SURAB Study- A randomised study comparing ABlation with active SURveillance, in the management of incidentally diagnosed small renal tumours: a feasibility study

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1. Protocol contacts

Chief Investigator:

*Mr Naeem Soomro
Department of Urology,
Freeman Hospital,
Freeman Road,
Newcastle upon Tyne
NE7 7DN
Phone: 0191 213 7597
Email: Naeem.Soomro@nuth.nhs.uk

Study Co-Applicants:

Dr David J. Breen MRCP FRCR
University Hospital of Southampton
Southampton
SO16 6YD
Phone: 0238 079 4709
Email: David.Breen@uhs.nhs.uk

Mr Michael Aitchison
Consultant Urologist
Gartnavel General Hospital
1053 Great Western Road
Glasgow, G12 0YN
Email: michael.aitchison@nhs.net

Dr Tze Wah
Diagnostic and Interventional Radiology
St James's University Hospital
Beckett Street, Leeds
LS9 7TF
Phone: 0113 2066043
Email: Tze.wah@leedsth.nhs.uk

Dr Philip Haslam
Consultant Radiologist
Freeman Hospital
Freeman Road
Newcastle upon Tyne, NE7 7DN
Phone: 0191 2231120
Email: Philip.Haslam@nuth.nhs.uk

Mr Mark Sullivan
Consultant Urologist & Honorary Senior Lecturer
Churchill Hospital
Old Road, Headington
Oxford
OX3 7LE
Phone: 01865 226145
Email: sullyme@hotmail.com

Mr Tim O'Brien
Consultant Urologist
Guy's Hospital
Great Maze Pont
London
SE1 9RT
Phone: 020 7188 7338
Email: tim.obrien@gstt.nhs.uk

Prof Stewart Fleming
Professor of Histopathology
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Phone: 01382 496488
Email: s.fleming@dundee.ac.uk

Mr Frank Keeley
Consultant Urologist
Southmead Hospital,
Westbury-on-Trym, Bristol
BS10 5NB
Phone: 0117 323 5690
Email: francis.keeley@nbt.nhs.uk

Statistician (& Co-applicant):
*Dr Ian Nicholas Steen
Institute of Health and Society
Newcastle University
Baddiley-Clark Building
Richardson Road
Newcastle upon Tyne, NE2 4AX, UK
Phone: 0191 222 7045
E-mail: nick.steen@ncl.ac.uk

Qualitative Researcher (& Co-applicant):
*Jan Lecouturier
Institute of Health & Society
Newcastle University
Baddiley-Clark Building
Richardson Road
Newcastle upon Tyne, NE2 4AX
Phone: 0191 222 5629
Email: jan.lecouturier@ncl.ac.uk

Health Economist (& Co-applicant):
*Dr Jing Shen
Institute of Health and Society
Newcastle University
Baddiley-Clark Building
Richardson Road
Newcastle upon Tyne, NE2 4AX, UK
Phone: 0191 208 7905
Email: jing.shen@ncl.ac.uk

Contacts at Newcastle Clinical Trials Unit:

Senior Trial Manager:
*Claire Macdonald
Institute of Health & Society
Newcastle Clinical Trials Unit
Newcastle University
1-2 Claremont Terrace
Newcastle upon Tyne, NE2 4AE
Phone: 0191 208 3825
E-mail: claire.macdonald@ncl.ac.uk

Trial Manager:
*Josh Wood
Institute of Health & Society
Newcastle Clinical Trials Unit
1–2 Claremont Terrace
Newcastle University
Newcastle upon Tyne
NE2 4HH
Phone: 0191 2088211
E-mail: josh.wood@ncl.ac.uk

Assistant Trial Manager:
*Ann Marie Hynes
Institute of Health & Society
Newcastle Clinical Trials Unit
1–2 Claremont Terrace
Newcastle University
Newcastle upon Tyne
NE2 4HH
E-mail: ann.hynes@newcastle.ac.uk

*These individuals are members of the trial management group (TMG)

Independent Trial Steering Committee Members:

Chairman:
Professor John Kelly
Professor of Uro-oncology
Translational Uro-Oncology Group
4th Floor, Division of Surgery & Interventional Science
74 Huntley Street
London
WC1E 6AU
E-mail: j.d.kelly@ucl.ac.uk

Independent statistician:
Caroline Bray
Senior Statistician
Cancer Research UK Clinical Trials Unit, Glasgow
(partner in CaCTUS - Cancer Clinical Trials Unit Scotland)
The Beatson West of Scotland Cancer Centre
Level 0
1053 Great Western Road
Glasgow
G12 0YN
Phone: 0141 301 7190
E-mail: Caroline.Bray@glasgow.ac.uk

Independent Clinician
Mr Grant D Stewart
Clinical Senior Lecturer and Honorary Consultant in Urological Surgery
University of Edinburgh
Department of Urology
Western General Hospital
Crewe Road South
Edinburgh
EH4 2XU
Phone: 0131 537 3223
E-mail: grant.stewart@ed.ac.uk

Mr Pat Hanlon
Patient Representative
Senior lecturer
School of Business University of Birmingham
B15 2TY
Email: J.P.HANLON@bham.ac.uk

Mrs Rose Woodward
Lay member
Kidney Cancer Support Network
C/O The Bungalow

West Cliff
Porthtowan
Nr. Truro
Cornwall
TR4 8AE
Phone: 01209 891 307
Email: rose.woodward@btinternet.com

Independent Data Monitoring Committee Members:

Chairman
Professor Sam McClinton
NHS Grampian Department of Urology
Ward 209
Aberdeen Royal Infirmary
Foresterhill
Abderdeen
AB25 2ZB
Phone: 01224 550517
Email: smcclinton@nhs.net

Independent statistician
Dr Robert Hills
Reader in Translational Statistics
Head HCTU
Department of Haematology
Cardiff University School of Medicine
Heath Park
Cardiff Cf14 4XN
Phone: 029 20744647
Email: HillsRK@cardiff.ac.uk

Independent Clinician
Neil Burgess
Dept of Urology
Norfolk and Norwich University Hospital NHS Trust
Colney lane
Norwich

Norfolk
NR4 7UY
Phone: 01603 286777
Email: neil.burgess@nnuh.nhs.uk

2. Protocol signature page

2.1 Protocol authorisation signatories

Signature …… Date ……

Mr Naeem Soomro, Chief Investigator

Signature …… Date ……

Dr Ian Nicholas Steen, Statistician

Signature …… Date ……

Claire Macdonald, Senior Trial Manager

2.2 Principal/Chief Investigator signature

I confirm that I have read and understood protocol version 4.0 dated 20 February 2015. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date ……

Print Name ……

Site Name/I.D.……

3. Contents Page

4. Glossary of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ASA	American Society of Anesthesiologists
BAUS	British Association of Urological Surgeons
CI	Chief Investigator
CRA/CRYO	Cryoablation
eCRF	Electronic Case Report Form
CSP	Coordinated System for gaining NHS Permission
CT	Computerised tomography
CTA	Clinical Trial Agreement
DMC	Data Monitoring Committee
eGFR	Estimated Glomerular filtration rate
FACT-G	Functional Assessment of Cancer Therapy - General
FBC	Full Blood Count
GCP	Good Clinical Practice
LPN	Laparoscopic
MDRD	Modification of diet in renal disease
MDT	Multi-Disciplinary Team
MRI	Magnetic resonance imaging
MWA	Microwave ablation
NCRI	National Cancer Research Institute
NCTU	Newcastle Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR-HTA	National Institute for Health Research Health Technology Assessment
OPN	Open partial nephrectomy

PCQ	Participant costs questionnaire
PI	Principal Investigator
QOL	Quality of Life
RCC	Renal cell cancer
REC	Research Ethics Committee
RFA	Radio frequency ablation
SAE	Serious Adverse Event
SF-36	Short Form (36) Health Survey
SRM	Small renal mass
STAI	State-Trait Anxiety Inventory
TMG	Trial Management Group
TSC	Trial Steering Committee
US(S)	Ultrasound (scan)
U & E	Urea & Electrolytes

5. Responsibilities

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study.

Funder: The UK NIHR HTA Programme is funding this study. Contact at NIHR HTA: Alexa Cross, Programme Manager, Direct Line: 02380595594. E-Mail: A.Cross@southampton.ac.uk

Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trials Unit.

Principal Investigator: The Principal Investigator will have overall responsibility for the conduct of the study at a particular trial site.

Trial Management:

The following functions falling under the responsibility of the sponsor will be delegated to Mr Naeem Soomro [Chief Investigator]:

- Authorisation and Ethics Committee Opinion (including CTA request, research ethics committee opinion, notification of protocol amendments and end of trial, site specific assessment & local approval)
- R&D Approval (including application for global checks, via NIHR CSP)
- Good Clinical Practice and Trial Conduct (including GCP arrangements, data monitoring, emergency & safety procedures)
- Safety (including ensuring SAEs are reviewed by an appropriate committee for safety monitoring, annual listings and safety report).
- Administration of funding for the study

Trial conduct at site:

Investigator responsibilities:

- Study conduct and the welfare of study subjects.
- Familiarity with the study intervention(s).
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events.
- Screening and recruitment of subjects.
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event.
- Obtaining local approval and abiding by the policies of Research Governance
    - Assistance will be provided by Josh Wood(Trial Manager) and trial management colleagues in Newcastle Clinical Trials Unit (NCTU).
- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, the Data Protection Act and any other relevant legislation and regulatory guidance.

- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- The Principal Investigator (PI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed & dated curriculum vitae as evidence for the Trial Master File.
- Ensuring Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintaining study documentation and compliance with reporting requests.
- Maintaining a site file, including copies of study approval, list of subjects and their signed informed consent forms.
- Documenting appropriate delegation of tasks to other study personnel e.g. Research Nurse, Co-Investigator(s), Trial Coordinators, Data Managers.
- Ensuring data collected is accurate, timely & complete.
- Providing updates on the progress of the trial.
- Ensuring subject confidentiality is maintained during the project and archival period.
- Ensuring archival of study documentation for a minimum of 15 years following the end of the study, unless local arrangements require a longer period.

6. Protocol Summary

Full Title:	SURAB Study: A randomised study comparing ABlation with active SURveillance, in the management of incidentally diagnosed small renal tumours: a feasibility study
Short title:	SURAB
Protocol version:	4.0
Protocol date:	20 February 2015
Chief Investigator:	Mr Naeem Soomro
Sponsor:	Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	UK NIHR-HTA
Study design:	Multicentre randomised controlled feasibility trial
Study Intervention:	Participants will be randomised on a 1:1 ratio (stratified by centre) to either active surveillance or ablative treatment. Currently, centres have tended to develop expertise in either cryotherapy or radiofrequency ablation; centres will therefore offer only one form of ablation (the one in which they have expertise). There will also be an opportunity for departments which offer microwave ablation to participate in the trial.
Primary objective:	The aim of this study is to establish whether a future definitive trial comparing active surveillance with ablative treatment for small kidney cancer is feasible.
Secondary objective:	We will rehearse the procedures for assessment of complete ablation of tumour at six months. Secondary outcomes include: persistence of cancer at six months post treatment, assessed via CT scan, plus a biopsy performed under local anaesthetic (in the ablative group); complications of treatment; a general health questionnaire (SF-36); cancer specific health status and quality of life (FACT-G); state-trait anxiety inventory (STAI). We will also develop and test health economics data collection tools and assess the ease of data collection required for health economic analysis to inform the full economics evaluation in a definitive trial.
Primary outcome:	This will be assessed quantitatively in terms of recruitment and retention rates and qualitatively in terms of the barriers and facilitators to participation from the perspectives of patients and recruiting clinicians.
Number of study sites:	Up to 8 UK sites
Study population/size:	We aim to recruit a total of 60 patients (30 to the surveillance arm; 30 to the ablation arm).
Study duration:	34 Months (expected end date 31st October 2016) Outcome data collection will be timed to coincide with routine clinical assessments and will be collected from

patients at 4 and 7 months post randomisation (3, 6 months post treatment).

7. Background

Importance of the health problem to the NHS:

Kidney cancer accounts for 3% of new cancers and 2% of cancer related deaths making it the eighth most common cancer in UK. In UK in 2008, 8757 new cases of kidney cancers were diagnosed, approximately two thirds of these were < 4 cm and 3,848 patients died of kidney cancer.[1-4] SEER's data shows that 65,150 patients were diagnosed and 13,680 patients died of renal cancer in USA in 2013[5].

The treatment of small renal masses (SRM) < 4 cm is evolving, 80% of these are malignant. The standard treatment in the past had been radical nephrectomy. It is now accepted the nephron sparing techniques have similar oncological outcomes but have additional benefit of preserving kidney function.[6] Among these techniques partial nephrectomy has emerged as the preferred treatment of SRM, as it effectively treats the cancer, broadly preserving the kidney function (dependent on ischaemic time) and has good long term oncological safety.[7] It is however associated with post-operative morbidity, long hospital stay and recovery. For these and other factors such as lack of surgical skills and patient's co morbidities, it still remains under-utilised. Ablative techniques such as cryoablation and radiofrequency ablation (RFA) are also being increasingly used in patients with SRM. These are particularly attractive as the mean age of diagnosis of renal cancer is 64 and the procedure incurs significantly less complications, inpatient bed stay and is associated with early recovery.[8]

However ablation still represents an invasive procedure with consumables costs particularly in the case of cryoablation. There are also concerns with ablative techniques about the possible persistence of microscopic cancer and a slightly higher chance of persistence of tumour perhaps necessitating secondary treatment. This leads to increased patient anxiety and additional cost for the providers. In view of these factors and because current evidence is based mainly on single centre series[9,10] and a few meta-analyses[11,12] there is uncertainty about best treatment of SRM. Minimally invasive ablation for small renal tumours (<4cm) clearly makes available a new treatment option but robust data comparing relative effectiveness and cost effectiveness of active surveillance with ablative techniques (CRYO/ RFA) is currently not available. A randomised controlled trial to answer this question has been identified as a priority by the renal cancer sub group of national cancer research institute (NCRI) and has the support of BAUS section of oncology and local NIHR clinical research network. As there remains uncertainty as to the willingness of patients and surgeons for randomisation to this trial, and whether recruitment and retention would be adequate, a rehearsal pilot, addressing the feasibility of a definitive randomised controlled trial is required.

Summary of the current evidence:

The natural history of small renal tumours remains unclear, almost 66% of newly diagnosed renal cancers are <4 cm.[13] A meta-analysis has shown that majority of small lesions have a slow growth rate (mean rate, 0.28 cm per year) and they rarely metastasize while under surveillance.[14] Partial nephrectomy has become accepted as a standard of care for SRM when a series of 485 patients was reported over 10 years , which showed a cancer free survival for renal tumours of < 4cm for five and 10 years was 96 % and 90 % respectively.[15] The local tumour recurrence was 3.5%. Similar results were reported in a meta-analysis looking at a series of partial nephrectomy from 1980-2000[16]. A study which compared 100

cases of laparoscopic (LPN) with open partial nephrectomy (OPN) concluded that OPN remains the standard of care for SRM. Laparoscopic partial nephrectomy was associated with longer ischaemic time, major intraoperative complications and increased post operative urological complications[17]. However in experienced hands LPN has a comparable oncological efficacy and complication profile[18]. Despite this clear evidence favouring partial nephrectomy the BAUS cancer registry data showed that only 721 partial nephrectomy were performed in England and Wales in 2007/8, whereas approximately 2/3 patients with renal cancer < 4cm underwent radical nephrectomy. [19] This practice alone is contributing to the net population burden of significantly impaired renal function in a population that may already have other co morbidities such as obesity, hypertension and diabetes.

Radiofrequency ablation (RFA): Radiofrequency probes are applied into the renal tissue percutaneously under ultrasound, CT or MRI. There has been some concern that the thermal RF ablation zone might not be homogeneous[20] and there may be persistence of viable tumour which is not evident on routine radiological surveillance[21].This may be due to the method of tissue heating in RFA which is considerably reliant on conductive heating. A multi-institutional meta analysis of 1375 renal lesions treated by CRA and RFA, applied both percutaneously and laparoscopically, detailed 600 RFA outcomes at a mean follow-up duration of 15.8months.[22]Mean patient age was 67.8years and mean tumour size 2.69cm.This analysis yielded a combined subtotal treatment rate and (unexpected) local tumour progression rate of 12.9% with 8.5% undergoing repeat ablation for treatment completion. It was suggested that true disease persistence might only be determined by delayed post-ablation biopsy. NICE has accepted the broad efficacy of radiofrequency ablation but centres are still advised to audit results and outcomes carefully.[23]

Cryoablation (CRA): CRA can be performed percutaneously[24] under image-guidance or laparoscopically[25] by direct visualization. Again the meta-analysis by Kunkle and Uzzo[12] reviewed multi-institutional outcomes from cryoablation, with the majority performed in North American practice under laparoscopic guidance. 775 renal lesions were treated for a mean tumour size of 2,58mm and mean age of 66.3years. This yielded a combined subtotal and (unexpected) local tumour recurrence rate of 5.2% with only 1.3% undergoing repeat ablation largely due to the difficulties of a repeat laparoscopic procedure. In this meta-analysis the rate of progression to metastatic disease was similar to nephron sparing surgery, cryoablation and RFA. However in these series ablative techniques were selected in older patients with small tumours, where partial nephrectomy was undertaken in younger patients with larger tumours and had longer post treatment surveillance. NICE has accepted the broad efficacy of cryoablation but centres are still advised to audit results and outcomes carefully.[26,27]

A case for active surveillance

Active surveillance studies have reported on small series of patients, showing varying growth rates ranging from 0.09cm/year to 0.86cm/year, with most concluding that small renal masses grow slowly with a low rate of progression.[13,14,28-33] The rate of metastatic disease is low, between 1% to 7%, with varying lengths of follow up.[14,34,35] In most cases with metastatic disease the primary tumour had grown to greater than 4cm in diameter.[34] It has also been demonstrated that larger renal cell cancers (RCCs) are significantly associated with higher histological grade, advanced stage and distant metastases, with the significant size cut-off between 3cm and 5cm.[36,37] This has resulted in the current opinion that small RCCs may grow slowly but then become more aggressive at a size threshold of approximately 4 cm.

However some small RCCs metastasize when they are less than 4cm in size and this has led some authors to question the safety of an active surveillance approach.[35,38] Presently it is not possible to identify these aggressive tumours on standard radiological characteristics alone.

