitative and quantitative aspects of the study, we will employ purposive sampling of patients to enable the sample to be representative of different demographic characteristics including age, gender, ethnicity, work and social commitments, to ensure we collect a wide range of experiences.

## EXCLUSION CRITERIA

None applicable

## DISCONTINUATION/WITHDRAWL OF PARTICIPANTS

If participants withdraw from the study, we will keep any anonymised information that were obtained, but withdraw any data that can be identified as the participant’s contribution.

# PARTICIPANT RECRUITMENT PROCESS

The study will only commence once evidence of the following approval/essential documents are in place:

1. The main REC approval (if applicable),
2. HRA approval
3. 2. Final sponsorship and host site confirmation of capacity and capability,

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA),

2. Host site permission

All participants who wish to enter the study will be fully screened and consented by the Chief Investigator, or one of the qualified clinicians involved in the study as Clinical Co-investigator.

The relevant healthcare professionals will be identified by the principal investigator at each site by identifying the individuals responsible at different sites. The patients will be identified through the relevant healthcare professionals. Any travel and subsistence for the research purposes will be covered.

**Interviews**

Participants will be recruited from 5 hospitals (to include teaching and district general hospitals) ranging from low to high procedural volume. We plan to interview 3-4 individuals per professional grouping (subject to revision as the interviews are being carried out as this figure is dependent on whether saturation is reached), at least 1 per professional grouping per hospital surgical nephrectomy volume (high, medium and low). We will also interview 2-3 clinical commissioning leads (from within and outside of London) and have already established collaborative support from Professor Kathy Pritchard-Jones (Chief Medical Officer for London Cancer) who has extensive experience in service design and delivery, having led the development of the London Cancer integrated cancer system and re-organisation of specialist cancer services in London and Manchester; and Caroline Blair (Programme director for Renal Cancer, NHS England).

Maximum variation sampling will be employed to obtain as wide a range of perspectives as available to us. Using this sampling technique will permit us to describe the range of factors that influence participants’ experiences and/or perceptions regarding RTB and the extent to which these are shared between participants. Healthcare professionals will be selected purposively according to their experience and familiarity of RTB, including surgical/radiological and pathology trainees. Patients and members of the public will also be purposively selected according to whether they have undergone a RTB, and demographic factors such as gender, age, ethnicity and co-morbidity. It is anticipated that saturation will be reached with between 10-16 patients. This focused approach will give a total of between 32-39 interviews.

**Questionnaire**

We anticipate recruiting 100 participants, but it has to be highlighted however, that although this information is desirable, further steps of the research are not solely dependent on achieving this.

All surgeons (including trainees), radiologists, pathologists and clinical leads involved in the administration of RTBs, as well as patients and members of the public across the 5 hospitals will be invited to complete an online questionnaire. We will also request BAUS for support to extend our questionnaire (online) to all urological surgeons currently entering data onto the BAUS audit, although we anticipate this to be ambitious.

To maximise recruitment and response rate, we will also distribute the questionnaire (printed version) at the Renal Oncology section meeting at the annual BAUS conference and BAUS oncology sub-section meeting.

**Patient and public focus groups and roundtable discussions**

4 – 6 per group until data saturation.

Patients, members of their family and the public will be invited from all the hospitals, KCUK website and the UCL Biomedical research PPI network, to take part in focus group discussions hosted locally

# STUDY PROCEDURES

## INFORMED CONSENT

***Interviews***

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

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

Potential participants will be offered sufficient time (at least 24 hours) to consider the study. The participant will be given the opportunity to ask questions and to be satisfied with the responses prior to verbal consent being taken and recorded. No further questions will be conducted prior to the participant consent to participate in the study by verbal consent. Following consent, the patient will be enrolled in the study and allocated a unique pseudo-anonymised subject number. The copy of the verbal consent will be retained in the investigator site file. The PIS will be reviewed and updated (if necessary) throughout the study (e.g. where new information becomes available) and participants will be re-consented as appropriate.

A verbal consent allows remote interviewing, resulting in significant time and cost savings. This will also increase participation of a wider group of participants, who may not be willing or able to travel to hospital solely for the interview.

***Questionnaire***

Before the participant answers any questions, they will be provided information that by answering the questions, they are willing to allow the use of the anonymous data for research purposes and that they could withdraw from the study any time before submission by not clicking on the ‘submit’ button.

