The PARTIAL study

A randomised trial of the clinical and cost effectiveness of complex PARTIAL vs radical nephrectomy for clinically localised renal cell carcinoma

PROTOCOL

A UK Collaborative Trial funded by the NIHR HTA Programme

This Protocol has regard for the HRA guidance and order of content.

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SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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VERSION HISTORY

Amendment no.	**Protocol version no.**	**Description of changes (*incl. author(s) of changes*)**	**Date of document**
	Version 1	New Document, based on CHaRT protocol template version 4	24/10/2022

TABLE OF CONTENTS

TRIAL SUMMARY

Trial title	The PARTIAL study – a randomised trial of the clinical and cost effectiveness of complex PARTIAL vs radical nephrectomy for clinically localised renal cell carcinoma.
Short title	PARTIAL
Rationale	Every year in the UK over 13,000 people are diagnosed with kidney cancer. Localised renal cell carcinoma, in patients with a normal contralateral kidney, has been historically treated by removal of the entire kidney - a radical nephrectomy. The renal function for these patients is partly compensated for by the remaining kidney, but the degree to which it can compensate may be compromised by the effects from ageing and/or commonly occurring medical conditions (such as hypertension and diabetes). It has become standard for small tumours (<4cm, stage T1a), with normal contralateral kidneys, to undergo nephron sparing approaches - primarily involving partial nephrectomy. However, there is uncertainty over the benefits of partial nephrectomy for intermediate sized tumours (4-7cm, stage T1b) and small complex tumours, as there are increased surgical complications and in some cases more tissue is excised (reducing preservation of renal function) - all of which makes potential gains over radical nephrectomy less clear. There are no high-quality studies to address this uncertainty. As such, an RCT is required to test if gains from partial nephrectomy are superior to radical nephrectomy and offset the potential harms and possible increased costs in the more complex renal tumours suitable for either approach. If partial nephrectomy is not found to provide clinically significant gains and excess complications are confirmed, then a practice-changing case for radical nephrectomy as standard of care could be made.
Trial design	A pragmatic patient-randomised controlled, parallel group superiority trial (with an internal pilot), with an embedded economic evaluation comparing partial nephrectomy and radical nephrectomy. An embedded process evaluation will identify challenges relating to design or conduct during the internal pilot.
Eligibility criteria	**Inclusion criteria** • Adults ≥18 years; • Newly diagnosed clinically localised renal cancer (suspected on cross-sectional imaging or histologically confirmed)*; • Local multi-disciplinary review identifying those cases thought to be suitable for both minimally invasive RN or PN; (for minimally invasive we mean laparoscopic or robotic surgery; cases where open surgery is planned are not eligible) • Cross-sectional imaging showing a single tumour, stage T1 (up to 7cm), where there is equipoise in the MDT and willingness to recruit into the trial; • On imaging, evidence of a radiologically normal contralateral kidney.

	• Patients that have been fully counselled of all the available treatment options (including non-surgical approaches, where appropriate); • Able and willing to give informed consent to participate and to participate in study procedures. **Exclusion criteria** • Solitary functioning kidney • Metastatic disease • Existing CKD (>stage 3b; eGFR<45) • Medically unfit for surgery • Congenital renal abnormality which includes fusion, assent and malrotation • Suspected or confirmed inherited kidney cancer syndrome • Current pregnancy or breast feeding • People without capacity	
Interventions	Partial nephrectomy vs radical nephrectomy	
Randomisation and blinding	Eligible and consenting participants are randomised using the proven 24-hour web-based randomisation application hosted by CHaRT. Participants will be randomly allocated 1:1 to either partial nephrectomy or radical nephrectomy using a remote central, computer generated randomisation schedule, minimised by previously reported major confounders of centre, pre-operative eGFR (45-59; ≥60), tumour size (T1a; T1b) and pre-randomisation biopsy (yes; no). Blinding for participants is not possible. Similarly, the immediate clinical, nursing and research teams cannot be blinded. However, the primary outcome kidney function, is determined objectively.	
Planned sample size	420 randomised participants (210 in each arm)	
Duration of trial	Each participant will be in the study for 24 months. The total duration of the trial is 60 months.	
	Objectives	Outcome measures
Primary	*Gains* in preserving renal function over two years	eGFR at baseline, 1 week and 1 month post-intervention, and 6, 12 and 24 months post-randomisation
	Harms	Comprehensive Complication Index (CCI) over the peri-operative period
Secondary	(i) HRQoL	EORTC QLQ-C30 and SF-36 (Acute version – 1 week recall)