Currently a strategy of active surveillance, or watchful waiting, is adopted in cases where the peri-operative risks are deemed too high, or where an informed choice is made after balancing the potential risks and benefits of surgery.

Many small RCCs have a slow or immeasurable growth rate; as such these cancers may not lead to symptoms or metastatic disease within the lifetime of the patient.

Whilst many small RCCs are indolent, there is significant uncertainty as to which small tumours will behave in a benign fashion and which are more likely to progress and metastasize. A reliable means to predict the behaviour of these small RCCs might enable early definitive treatment, for those that are likely to progress or metastasize early, and avoid unnecessary procedures, along with the associated morbidity and costs, for those patients with slow or non-growing RCCs that are unlikely to progress within the lifetime of the patient.

At present, the main prognostic factor available is tumour size. This is most commonly measured on CT scan, with follow up CT scan performed to identify an increase in tumour size. A systematic schedule of serial CT scans allows growth and any acceleration in growth to be identified, which might suggest tumour progression and likely metastasis.

Most of the masses will be discovered incidentally on CT and ultrasound (US). Critically the technique for follow up must be able to detect significant increases in renal mass size and provide minimal inter-observer and intra-observer variability. US cannot provide reliable measurement sequentially, and either CT or MRI is ideally required.

The literature to date from one randomised controlled study and several retrospective studies suggests active surveillance may be an initial option for management of small renal tumours in healthy individuals with careful follow up.[13,14,28-34] Size progression of the tumour (>0.5cm/yr or above 3.5cm maximum diameter) (approximately 25% of patients) whilst on surveillance may identify a more precise cohort who will actually require intervention.

This approach may produce substantial benefits in terms of reduced morbidity, reduced overall mortality and long-term quality of life and these may outweigh the small risk of metastatic disease in patients equal to or over 70 years old. This is however predicated on the relative morbidity of ablation and surgery.

Need for research

NICE has published its guidance on cryoablation and RFA and has stated that both are effective in ablating cancer tissues and are safe. However evidence about long term cancer control and survival using these techniques is not adequate. These have been based on single institution case series.[9,10,24] Because of these deficiencies it was suggested that there was a need for a long term prospective randomized trial to determine the proper application for these treatments for SRMs.

8. Objectives

The overall aim of this study is to determine the feasibility of a definitive randomised control trial to compare active surveillance with ablation in the management of small renal tumours.

Pilot feasibility trial with parallel qualitative component objectives:

- Test patient information to gauge comprehensibility and whether information perceived to be important for study participants is included.
- Quantify the number of patients eligible.
- Test patient identification system and randomisation.

- Test appropriateness and feasibility of outcome measures.
- Assess factors which promote or inhibit recruitment and retention in the trial.
- Assess potential bias in recruitment and retention, systematic differences between those eligible to be randomised and those eligible but unwilling either by the clinician or the patient.
- Examine the mechanism of data collection and assess the completion rates of data collection instruments to inform the full trial.

9. Study Design

This is a multi-centre two arm trial which will evaluate the relative effectiveness between ablation and active surveillance in patients with small renal cancer (<4cm).

This is a pilot study and is not expected to produce definitive results but should provide a basis for planning a larger definitive trial on this topic.

9.1 Primary outcome measures:

The aim is to establish whether a future definitive trial comparing active surveillance with ablative treatment for small kidney cancer is feasible.

This will be assessed quantitatively in terms of recruitment and retention rates and qualitatively in terms of the patients' experiences and understanding of the randomisation process and treatment options.

Partition of reasons for loss to follow up, together with clinical data, will allow us to project likely retention at 5 years.

9.2 Secondary outcome measures:

All secondary outcomes will be rehearsed during the pilot trial with a view to refining the choice of outcomes for the main trial, based on data yield and quality.

Outcome data collection in the pilot feasibility trial will be timed to coincide with routine clinical assessments and will collected from patients at 4,7 months post randomisation (3, 6 months post treatment).

The following secondary outcome questionnaires will be completed at baseline and at 3 and 6 months post treatment:

- a general health questionnaire (SF-36)
- cancer specific health status and quality of life (FACT-G)
- anxiety and depression (STAI)

We will also develop and test health economics data collection tools in the form of a participant costs questionnaire (PCQ). The PCQ has two parts: Part A to be administered at 3 month and 6 month and Part B at 6 month only.

9.3 Definition of end of study:

The end of study will be the last participant's final study contact, at their 6 month post treatment follow up.

10. Participants

Participants will be patients with renal cancer masses <4cm.

10.1 Inclusion criteria

- Adult diagnosed with renal cancer < 4 cm (confirmation by radiology* or by biopsy**)
- Age ≥18 years of age
- CT/MRI abdomen/chest with no evidence of metastases
- Patient has provided written informed consent prior to any study specific procedures

*Radiological confirmation requires noting an enhancing renal mass of >20 Hounsfield units.

**At some centres a routine diagnostic biopsy is not performed as standard care. At these centres, consent to the study must be taken with a biopsy performed POST consent but PRIOR to randomisation. Should this biopsy show that the growth is non-cancerous, the participant should be withdrawn from the study.

10.2 Exclusion criteria

- Patients clinician does not feel would be suitable for the trial (eg due to concomitant disease).
- Multiple small renal cancers in one kidney.
- Coagulopathy that cannot be corrected.
- Previous participation in this study
- Inability to give informed consent; carer/proxy consent will not be allowed in this study.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS MUST NOT BE USED.

11. Screening, Recruitment and Consent

11.1 Identification and recruitment of patients for testing of pilot trial information

To ensure information is clear to patients in the pilot feasibility trial and contains what they require, we will test information with patients who have been newly diagnosed with a small renal tumour and those who have recently received treatment (including those under surveillance). We will also explore their views on the proposed trial and trial processes.

Before the beginning of formal recruitment into the pilot feasibility trial clinicians from a centre in the North East will identify eligible patients. These patients will be approached by a renal cancer nurse specialist who will provide them with written information and ask for their permission to pass their contact details on to the SURAB team. These patients will then be contacted by the qualitative researcher who will answer any questions they may have and, if they are happy to participate, arrange a convenient time to conduct an interview. Consent will be obtained prior to the interview.

11.2 Identification and screening of patients for the pilot feasibility trial and parallel qualitative component

- Potential participants will be identified in the renal cancer clinics at participating sites. Site PIs and/or clinical colleagues with documented delegated responsibilities for patient identification and screening will perform this task.
- An eligibility screening log will be completed by the investigator to document participants' fulfilment of the entry criteria for all patients considered for the study and parallel qualitative component and subsequently included or excluded. This information will be anonymised and transcribed onto screening logs which will be on-going basis via a secure on-line database.

11.3 Recruitment procedures for the pilot feasibility trial and parallel qualitative component (only applicable to sites in the North East)

- Eligible patients will be contacted by the centre PI / nurse lead / nurse specialist to invite them to participate in the trial and parallel qualitative component.
- Informed consent discussions will be undertaken by appropriate site staff as per the site delegation log. The delegated staff member (usually the centre nurse lead/specialist/PI) will explain the trial and parallel qualitative component to the patient, give them the information leaflet and answer any questions they may have.
- The patient will be encouraged to take the information leaflet home and discuss it with family and friends and arrange a suitable time for a second meeting (allow at least 24 hours for this). However, in some instances where participants have travelled a long distance to the hospital and are not returning until an intervention visit and for whom returning to hospital for the consent process would be a burden, consent can be taken on the same day as information provision. In this instance, participants MUST receive a phone call from the local study team 48 hours later to confirm that they still wish to take part. This conversation must be documented in the patients medical notes.
- For subjects who decline participation in the trial and/or qualitative component, the study team should (with permission from the patient) document any reasons available for non-participation in the eligibility screening form and transfer this to the anonymised site screening log. The screening forms and logs will ensure potential participants are only approached once.

- After the delegated research team member for taking consent has ensured that the patient has understood the information, he/she would be asked to sign and date the consent form agreeing to participate in the pilot feasibility trial and/or the parallel qualitative component*. Consent by the patient will be witnessed and dated by the delegated research team member taking consent.
- Written informed consent should always be performed before randomisation or any other study specific procedures/investigations.
- The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes, a copy faxed to Newcastle Clinical Trials Unit (for centralised monitoring) and a copy provided to the participant.

*The main consent form for the pilot feasibility trial is worded so that patients can indicate whether they wish to be included in the pilot feasibility trial and/or have their contact details forwarded to the qualitative researcher so that they can be approached to discuss participation (interview) in the parallel qualitative component. This is because we would like to interview a small number of trial participants as well as those who decline to be randomised and those who withdraw from the study, about their views on this research. The consent form requires that patients indicate that they understand that they do not have to give reasons for withdrawal unless they are happy to discuss these. Patients will specifically consent to their GPs being informed of their participation in the pilot feasibility trial**.**

For patients who agree to be interviewed a different consent form will be completed at the time of the interview.

Due to the small subject population, the information sheet and consent forms will be available only in English.

12. Pilot Feasibility Study Interventions

12.1 Interventions being assessed

Patients recruited to the pilot feasibility trial who agree to be randomised to either ablation or active surveillance will undergo routine biopsy of the renal tumour to confirm that it is a cancerous growth. At centres where this biopsy is not routine, the participant must consent to the biopsy and the study prior to the biopsy being performed. Details of the biopsy can be seen in section 14.1.5 of the protocol.