**Patient and public focus groups and roundtable discussions**

A written consent will be obtained for participants in the focus group and roundtable discussions.

***Withdrawal of consent***

If participants withdraw from the study, we will keep any anonymised information that were obtained, but withdraw any data that can be identified as the participant’s contribution.

# DATA MANAGEMENT AND QUALITY ASSURANCE

## CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act 1998.

The data collection forms will not bear the subject’s name or other directly identifiable data. The subject’s trial Identification Number (ID) only, will be used for identification. The sponsor Subject ID log RFLRD0002 should be used to cross reference subject’s identifiable information.

## 11.2 DATA COLLECTION TOOL

Data Collection Forms will be designed by the CI. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator’s responsibility to ensure the accuracy of all data entered and recorded in the forms. The Staff Delegation of Responsibilities Log RFLRDLOG0004 will identify all trial personnel responsible for data collection, entry, handling and managing the database. The data custodian for this study is Miss Maxine Tran.

## 11.3 INCIDENTAL FINDINGS

The methods used are interviews, surveys, and focus group discussions. No questions that can be considered personally embarrassing and difficult to share with others will be asked. However, we acknowledge that questions and discussions about cancer, survival, and health-related quality may be upsetting for some people. We will highlight that there will be questions and discussions about cancer, survival, and health-related quality in the participant information sheet to minimise the risk.

As mentioned above, the only risk to the participants is that questions and discussions about cancer, survival, and health-related quality may be upsetting for some people. We will highlight that there will be questions and discussions about cancer, survival, and health-related quality in the participant information sheet, to minimise this risk. We will also inform the participants that they could discontinue any time, if they feel emotionally distressed during the interview or contact the research team. We will also encourage them to contact their general practitioner or the Samaritans at 116 123.

## 11.4 DATA HANDLING AND ANALYSIS

All interviews will follow the structure set out in a topic guide, which will draw on both a theoretical domains framework (TDF)[30] and the published empirical literature. The TDF was developed by implementation scientists and selected as a comprehensive, validated framework for determining barriers and facilitators to the implementation of best practice. Interviews will be transcribed verbatim and coded using Computer Assisted Qualitative Data Analysis Software (i.e. NVivo). Braun and Clarke’s model of thematic analysis with a six-phase approach will be used to generate, review, and define themes within the interview transcripts.

For the questionnaires, data will be extracted from the online and paper questionnaires and entered into statistical analysis software (i.e. SPSS). The analysis will comprise of both descriptive data (mean and standard deviation/median and interquartile range as appropriate) and inferential statistics, where we will examine whether the prevalence of influences and preference for potential solutions differ between participant groups and according to demographic variables.

Data will be required to identify and contact the participants. The data will pseudonymised and the cipher stored in a password protected University computer and/or NHS computers kept in locked premises. Identifiable data will be stored in Data Safe Haven (DSH).

## 11.5 TRANSFERRING/TRANSPORTING DATA

We will not store or transport any person-identifiable information on any portable device, for example laptops, memory sticks, CD/DVDs, unless it is encrypted.

We will not send identifiable information outside the Trust without the explicit consent of the participant. Where data are transferred electronically this will be in accordance with the UK Data Protection Act 1998.

# ARCHIVING

During the course of research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions.

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP0044. The agreed archiving period for this trial will be 20 years. This will include any study databases.

Each PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement.

# 13.0 STATISTICAL DESIGN

Data extracted from the online and paper questionnaires will be entered into statistical analysis software (i.e. SPSS). The analysis will comprise of both descriptive data (mean and standard deviation/median and interquartile range as appropriate) and inferential statistics, where we will examine whether the prevalence of influences and preference for potential solutions differ between participant groups and according to demographic variables.

## 13. 1 ENDPOINTS

## 13.1.1 PRIMARY ENDPOINTS

The primary measure for the quantitative aspect of the study (questionnaire) are evaluating the wider prevalence of key factors that influence decision-making in relation to adopting RTB, and the applicability and preferences for a range of potential solutions.

## 13.1.2 SECONDARY ENDPOINTS

None applicable.

## STATISICIAL ANALYSIS PLANS

### SUMMARY OF BASELINE DATA AND FLOW OF PATIENTS

Data will be extracted from the online and paper questionnaires and entered into statistical analysis software (i.e. SPSS). The analysis will a summary of baseline descriptive data (mean and standard deviation/median and interquartile range as appropriate.