	(ii) cost and cost-effectiveness	Care pathway costs, QALYs based on SF-6D
	(iii) quality of recovery	QoR-15
	(iv) rates of positive surgical margin rates (and retreatment/ surgical revision)	Pathology report
	v) recurrence free and overall survival (including local recurrence)	Extracted from medical records
	(vi) rates of cardiovascular events (heart attack and stroke)	Extracted from medical records
	(vii) progression to chronic kidney disease (CKD)	eGFR
	(viii) operative conversion	Extracted from surgical notes
	(ix) patient acceptability	interviews in embedded mixed methods trial process evaluation
Statistical methods	All analyses will be based on the intention-to-treat principle. All statistical analyses will be pre-specified in a comprehensive Statistical Analysis Plan which will be agreed with Trial Steering and Data Monitoring Committees. There will be one analysis of effectiveness outcomes at the end of the trial after all follow-up is complete. There will be no planned interim analysis for efficacy or futility. Safety data will be monitored throughout the trial by an independent DMC.	
Methods for the economic evaluation	The study will include a within trial and model based economic evaluation. Full details of the health economics analyses will be set out in the Health Economics Analysis Plan.	
Methods for the process evaluation	A mixed methods approach will be used, modelled on the Quintet Recruitment Intervention, and augmented with the application of behavioural science to inform key components of data collection, analysis, and development of feedback.	
Co-ordination	Local: by local research teams Central: by Trial Office in Aberdeen (Telephone 01224 438144). Overall: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring Committee.	

LAY SUMMARY

Background: Each year over 13,000 people in the United Kingdom are diagnosed with a kidney cancer (7th commonest cancer). Historically, many patients presented late with symptoms from large cancerous growths and in individuals with a normal kidney on the unaffected side, the standard treatment was to remove the entire affected kidney. Nowadays, most kidney cancers are found at a much earlier stage when a scan is performed for an unrelated condition. These smaller cancers can either be treated by removing the entire affected kidney or just the portion of the kidney affected by the tumour. However removing just the kidney tumour is more difficult than taking the entire kidney out. Partial kidney removal comes with a slightly greater risk of inadvertently leaving some cancer behind requiring retreatment. Bleeding and urine leakage are also a risk with partial removal of the kidney, also possibly requiring further treatments. Nevertheless, partial kidney surgery remains attractive as these additional risks could be traded off with potential benefits from maintaining more kidney function. This may reduce the chances of developing kidney failure and requiring dialysis. Loss of kidney function is also associated with developing heart disease in the future and potentially dying from a heart attack or stroke. However, there are no high quality successfully completed clinical trials comparing which approach is better. Despite the lack of good data, surgery to remove part of the kidney is (becoming) (more) common, as modern robot assisted key-hole approaches make it more accessible

Aim: In patients with kidney cancer and a normal kidney on the other side, we plan to conduct a clinical trial to answer the question of whether a partial removal of the kidney (partial nephrectomy) is better than removing the whole kidney (radical nephrectomy) for a group of more complex kidney tumours suitable for either approach.

Design & methods: Everyone that takes part on our study will have an equal chance of either partial or total removal of the kidney. We will compare the two treatments in terms of their effect on how well the kidney(s) are working (through regular blood tests), quality of life, complication rates and survival. We will also compare the use of NHS resources. The study will recruit 420 patients from 30 hospitals spread across the UK and will investigate what happens to those treated in either way over 2 years. The study team brings together patients, clinicians and researchers to answer this question.

Patient and public involvement (PPI): Mr David di Mambro is leading our Patient and Public Involvement. He has lived experience of kidney cancer and surgery and, supported by our Patient Advisory Group and Kidney Cancer UK charity, brings invaluable experience in guiding the co-production of this application. Our Patient and Public Involvement (PPI) group will provide advice about the conduct of the trial from a patient perspective and support the research team in development of patient-facing resources and activities to foster participant connectedness with the study.

Dissemination: Results of the study will be distributed to patients and families affected with kidney cancer through bespoke plain English summaries generated in conjunction with our PPI group through lay media outlets, social media and charity run patient portals (e.g. Kidney Cancer UK, Cancer Research UK, and the British Association of Urological Surgeons). Scientific output will be through academic conferences and publications.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
AR	Adverse Reaction
AUC	Area under the curve
BAUS	The British Association of Urological Surgeons
CCA	Cost consequence analysis
CCI	Comprehensive Complication Index
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRF	Case Report Form
CTA	Clinical Trial Application
CTU	Clinical Trial Unit
CUA	Cost Utility Analysis
DMC	Data Monitoring Committee
ESKD	End-Stage Kidney Disease
GCP	Good Clinical Practice
(e)GFR	(estimated) glomerular filtration rate
GP	General Practitioner
HEAP	Health Economics Analysis Plan
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MDT	Multidisciplinary Team
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute Health Research
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
PN	Partial nephrectomy
PPI/PPIE	Patient and Public Involvement/and Engagement
PQ	Participant Questionnaire
PSS	Personal social services
QA	Quality Assurance
QALY	Quality Adjusted Life Year
RCC	Renal Cell Carcinoma
RCT	Randomised Controlled Trial
R&D	Research and Development
RCC	Renal cell carcinoma
REC	Research Ethics Committee
RN	Radical nephrectomy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UoA	University of Aberdeen