Patients randomised to the ablation arm will undergo second compulsory biopsy six months after treatment. This will be conducted under ultrasound or CT guidance using local analgesia.

The ablation methods used will depend on what expertise is available at study sites. Sites will offer only one form of ablation. The permitted ablation methods will include Radiofrequency ablation (RFA), cryoablation (CRA) and microwave ablation (MWA).

The paragraphs below give more detail about the ablative procedures and active surveillance.

Radiofrequency ablation (RFA): Radiofrequency probes are carefully positioned into the renal mass lesion percutaneously by image guidance (usually using CT) and laparoscopically by direct vision.
RF probes deliver localized monopolar currents at 'radiofrequency' (400-500kHz) to generate frictional heating in the adjacent tissue. Through direct and conductive heating, this achieves temperatures of up to 105°C. Tissue destruction occurs by protein denaturation, cell destruction and coagulative necrosis in a sometimes ill-defined sphere around the probe tip. This ablation zone can be compromised by tissue perfusion-mediated cooling and larger adjacent flowing vessels but can usually achieve ablation zones of up to 4-5cm in diameter. Sometimes probes may be re-positioned to achieve the required ablation volume.

The procedure is well-tolerated but now more usually performed under general anaesthesia to achieve optimal probe positioning and outcomes. Where necessary, adjacent bowel or other structures are displaced by contrast-tinted 5% dextrose for retroperitoneal hydrodissection (however, carbon dioxide can also be used). Therapeutic outcomes are confirmed by contrast-enhanced CT or MR within 3 month post-ablation[40].

Cryoablation (CRA): Cryoprobes are applied laparoscopically or percutaneously by image guidance. Localised tip temperatures of –150°C and lower can be achieved by utilising the phase change of compressed argon gas delivered through multiple closed needle applicators, arranged in a format to create a confluent 'therapeutic' ice ball. Within the induced ice ball a range of tissue-lethal temperatures are achieved. At the -30°C isotherm a double freeze-thaw cycle is believed to yield uniform cell death. Tissue destruction is achieved through disruptive cell necrosis and microvascular injury.

Microwave ablation (MWA): Microwave ablation is very similar to RFA. A similar sized needle/probe is inserted into the lesion under imaging guidance exactly as for RFA. The microwave probe causes heating of the tissue by heating the water molecules within it achieving similar temperatures to RFA causing cell destruction and coagulative necrosis.

Active surveillance: Patients randomised to active surveillance will be put on the following schedule:

Urea and Electrolytes including eGFR (glomerular filtration rate), MDRD (Modification of Diet in Renal Disease) equation if performed clinically (there is no need to report this to the study team), and 6 month CT of the abdomen. Participants will undergo CT scan of the abdomen (phasing and sequencing details to be determined by site as per their local practice).

Tumour volume would be calculated from the 3-dimensional diameters using the formula to calculate an ellipsoid volume:

Volume = 0.5326 x (diameter 1) x (diameter 2) x (diameter 3)

If there is progression of the growth rate or the size of the tumour in patients on the active surveillance arm, ablation or partial nephrectomy will be offered depending on the facilities available in the participating centre.

Progression will be considered to have occurred when either

(i) Growth rate exceeds 2.5mm/six months

(ii) There is a doubling of tumour volume by 6 months

12.2 Routine imaging for monitoring disease progression and recurrence

All patients will also undertake Computerised Tomography (CT) scans to assess for disease progression and recurrence.

CT scans of the abdomen will take place within 3 and 6 months post-treatment for patients undergoing radiofrequency ablation, cryoablation or microwave ablation and at 6 months for patients having active surveillance. If sites happen to have any routine scan results available for active surveillance patients at 3 months post-randomisation then the study team would be interested in receiving these data – however, this is optional depending on local practice. Sites also have the flexibility to perform any other scans which are deemed clinically necessary/standard practice at site. The scan sequencing will be determined by the local site.

We would like a record of the number of scans performed by site clinically on each participant in addition to the 3 and 6 month scans reported for the study.

Magnetic Resonance Imaging (MRI) scans may be used as an alternative to CT scans if the normal practice within a site is to undertake MRI scans as part of routine clinical practice.

12.3 Qualitative Interviews in a sub-set of patients for the Parallel Qualitative Component

In parallel to the pilot feasibility trial, we will explore the barriers and facilitators to participation in the trial. We believe it is important to do so with patients approached to participate in a real rather than hypothetical trial since what people say they will do is often different to how they will react when faced with a real decision.

In terms assessing the feasibility of a future definitive trial we wish to interview a mix of patients taking part in this pilot feasibility trial in order to address and find solutions to issues around recruitment and retention. We will conduct in-depth face to face interviews with patients who:

- consent (5 in ablation and 5 in active surveillance group)
- decline (5)
- withdraw following randomisation (5)

In the interviews we will explore patients' views on: aspects of the informed consent process including method of approach, time to make a decision, the content and amount of written

and verbal trial information and their understanding of it and what was required of them in the trial; reasons they declined/agreed to participate; under what circumstances would they participate/not participate. We will not formally assess understanding but will ask patients what they believe to be the purpose of the trial, what the two 'treatment' arms involve, what are the risks and benefits and what is required of participants. From this we will be able to determine whether the verbal and written trial information is effective in informing patients and detect areas that need to be improved in any future trial.

With the group who do not decline or withdraw following randomisation we will also explore their experiences of participating in the trial, including their views on the arm they were randomised to, whether they underwent any further treatment and completion of the outcome measures (SF36, STAI, FACT-G). These interviews will be conducted after the final follow up (treatment plus 6 months). If possible we will also interview any patients who drop out of the trial between treatment and final follow up to explore their reasons for doing so.

12.4 Clinician Interviews for the Parallel Qualitative Component

We will interview clinicians about their views on:

- participating and recruiting to the trial
- the trial patient information
- instances where they were unwilling or unhappy to recruit certain eligible patients to the trial
- explore why and whether they consider there has been a change in their clinical equipoise from first agreeing to be part of the trial to the point where they were recruiting patients.

During the set up phase we will consult with clinicians participating in the pilot trial about how best to capture cases where they were unwilling to recruit; for example whether it would be appropriate for them to briefly document these cases which can then be referred to during their interviews.

Wherever possible we will conduct face to face interviews with clinicians but envisage some may have to be carried out over the telephone in some sites or if it is difficult for them to find the time to meet with the researcher.

13. Randomisation and Blinding

13.1 Randomisation

When all eligibility checks have been made and written informed consent has been given, participants in the pilot feasibility trial will be randomised on a 1:1 ratio (stratified by centre) to either active surveillance or ablative treatment (radio frequency ablation or cryotherapy ablation or microwave ablation). The exact nature of ablation (RFA or CRA or MWA) would depend on the equipment and expertise available in the participating centre; currently, centres have tended to develop expertise in either cryotherapy, microwave or radiofrequency ablation; centres will therefore offer only one form of ablation (the one in which they have expertise).

Randomisation will be undertaken using the central web based randomisation service available in the Newcastle Clinical Trials Unit. The PI at site, or individual with delegate authority, will access the web-based randomisation system. Patient screening ID, initials and centre (the stratifying variable) will be entered into the web-based system, which will return the allocation status (successful randomisation will be followed up by an automated confirmatory email to the site and relevant Newcastle Clinical Trials Unit staff).

Participants will then be informed of their allocated treatment group by the site PI or delegated individual following randomisation.

Following allocation the site will

1. Organise procedure date for those allocated for ablative treatment
2. Organise active surveillance protocol for those allocated to active surveillance arm

Contact details for Randomisation:

Randomisation service website: http://apps.ncl.ac.uk/random/

(Available 24 hours a day)

Queries about the randomisation system can also be addressed to:

nctu-enquiries@newcastle.ac.uk (normal office hours)

13.2 Blinding

This is a feasibility study with primary outcome listed as recruitment and retention rates and qualitatively in terms of the patients' experiences and understanding of the randomisation process and treatment options. Due to this, it will not be necessary to blind staff to the treatment allocated to patients for the follow up assessments.

The baseline data capture assessments will however be completed by research nurses before randomisation in order to reduce any bias in terms of patient attitude to allocated treatment affecting baseline data.

14. Study Data

14.1 Patient Assessments / Data Collection

14.1.1 Screening and Baseline visit (for all participants)

Pre-Screening & Screening

- PIS provided
- Eligibility criteria checked

Baseline

Written informed consent will be taken. If not already done, arrangements will then be made for a biopsy procedure to take place before randomisation is performed.

The baseline visit will involve collection and retrospective collation of the following data:

- Demographics (age, gender)
- Medical history
- Blood test and urinalysis will be taken as per local policy. There is no requirement to report these to the study team or record them on the study eCRF.
- SF-36
- STAI
- FACT-G
- Biopsy results are to be recorded in the baseline eCRF – to document relevant details and presence of cancerous growth. If a routine diagnostic biopsy is NOT standard care at site, consent for the biopsy and the study MUST be given prior to the biopsy procedure.
- Tumour size and volume are to be recorded from routine CT/MRI imaging already obtained during diagnosis of tumour. Size is to be recorded in 3 planes of measurement. Size is to be recorded in 3 planes of measurement. Volume = 0.5326 x (diameter 1) x (diameter 2) x (diameter 3). The volume calculation is not to be completed by site.
- Confirmation must be recorded in the eCRF that study inclusion criteria are fulfilled and no exclusion criteria apply.