### 13.2.2 PRIMARY ENDPOINT ANALYSIS

The analysis will comprise of both descriptive data (mean and standard deviation/median and interquartile range as appropriate) and inferential statistics, where we will examine whether the prevalence of influences and preference for potential solutions differ between participant groups and according to demographic variables.

### 13.2.3 SECONDARY ENDPOINT ANALYSIS

None applicable.

# DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

# ETHICS AND GOVERNANCE REQUIREMENTS

Before any site can enrol patients into the trial, the Principal Investigator must ensure written permission to proceed has been granted by that Trust Research & Development (R&D). If conducting the study at Royal Free London NHS Foundation Trust, contact the R&D team for any assistance.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, which was given favourable opinion by the Research Ethics Committee (REC) and the Health Research Authority (HRA) where applicable.

The Chief Investigator will be provided (via the Sponsor) with file indexes TMF Index RLFRDDOC0013 and ISF index RFLRDOC0003 for use with SOP019 ‘Preparation and Maintenance of the Site File – and SOP054 ‘Preparation and Maintenance of the Trial Master File’. The CI will be responsible for the maintenance of the TMF and may delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. Refer to R&D OFFICE SOP0016 ‘Protocol amendments of RFL Sponsored Studies’ and R&D OFFICE SOP003 ‘Reporting amendments’.

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the 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. Refer to R&D OFFICE SOP0030 ‘Study Close Down’

The CI will supply an End of Study report of the clinical trial to the REC within one year after the end of the trial. The sponsor can provide an End of study Report template RFLRDDOC0005.

## 15.1 DEFINITION OF THE END OF TRIAL

As this is a mixed-methods approach study, then end of trial is defined as the latest occurrence of:

• Qualitative semi-structured interviews with clinicians, commissioners and patients.

• Patient and public focus

• Questionnaire return.

• Roundtable workshops.

• Health economic analysis data collection.

## 15.2 ANNUAL PROGRESS REPORTS (APRs)

The Chief Investigator will prepare the APR in accordance with the RFL R&D Office’s SOP 056 ‘Annual Progress Reports’. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

## 15.3 PROTOCOL COMPLIANCE

Any Protocol Deviations, Violations will be documented using the deviation reporting form (RFLRDDOC0006), and entered onto the Sponsor’s deviation log (RFLRDLOG0005) and processed according to R&D OFFICE SOP 032

The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a violation of the protocol or a breach of Data protection.

# FINANCE

This study is funded by a grant from the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) scheme (NIHR200536).

# PEER REVIEW

This protocol has been peer reviewed in accordance with the Sponsor’s SOP on Peer Review (SOP 055)

# PUBLIC AND PARTICIPANT INVOLVMENT

A patient and public representative was involved in the design of this research and will be involved in the management of the research, help with interpretation of results, design the next study, and dissemination of findings.

# INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

# IP AND DEVELOPMENT POLICY

Unless otherwise specified in agreements, the following guidelines shall apply: All Intellectual Property Rights and Know How (IP) related to the Protocol and the Trial are and shall remain the property of the Sponsor excluding

1) Pre-existing IP related to clinical procedures of any Hospital.

2) Pre-existing IP related to analytical procedures of any external laboratory.

All contributors

shall assign their its rights in relation to all Intellectual Property Rights and in all Know How, not excluded above to the Sponsor and at the request and expense of the Sponsor, shall execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake treat such Know How as confidential information jointly owned between it and the Sponsor

Nothing in this section shall be construed so as to prevent or hinder a medical professional from using Know How gained during the performance of the Trial in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.

# PUBLICATION AND DISSEMINATION POLICY

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

## BEFORE THE OFFICAL COMPLETION OF THE TRIAL

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the **Funder** shall have the final say.

## UP TO 180 DAYS AFTER THE OFFICAL COMPLETION OF THE TRIAL

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

* The Chief Investigator shall be senior and corresponding author of the Main Publication.
* Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
* Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
* Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
* If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

## BEYOND 180 DAYS AFTER THE OFFICIAL COMPLETION OF THE TRIAL

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor’s reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

# 21.0 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, Sponsor’s Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC (if applicable) and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC

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# APPENDICIES

# Appendix 1 – Amendment History

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
|  |  |  |  |  |

# Appendix 2 – Topic guide for interviews (patient version)

1. **Introduction**

Aim: To introduce the study and establish informed consent.