Randomisation should occur <u>after</u> the baseline visit and after review of biopsy results and checking of inclusion/exclusion criteria. Randomisation should not occur if the biopsy shows a non-cancerous result.

14.1.2 Treatment (for participants randomised to Ablation)

Our expectation would be that ablative treatment will be ideally provided within 1 month of randomisation (+/-14 days) or as per standard national NHS protocols.

The following data will be copied into the study eCRFs from NHS medical records in relation to the provision of ablative treatment:

- Type of ablative treatment provided and date/time.
- Whether the treatment was provided as per the randomisation allocation.

- Any reason(s) for not providing treatment as per the randomisation allocation.
- Any alternative treatments provided (eg. surgical excision as an alternative).
- Complications of treatment and adverse events will be recorded.

14.1.3 Three Month Follow up (for all participants)

The three month follow up will take place at 3 months (+/-14days) after the treatment date for patients in the ablation arm.

The three month follow up will take place at 3 months post randomisation (+/-14days) in the active surveillance arm.

At the 3 month, follow up the following will be administered to all patients:

- Blood test and urinalysis will be taken as per local policy. There is no requirement to report these to the study team or record them on the study eCRF.

- SF-36
- STAI
- FACT-G

Imaging results will need to be obtained in order to document any changes in tumour progression as follows:

- For patients receiving ablation (using any of the methods) data is to be captured from a routine CT/MRI scan of the abdomen performed within 3 months of the ablative procedure
- For patients receiving active surveillance: a 3 month post randomisation scan of the abdomen is optional depending on routine practice at site.

The imaging will allow capture of the following data on the CRF:

- Tumour size and volume. Size is to be recorded in 3 planes of measurement. Size is to be recorded in 3 planes of measurement. Volume = 0.5326 x (diameter 1) x (diameter 2) x (diameter 3). The volume calculation is not to be completed by site.
- Confirmation of any progression of the tumour.

The following additional data will also be captured for all patients:

- Any changes in treatment plan (eg switching from active surveillance to ablation or surgical excision). Dates and times and types of procedures to be recorded. Reasons for a switch in treatment (i.e. reason for cross-over).
- Complications of treatment and adverse events will be recorded
- Administration of health economics questionnaire: PCQ (Part A)

14.1.4 Six Month Follow up (for all participants)

The six month follow up will take place at 6 months +/- 14days after the treatment date for patients in the ablation arm.

The six month follow up will take place at 6 months post randomisation +/- 14days in the active surveillance arm.

At the 6 month follow up the following will be administered to all patients:

- Blood test and urinalysis will be taken as per local policy. There is no requirement to report these to the study team or record them on the study eCRF.
- SF-36
- STAI
- FACT-G

For patients receiving active surveillance: data is to be captured from a routine follow up CT/MRI scan of the abdomen performed at 6 months after randomisation in order to document any changes in tumour progression.

For patients receiving an ablative procedure: data is to be captured from a routine follow up CT/MRI scan of of the abdomen performed at 6 months after the procedure in order to document any changes in tumour progression.

The imaging will allow capture of the following data on the eCRF:

- Tumour size and volume. Size is to be recorded in 3 planes of measurement. Volume = 0.5326 x (diameter 1) x (diameter 2) x (diameter 3). The volume calculation is not to be completed by site.
- Confirmation of any progression of the tumour.

The following additional data will also be captured for all patients:

- Any changes in treatment plan (eg switching from active surveillance to ablation or surgical excision). Dates and times and types of procedures to be recorded. Reasons for a switch in treatment (i.e. reason for cross-over).
- Complications of treatment and adverse events will be recorded.
- Administration of health economics questionnaire: PCQ (Part A and Part B)

14.1.5 Renal Biopsy (for any patients receiving ablation)

A routine, standard care biopsy will be performed post-consent as part of standard care prior to randomisation in study participants who have not already received this clinically. Should sites not perform this procedure as standard care, consent must be given by the participant to the procedure and the study prior to the biopsy.

A compulsory renal biopsy at the core of the ablated lesion will be performed on all patients who have received ablative treatment. This will normally take place within two weeks of the 6 month follow up visit. Results from the renal biopsies will be recorded in the trial eCRF.
Any further complications of treatment and adverse events will also be recorded at this time.
The biopsy will be reported locally by a consultant urological pathologist (There may be an opportunity for central review). The biopsy report will contain the following information:

This data will be collected for biopsies at baseline and end of study

Lesional tissue present Y/N

Viable renal carcinoma tissue present Y/N

Renal carcinoma histological type and grade:

Type: (1) clear cell carcinoma, (2) papillary cell carcinoma type 1, (3) papillary cell carcinoma type 2, (4) chromoplate carcinoma; (5) oncocytoma; (6) can't determine

Grade: (1) Fuhrman grade 1/2, (2) Fuhrman grade 3/4, (3) can't determine

Presence of inflammation and/or sclerosis Y/N

Necrotic tumour present Y/N

The following data will be recorded at end of study biopsy only:

Biopsy outcomes

There will be three possible biopsy outcomes based on the histology and immunohistochemistry interpretation. Pathology should be reported locally as belonging to one of the biopsy outcome categories based on the biopsy protocol provided by Professor Stuart Fleming - Professor of Histopathology.

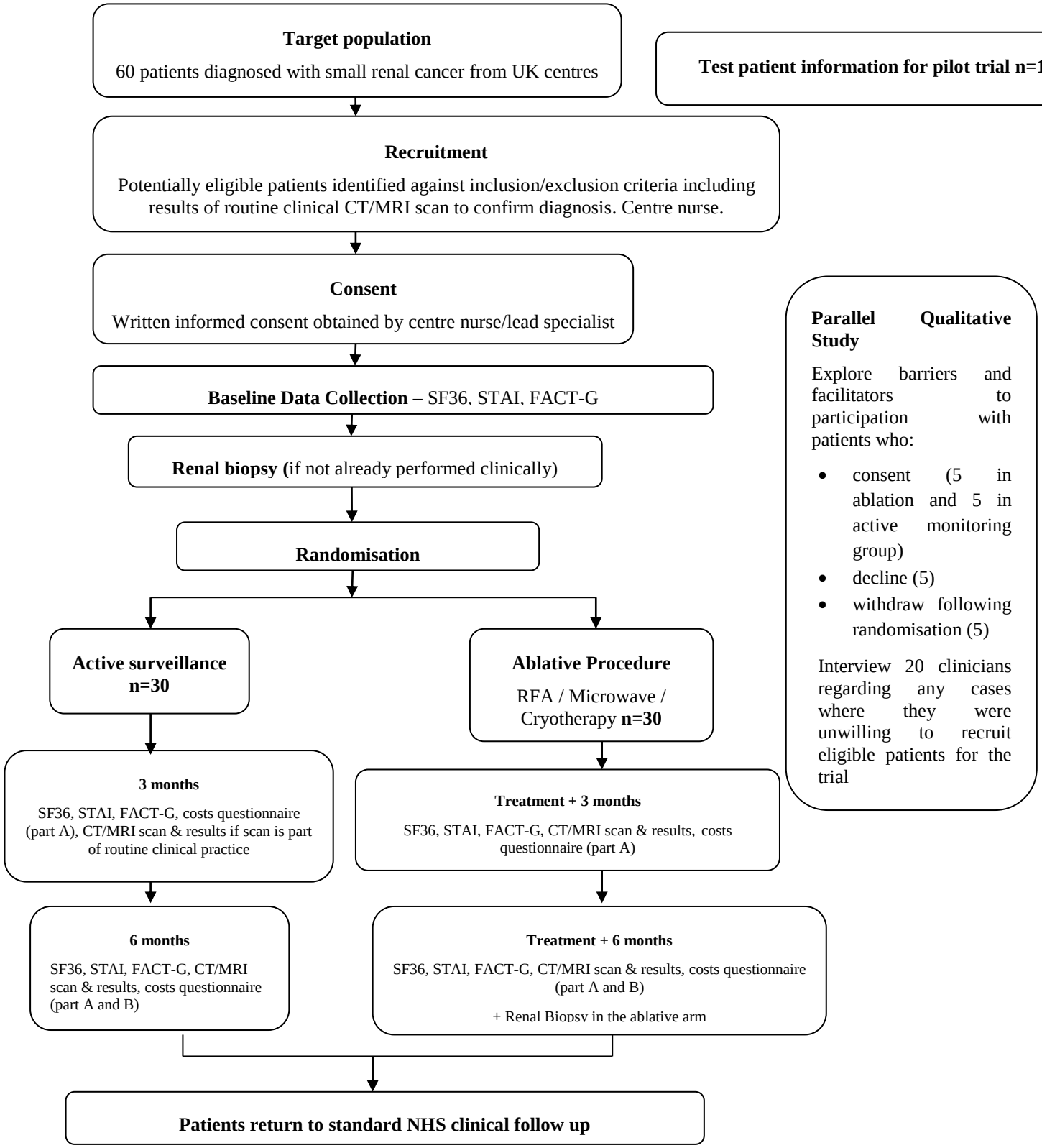
1. Failed biopsy
    a. No tissue or non-renal tissue
    b. Normal renal tissue
2. Fibrosis
    a. Suggestive of ablation site (Inflammation, haemorrhage, haemosiderin)
    b. Not suggestive of ablation site (Old fibrosis, no evidence of recent inflammation or haemorrhage)
    c. Inconclusive
3. Renal tumour (Classify and grade)
    a. Tumour cells with Ki67 reactivity
    b. Tumour cells without Ki67 reactivity

Participating centres are to identify a Histopathologist at site that would be involved in the SURAB trial.

That pathologist should then contact Professor Fleming for guidance about interpretation of post ablation biopsies (contact details are in Section 1 of the protocol)

14.1.6 STUDY FLOW CHART

PILOT FEASIBILITY TRIAL



14.1.7 General information about Parallel Qualitative Component Data and Interviews

Interviews with patients and clinicians will be conducted by an experienced qualitative researcher with skills in interviewing vulnerable populations around sensitive topics and cognitive interviewing techniques. Interviews will be digitally recorded with the permission of the interviewees and transcribed verbatim. A topic guide will be developed from discussions with the wider team and from literature around trial participation. The topic guide will be used in the interviews but interviewees will be encouraged to speak freely about any other issues relating to the pilot feasibility trial. The guide will be revised as new issues emerge in each interview.

Transcript data will be managed using NVivo software. A thematic framework will be derived from the data through a process of data familiarization to look for emergent themes. This framework will be tested and refined and data will be coded using the final framework. Data will be analysed using the constant comparison method [39].

14.2 Data Handling & Record Keeping

Trial data collected on paper and any questionnaires will be entered on a secure validated clinical online data management system (MACRO database system). The MACRO database system will be managed by Newcastle Clinical Trials Unit.

Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Participants will be allocated a unique study identifier which will be used on all data report forms.

No participant identifiable data will leave the study site unless for the purposes of coordinating and undertaking qualitative interviews in which only the minimum data required will be used by the research team to facilitate contacting patients. Caldicott approval will also be sought from relevant NHS Trusts for patient identifiable information to leave study sites in order to enable the qualitative researcher to contact patients who express an interest in being contacted about the interviews.

The quality and retention of study data will be the responsibility of the Chief Investigator, Mr Naeem Soomro. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

14.3 Submission of accrual data to UK CRN

This study will apply for adoption to the NIHR CRN Portfolio. Accrual data will be submitted on a monthly basis, by Newcastle Clinical Trials Unit, in accordance with NIHR CRN guidelines.

14.4 Schedule of Events

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Procedure	Screening	Baseline	Randomisation	Treatment (ablation)	Follow up 1	Follow up 2
			At least 24 hours after screening	1 month post randomisation(±14 days)	3 months post randomisation in active surveillance or 3 months post ablation (±14 days)	6 months post randomisation in active surveillance or 3 months post ablation (±14 days)
PIS provided	X					
ICF signed		X [2]				
Patient randomised			X			
Eligibility criteria checked	X	X				
Medical History		X				
ASA physical status		X				
SF-36		X			X	X
STAI		X			X	X
FACT-G		X			X	X
CT/MRI scan[3]	X				X^^	X
Pre randomisation Biopsy		X[5]				
Post ablation Biopsy						X [1]
Ablation (ablation arm only)				X		
Adverse Events				X	X	X
PCQ – Part A					X	X
PCQ – Part B						X
Sub Study Interviews		X[4]				

[1] Ablation Arm Only

[2] Patient must be allowed at least 24hrs to review the patient information sheet prior to giving consent.

[3] Scan of abdomen is required. CT is preferred method however MRI can be used instead of CT scan. The same scan technique must be performed throughout the study. Pre-screening CT/MRI is NOT a study procedure – performed as part of routine clinical care. Sites can perform additional scans if deemed clinically necessary/as per local practice.

[4] Interviews conducted via telephone

[5] Unless already performed as part of routine clinical care

^ can be taken up to 4 weeks prior to ablation.

^^ should be done within 3 months of ablative procedure – at a time that fits in with local practice. The 3 month scan is performed in the active surveillance arm if part of routine clinical care at site.

15. Economic Evaluation Protocol

15.1 Aim

The pilot study aims to assess the feasibility of a definitive randomised controlled trial (RCT) comparing ablation with active surveillance for treating small renal tumours. The economic aspect of the pilot will develop and test the health economics data collection tool and assess the ease of data collection required for health economic analysis to inform the definitive trial. The study will adopt the view point of both the NHS and the patient, and collect resource use data which include the costs of treatments and the use of primary and secondary NHS services, as well as participants' out-of-pocket expenses relating to the condition.

15.2 Collecting data

Tables detailing data to be collected and their source are provided in Appendix 1. Dummy tables for response rates, resource use, unit cost, average cost for each trial arm are designed (Appendix 2), and will be populated with data collected through the trial.

15.3 Outcomes

Quality of life (QoL) outcome data will be collected through the administration of the SF-36 questionnaire, which will be completed by participants at 3 and 6 month follow-up. The completeness of the questionnaire will be assessed.

15.4 Costs

15.4.1 Intervention cost

The main cost driver of treating patients with small renal tumour is expected to originate from the intervention (ablation treatments): Cryoablation, Microwave and Radiofrequency ablation (RFA). The key cost components include staff, consumables, capital and overheads. Data on these costs will be obtained from participating centres. The following information to be used to derive resource use will be recorded in the Case Report Form (CRF) for each participant in the ablation arms of the trial:

- Type of anaesthetic used (general or local)
- Grade of anaesthetist present
- Grade of radiologist present
- Grade of assistant staff present
- Number of nursing & assistant staff present
- Time of patient entry and exit from CT Suite
- Time of patient entry and exit from recovery room
- Date of admission
- Date of discharge
- Post-treatment complications (Clavien- Dindo grade if applicable)

The unit costs of each item will be obtained from the following sources: the costs of consumables and reusable items used during the procedure will be derived from manufacturers' price lists; the standard time costs of different grades of staff will be obtained through Unit Cost of Health and Social Care documentation from Personal Social Services Research Unit (PSSRU)[42]; cost per unit of time for CT suite will be based upon data from each participating centre. In the event of a complication the cost can be obtained from the participating centre based on the grade of complication defined by the Clavien-Dindo[43].

Participants in both of the study arms will be offered CT and/or MRI scans to monitor small renal tumour progression. For patients receiving ablation (using any of the methods) data is to be captured from two routine CT/MRI scans performed within 3 and 6 months of the ablative procedure. For patients receiving active surveillance: data is to be captured from two routine follow up CT/MRI scans performed within 3 and 6 months from randomisation. The unit cost per scan will be obtained from participating centres.

15.4.2 Costs collected via participant cost questionnaires

Participant cost questionnaires (PCQ) will be developed and piloted. The PCQs will collect information on NHS resource use and patient out-of-pocket expenses. The PCQ has two parts: Part A collects information on patients' health service use; and Part B gathers information on patients' time and travel costs of attending different health services. In order to reduce recall bias, participants will be asked to complete the Part A of PCQ at 3 month intervals (at 3 and 6 month follow-up). The Part B of PCQ collects information on participants' latest visit to each of the listed services and the information will be used at aggregated level to produce unit cost for each arm, hence it will only be administered once at 6 month follow-up.

15.4.3 NHS Resource costs

In addition to the costs related to the intervention, NHS resource use will also include patients' use of primary and secondary care due to problems as a result of having a small renal tumour. Thus, participants will be asked about the number of hospital outpatient and inpatient visits, GP visits, nurse visits and other specialist visits in the Part A of the PCQ.

15.4.4 Patient out-of-pocket expenses

Patients' out-of-pocket expenses refer to any costs incurred by the participants associated with the treatment of small renal tumours. Part A of the PCQ will collect information on any private personal/health care participants may pay for, such as over the counter medications, and private health insurance. Part B of the PCQ will collect information on participants' travel and time costs for accessing NHS services.

15.4.5 Travel costs: Participants will be asked about their mode of transport and the costs associated with travelling to each service. Unit costs for each journey will be estimated from this data. For example, participants who travelled by car will be asked the approximate distance travelled and the cost of parking whilst participants who travel by bus will be asked the price of their one-way fare. Participants will also be asked to provide travel cost information for any relatives/carers that accompany them to each service.

15.4.6 Time costs: Participants will be asked the time spent travelling to and the time spent at each service and what activity they would have been undertaking during that time if not attending the health services. For example, a participant may have to take time off work or forego leisure time in order to attend each service. These data will be presented in their natural units, e.g. hours and minutes, and attached monetary value using standard economic conventions, e.g. the Department of Transport[44] estimates for the value of leisure time. Participants will be asked to provide the same information for any relative or carer who accompanied them to each service.

16. Statistical Considerations

As this is a feasibility study our aim is to provide the foundations for future research in this area and to ensure that a larger scale research project is feasible and acceptable. We therefore aim to make estimates of subject availability, the willingness of subjects to be randomised to a trial treatment, of the proportion of subjects enrolled who complete the trial, and to obtain the data necessary to inform a power/sample size calculation for a future definitive phase III trial. Our primary focus is therefore on descriptive statistics rather than hypothesis testing.

16.1 Sample Size

We aim to recruit a total of 60 patients (30 to the surveillance arm; 30 to the ablation arm). This figure is based on a recommendation by Lancaster (2004)[41] with respect to the number of patients required to yield meaningful estimates of parameters of interest. With six or more centres participating in the pilot we believe that is feasible to approach up to 120 patients; assuming an achieved recruitment rate of no less than 50% this should give us the sixty patients that we need.