* Introduce self and background to study;
* Explain the study and its rationale;
* Run through ethical issues: confidentiality, data protection, audio recording, presentation of final findings.

1. **Understanding of renal tumour biopsy**

Aim: To identify patients’ understanding of RTB, its purpose and implications

* Identify whether the patient had RTB as part of their management
* Describe patients’ understanding of RTB and its purpose;
* Explore patients’ understanding of the circumstances in which RTB is used.

1. **Perceived benefits to undertaking RTB**

Aim: To identify patients’ perceptions regarding the potential benefits of RTB

* Determine patients’ willingness to undergo RTB, and preference for screening;
* Appraise factors that influence patient’s willingness to undergo RTB;

1. **Perceived barriers to undertaking RTB**

Aim: To identify patients’ concerns regarding RTB

* Define potential barriers (psychological, practical or other) to undergoing RTB;
* Discuss how such concerns could be mitigated.

1. **Conclusion**

Aim: To summarise and conclude the interview.

* Summarise the content of the interview;
* Check if participant has questions they felt should have been asked;
* Close.

# Appendix 3 – Topic guide for interviews (healthcare professional version)

1. **Introduction**

Aim: To introduce the study and establish informed consent.

* Introduce self and background to study;
* Explain the study and its rationale;
* Run through ethical issues: confidentiality, data protection, audio recording, presentation of final findings.

1. **Experience of RTB**

Aim: To identify professionals’ understanding of RTB, its purpose and implications

* Describe professionals’ experiences of conducting RTB;
* Determine professionals’ current frequency of conducting RTB;
* Explore professionals’ understanding of the circumstances in which RTB is used.

1. **Perceived benefits to conducting RTB**

Aim: To identify professionals’ perceptions regarding the potential benefits of RTB

* Determine professional’s current willingness to conduct RTB;
* Appraise positive factors that influence patient’s willingness to conduct RTB;

1. **Perceived barriers to conducting RTB**

Aim: To identify professionals’ concerns regarding RTB

* Define potential barriers (psychological, structural NHS, practical, costs or other) to conducting RTB;
* Discuss how such concerns could be mitigated

1. **Conclusion**

Aim: To summarise and conclude the interview.

* Summarise the content of the interview;
* Check if participant has questions they felt should have been asked;
* Close.

# Appendix 4 – Topic guide for interviews (service commissioner version)

1. **Introduction**

Aim: To introduce the study and establish informed consent.

* Introduce self and background to study;
* Explain the study and its rationale;
* Run through ethical issues: confidentiality, data protection, audio recording, presentation of final findings.

1. **Understanding of RTB**

Aim: To identify service commissioners’ understanding of RTB, its purpose and implications

* Describe service commissioners’ awareness of RTB and its purpose;
* Explore their understanding of workflow of RTB (ie, who is involved, departments etc).

1. **Perceived benefits to implementing RTB**

Aim: To identify service commissioners’ perceptions regarding the potential benefits of RTB

* Determine their current willingness to implement RTB;
* Appraise positive benefits of implementing RTB (ie. cost efficiency, perceived efficacy);

1. **Perceived barriers to implementing RTB**

Aim: To identify service commissioners’ concerns regarding impact of implementing RTB

* Define potential barriers (psychological, structural NHS, workload/time, costs, delays or other) to implementing RTB;
* Discuss how such concerns could be mitigated, and what elements would be required for it to be implemented successfully (ie. clinician-driven business case vs change in national guidelines)

1. **Conclusion**

Aim: To summarise and conclude the interview.

* Summarise the content of the interview;
* Check if participant has questions they felt should have been asked;
* Close.

# Appendix 5 – Data collected from participants

**Demographic details**

Hospital/Organisation ID:

Participant ID:

Participant details: Patient

Clinician: Urologist/ Radiologist/ Pathologist/ Specialist Nurse

Service manager/Commissioner

Name:

DOB:

Sex:

Ethnicity:

**Patient specific details**

Previous treatment for kidney tumour?

Currently receiving treatment for kidney tumour?

Offered biopsy?

Received biopsy?

Declined biopsy?

Tumour: Cancer/Benign

Definitive treatment: Surgery: partial / radical nephrectomy

Ablation: Cryotherapy/ Radiofrequency ablation/ other

Active surveillance

Discharge

Other

If patient had received biopsy – did it change their management?