16.2 Statistical Analysis

The primary purpose of this feasibility study is to assess willingness to be randomised. It has not been designed to make an assessment of treatment efficacy, and sample sizes will be too small to make an interim assessment of efficacy. We anticipate that, even if the initial rates are disappointing, that the qualitative research might suggest improvements that could be made to recruitment procedures, hence we have not defined a stopping rule for futility. This trial does not involve the use of drugs and hence issues of toxicity are not expected to be a concern.

For this trial, we will determine interval estimates (using 95% confidence intervals) of key parameters of interest. These include:

- The proportion of patients who agree to be randomised.
- The proportion of patients receiving ablation who experience peri-operative complications.
- The proportion of patients for whom we can collect outcomes at 3 months 6 months post treatment.
- The standard deviation of the quality of life measures that will be used in the phase III trial.

We will also investigate the distribution of the quality of life scores at each time point with a view to inform the planning of future analyses. This will be done primarily by consideration of graphical displays of the data.

In addition we will assess whether the following criteria for evaluating the success of the pilot have been met:

- The upper 90% confidence interval for the proportion of patients recruited should exceed 50%. We should recruit at least 49 patients from 120 approached. This is based on a requirement that the underlying recruitment rate should be at least 50%. The exact 90% confidence interval corresponding to 49 successes from 120 Bernoulli trials is from 32.0% to 50.2%. (With 48 successes from 120 trials the upper interval drops to below 50%). Should we recruit less than 49 patients we would regard this as evidence that the recruitment rate was too low; the external validity of a randomised controlled trial would be questionable.

- The upper 90% confidence interval for the retention rate (the proportion of patients recruited who have been followed up) should be greater than or equal to 80%.

17. Compliance and Withdrawal

17.1 Participant Compliance

Recommended visit windows of +/- 14 days for follow up should ensure timely follow up visit organisation and attendance. Non-attendance by patients for study visits will be followed up by theresearch team at site. Attempts will be made locally by participating sites to rearrange any missed visit appointments in order to ensure high follow up rates.

17.2 Withdrawal of participants

Information sheets and consent forms will make it explicit that we will retain data collected up to the point of withdrawal.

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study intervention if s/he judges this to the in the patient's best interests.

Since this is a feasibility study, it is understood by all concerned that an excessive rate of withdrawals will indicate a potential lack of feasibility; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

Participants who wish to withdraw from the qualitative sub-study but have had feasibility trial treatment, will be asked to confirm if they are:

1. Withdrawing completely (i.e. withdrawal from both the qualitative interviews and main study follow up visits)

2. Withdrawing partially (i.e. withdrawal from qualitative interviews only)

Participants will be asked if they would be happy for the reason for the decision to withdraw to be recorded.

Participants who withdraw from study interventions prior to completion will not be replaced.

Following consent, but pre-randomisation, should the baseline biopsy reveal that the participant does not have cancer the participant will be withdrawn from the study.

17.3 Cross-over monitoring

Cross overs are not un-common in surgical trials. Cross-over will not be considered as a treatment failure and will not be cause to withdraw a patient from this feasibility study.

We will record all switches (cross-overs) from active surveillance to ablation/ surgery and vice versa. Reasons for cross-overs will be recorded.

Review of this information in this feasibility trial will inform any future trial design.

18. Data Monitoring, Quality Control and Quality Assurance

18.1 Discontinuation rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring & Ethics Committee and/or Trial Steering Committee, Sponsoror ethics committee concerned.

18.2 Monitoring, quality control and assurance

The trial will be managed through the Trial Management Group (TMG) (membership listed in project contacts section).

The Principal Investigators will be responsible for the day-to-day study conduct at sites.

Newcastle Clinical Trials Unit will provide day-to-day support for the sites and provide training through Investigator meetings, site initiation visit and routine monitoring visits.

Quality control will be maintained through adherence to NCTU SOPs, study protocol, the principles of GCP, research governance and clinical trial regulations.

An independent data monitoring (DMC) will be convened to undertake independent review. The purpose of this committee will be to review and monitor safety. At the first meeting, the DMC will agree on its charter of operation. They will also determine a schedule for further meeting(s) taking into account that this is a feasibility trial.

A Trial Steering Committee (TSC) will be established to provide overall supervision of the trial. The committee will meet twice during the first year of the study and then again at the end. A written charter will be agreed and used by the TSC.

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by NCTU. The main areas of focus will include consent, serious adverse events and essential documents in study.

Site monitoring will include:

- All original consent forms will be reviewed as part of the study file. All original consent forms will be compared against the study participant identification list.
- All reported serious adverse events will be verified against treatment notes/medical records (source data verification).
- The presence of essential documents in the investigator site file and study files will be checked.
- Source data verification of primary endpoint data and eligibility data for 10% of participants entered in the study.

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission.
- All documentation essential for study initiation will be reviewed prior to site authorisation.
- Regular review of outstanding data and data completion/data entry into the database system.

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The study may be subject to inspection and audit by Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

19. Adverse Event Monitoring and Reporting

19.1 Definitions

Adverse event (AE): Any untoward medical occurrence in a subject to whom a study intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, "treatment" includes all interventions (including comparative agents) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Related AE: An AE that results from administration of any of the research study procedures. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a study procedure qualify as 'related adverse events'. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality: The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e definitely, probably or possibly related) are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the main REC and other bodies will be informed of both points of view.

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs 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 treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Unexpected Adverse Event: An adverse event that is not listed in the study protocol as an expected occurrence in the circumstances of this trial.

Serious Adverse Event (SAE): an untoward occurrence (whether expected or not) that:-

- Results in death
- Is life-threatening (refers to an event in which the subject 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)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Severity (intensity) of Adverse Events and Adverse Reactions

Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, severe):

- Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
- Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

An AE may be severe but not serious.

19.2 Expected Adverse Events

Most adverse events that occur in this study, whether they are serious or not, will be expected due to the interventions and study procedures of this study. Expected AEs are summarised in the table below.

	Adverse event*		
Procedure	**Common & well understood consequences of treatment**	**Less common & unpleasant side effects**	**Rare events**
Radiofrequency ablation	• Hematoma Formation • Urinary infection	• Visceral Injury • Vascular injury • Urine leakage • Loco-regional disease progression	• Death
Cryoablation	• Hematoma Formation • Urinary infection	• Visceral Injury • Vascular injury • Urine leakage • Loco-regional disease progression	• Death
Microwave	• Hematoma Formation • Urinary infection	• Visceral Injury • Vascular injury • Urine leakage • Loco-regional disease progression	• Death
Active surveillance	n/a	• Loco-regional disease progression	n/a

* Crossover will NOT be deemed an adverse event in this trial but will be recorded in the eCRF

19.3 Protocol Specifications

For purposes of this protocol:

- All adverse events will be recorded at visits 2, 3, 4, 5 and 6.
- Any serious adverse events will be recorded throughout the duration of the trial until final follow up or 6 months post treatment.

- Serious adverse events exclude any pre-planned hospitalisations (e.g. hospitalisation for study procedure, elective surgery) not associated with clinical deterioration.
- Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Serious adverse events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.
-

19.4 Recording & Reporting Serious Adverse Events:

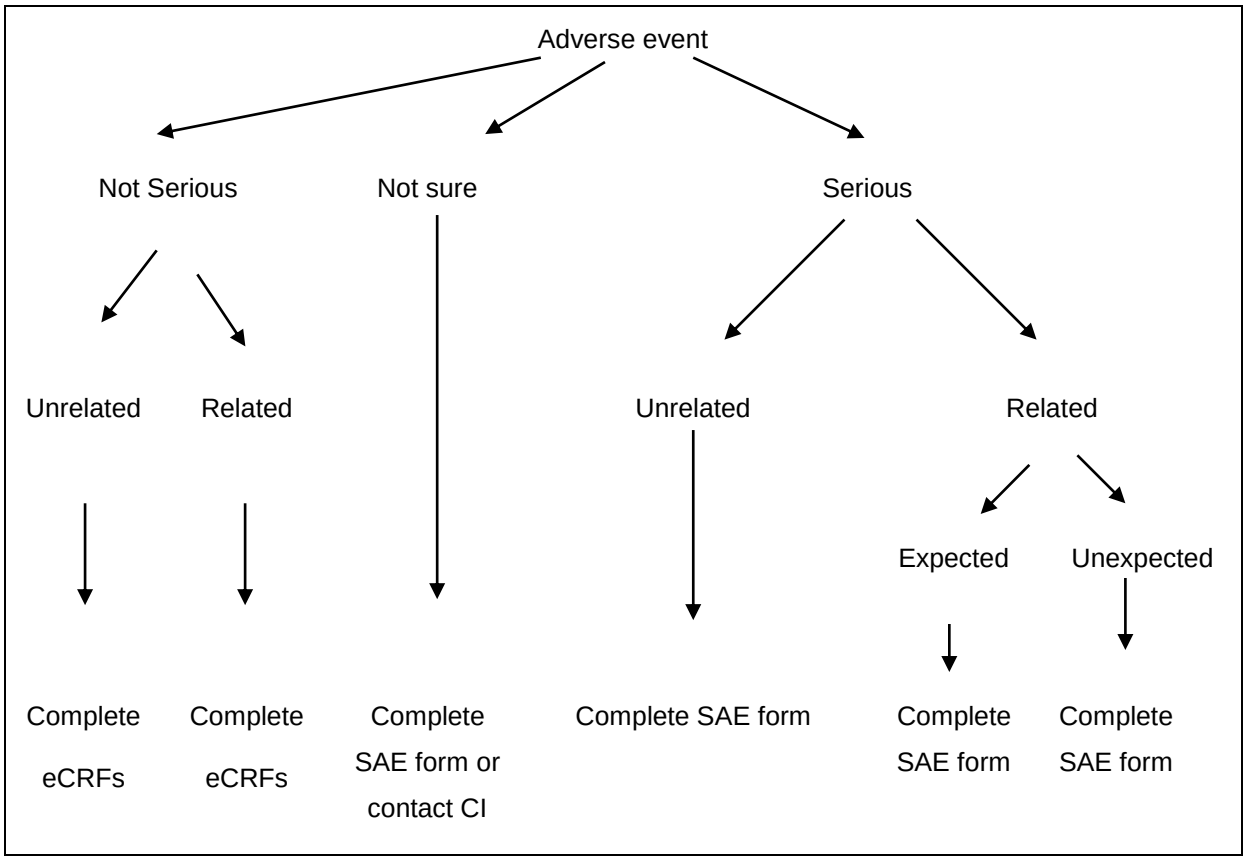
All adverse events should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance. A flowchart (figure 1) is given below to aid reporting procedures.

Adverse Event (AEs): All non-serious adverse events during study participation will be reported on the study CRF and sent to the trial manager within one month of the form being due. Severity of AEs will be graded on a three-point scale (mild, moderate, severe). Relation (causality) and seriousness of the AE to the treatment should be assessed by the investigator at site in the first instance. The individual investigator at each site will be responsible for managing all adverse events according to local protocols.

Serious Adverse Event (SAEs): All SAEs during study participation shall be reported to the Chief Investigator within 24 hours of the site learning of its occurrence. The initial report can be made by telephone or fax. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to study procedures should be assessed by the investigator at site, as should the expected or unexpected nature of the AE.

Local investigators should report any SAEs as required by their local Research & Development Office.

Figure 1



Contact details for reporting SAEs

Please send SAE form(s) via Fax: 0191 580 0137

20. Ethics & Regulatory Issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Favourable ethical opinion will be sought prior to commencement of the study. Local approvals will be sought before recruitment may commence at each site.

The NCTU will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures.

21. Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique study or screening identification code and date of birth only. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

Caldicott approval will be obtained for transfer of patient identifiable data from sites to the study coordinators for purposes of arranging patient interviews.

22. Insurance and Finance

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

UK National Institute for Health Research, HTA programme are funding the study.

23. Study Report / Publications

The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator.

It is planned to publish this study in peer review articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site. All manuscripts, abstracts or other modes of presentation will be led by the Trial Management Group and circulated to the Trial Steering Committee and Funder prior to submission. Individuals will not be identified from any study report.

24. Appendices

Health Economics - Appendix 1 – Data collection source tables

- **Table 1 – Source of Data Collection**

Resource used	**Source of data**
Intervention	
Number receiving general anaesthetic	CRF
Number receiving local anaesthetic	CRF
Number of hospital day cases	PCQ
Number of overnight hospital stays	PCQ
Mean CT scanner suite time	CRF
Mean recovery room time	CRF
Number NHS travel - ambulance	PCQ
Number NHS travel – hospital car	PCQ
Follow up care	
Number CT scans	CRF
Number MRI scans	CRF
Number further treatment	CRF
Number inpatient stays	PCQ
Number outpatient cases	PCQ
Number of A&E (day) cases	PCQ
Number of A&E (overnight) cases	PCQ
Number NHS travel – ambulance	PCQ
Number NHS travel – hospital car	PCQ
Primary Care	
Number visits to GP	PCQ

Number visits to Nurse	PCQ
Number GP home visits	PCQ
Number Nurse home visits	PCQ
Number out-of-hours consultations	PCQ
Number telephone consultations	PCQ

- **Table 2 – Source of Cost Data**

Resource Unit cost	**Source of cost data**
Intervention	
Cost of consumables	Manufacturers' price list
Cost of reusable	Manufacturers' price list
Cost per general anaesthetic	Manufacturers' price list
Cost per local anaesthetic	Manufacturers' price list
Cost per minute CT scan suite time	PSSRU
Cost per biopsy	PSSRU
Cost per minute recovery room	PSSRU
Cost per minute Anaesthetist	PSSRU
Cost per minute Interventional Radiologist	PSSRU
Cost per minute Radiographer	PSSRU
Cost per minute Operating Department Practitioner (ODP)	PSSRU
Cost per minute nurse assistant	PSSRU
Cost per minute recovery room staff	PSSRU
Cost per day case	PSSRU
Cost per inpatient stay per night	PSSRU
Cost per ambulance journey	PSSRU

Cost per hospital car journey	PSSRU
Follow up care	
Cost per CT scan	Participating centre
Cost per MRI scan	Participating centre
Cost per further treatment	Participating centre
Cost per inpatient stay per visit	PSSRU
Cost per outpatient stay per visit	PSSRU
Cost per A&E day visit	PSSRU
Cost per A&E overnight visit	PSSRU
Cost per ambulance journey	PSSRU
Cost per hospital car journey	PSSRU
Primary care	
Cost per GP visit	PSSRU
Cost per nurse visit	PSSRU
Cost per GP home visit	PSSRU
Cost per nurse home visit	PSSRU
Cost per out-of-hours consultation	PSSRU
Cost per telephone consultation	PSSRU

Appendix 2 – Dummy tables for pilot trial

- **Table 3 – Response Rates**

Collected Items		Intervention arm			Control arm		
		No. Total	**No. Received complete information**	**Response rate**	**No. Total**	**No. Received complete information**	**Response rate**
Outcome measures (QoL scores)	Generic scores (SF-36)						
Patients' out-of-pocket costs	Participant Costs Questionnaire						
NHS resources	CRF						

Table 4 – Resource Use in Trial

Resource used	**Intervention arm**		**Control arm**
	Cryoablation	*RFA*	
Intervention			
Number general anaesthetic			
Number local anaesthetic			
Number of hospital day cases			
Number of overnight hospital stays			
Mean CT scan suite time			
Mean recovery room time			
Number NHS travel - ambulance			
Number NHS travel – hospital car			
Follow up care			
Number CT scan			
Number MRI scan			
Number further treatment			
Number inpatient stays			
Number outpatient cases			
Number of A&E (day) cases			
Number of A&E (overnight) cases			
Number NHS travel – ambulance			
Number NHS travel – hospital car			

Primary Care			
Number visits to GP			
Number visits to Nurse			
Number GP home visits			
Number Nurse home visits			
Number out-of-hours consultations			
Number telephone consultations			

Table 5 – Resource Costs for Trial

Resource Unit cost	**Intervention arm**		**Control arm**
	Cryoablation	*RFA*	
Intervention			
Cost of consumables			
Cost of reusables			
Cost per general anaesthetic			
Cost per local anaesthetic			
Cost per minute CT scan suite time			
Cost per biopsy			
Cost per minute recovery room			
Cost per minute Anaesthetist			
Cost per minute interventional Radiologist			
Cost per minute ODP			
Cost per minute radiographer			
Cost per minute nurse assistant staff			
Cost per minute Recovery room staff			
Cost per day case			
Cost per inpatient stay per night			
Cost per ambulance journey			
Cost per hospital car journey			
Follow up care			
Cost per CT			

Cost per MRI			
Cost per further treatment			
Cost per inpatient stay per visit			
Cost per outpatient stay per visit			
Cost per A&E day visit			
Cost per A&E overnight visit			
Cost per ambulance journey			
Cost per hospital car journey			
Primary care			
Cost per GP visit			
Cost per nurse visit			
Cost per GP home visit			
Cost per nurse home visit			
Cost per out-of-hours consultation			
Cost per telephone consultation			

Table 6 – Average Cost per Participant

Mean Resource cost	**Intervention arm**		**Control arm**
	Cryoablation	*RFA*	
Intervention			
Mean consumables cost			
Mean reusables cost			
Mean general anaesthetic cost			
Mean local anaesthetic cost			
Mean CT scan suite time cost			
Mean biopsy cost			

Mean recovery room cost			
Mean Anaesthetist cost			
Mean Interventional Radiologist cost			
Mean Radiographer cost			
Mean ODP cost			
Mean Nurse assistant cost			
Mean Recovery room staff cost			
Total mean intervention cost			
Mean day case cost			
Mean inpatient stay cost			
Mean ambulance journey cost			
Mean hospital car journey cost			
Total mean admission cost			
Follow up care			
Mean CT cost			
Mean MRI cost			
Mean further treatment cost			
Mean inpatient stay cost			
Mean outpatient stay cost			
Mean A&E day visit cost			
Mean A&E overnight visit cost			
Mean ambulance journey cost			
Mean hospital car journey cost			
Total mean follow up cost			

Primary care			
Mean GP visit cost			
Mean nurse visit cost			
Mean GP home visit cost			
Mean nurse home visit cost			
Mean out-of-hours consultation cost			
Mean telephone consultation cost			
Total mean primary care cost			
TOTAL MEAN COST			

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