TRIAL PERSONNEL

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Co-Chief Investigator
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Trial Office Team

1 Chief Investigator
2 CHaRT Director
3 Trial Manager
4 Data Co-ordinator
5 Senior Trial Manager
6 Senior IT Manager
7 Trial statistician
8 Qualitative/mixed methods researcher
9 Health economist

Project Management Group (PMG)
This group is comprised of the grant holders along with representatives from the Trial Office team.

Trial Steering Committee (TSC) Members
The membership of this committee comprises independent members along with the Chief Investigator (CI) (Professor Naeem Soomro) or a nominated delegate. The other PARTIAL grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

Data Monitoring Committee (DMC) Members
This committee is comprised of independent members and the trial statistician contributes as appropriate. The CI and / or a delegate may contribute to the open session of the meetings as appropriate.

Role of the Trial Sponsor and Funder

The Sponsor has responsibility for the initiation and management of the trial as defined by the UK Policy Framework for Health and Social Care Research v3.3 07/11/17. This is further defined within a sponsorship agreement outlining the roles and responsibilities of the parties involved in the research. Specific responsibilities delegated to another party are formally agreed and documented by the Sponsor.

The funder has oversight of the study through regular reports from the trial office. The funder appoints the independent members of the Data Monitoring and Trial Steering Committees and receives minutes from these. The funder is made aware of all outputs from the study but does not have a role in the decision to publish results from the study. In any publications, the funder is acknowledged, and appropriate disclaimer used to indicate that the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

The PARTIAL study – a randomised trial of the clinical and cost effectiveness of PARTIAL vs radical nephrectomy for clinically localised renal cell carcinoma.

1. INTRODUCTION

1.1 Background

Widespread use of imaging investigations has led to a major increase in incidental diagnoses of early small kidney cancers. Thus, the incidence of renal cancers has almost doubled over the last 20 years and is one of few cancers projected to increase in incidence to 2035 (Smittenaar 2016). It is the 7th most common cancer in the UK with over 13,000 new cases/year (Cancer Research UK 2017). Renal cell carcinoma (RCC), the commonest type of kidney cancer, historically was managed by radical nephrectomy (RN) to remove the whole kidney. Most of these patients managed without significant problems with their remaining kidney (Scosyrev 2014), which partly compensates for the lost function (meaning that function is not halved). In those patients with pre-existing chronic kidney disease (CKD; eGFR<60 ml/min/1.73 m^2) or a solitary kidney, nephron-sparing partial nephrectomy (PN) (where only the portion of the kidney containing the cancer is removed) became the preferred surgical treatment option. PN is technically more challenging and associated with increased operative risks, but in situations of renal compromise it minimises deterioration of kidney function, and therefore a risk of end stage kidney disease (ESKD) (Campbell 2017). Over time, as experience of PN has grown its application expanded to also include early small tumours (<4cm, clinical stage T1a) in those cases with a normal contralateral kidney and kidney function. Early cohort studies suggested that higher surgical complication, positive surgical margins and recurrence rates with PN were offset by maintained renal function; that in turn potentially reduced cardiovascular events and helped avoid CKD. With surgical advances afforded by robotic surgery (Choi 2015), guidelines recommend that surgeons increasingly tackle (i) bigger tumours (intermediate sized 4-7cm (T1b) and/or (ii) higher complexity surgeries involving central (hilar) tumours with PN in those patients with normal contralateral kidneys. However, these PNs can be associated with a greater loss of renal mass and the benefits from the smaller degree of maintained renal function over that from RN is less clear cut. Additionally, in these more complex PN, there are higher risks of significant perioperative complication and surgical margins (ie on histological examination tumour cells were seen on the resection margin) (Buffi 2020). Therefore, the harms, health gains and associated costs for modern day PN compared to RN are not clearly understood and a high-quality trial is required (Kim 2017).

1.2 Rationale for the trial

Why is this research needed now?

(i) Size of patient population in the UK: In the UK, looking at those patients with kidney cancers undergoing surgical treatment, there were 3,130 RNs (73% laparoscopic, 5% robotic, 19% open, 3% not available) and 1,562 PNs (76% robotic, 9% laparoscopic 14% open, 1% not available) that were reported in the BAUS Nephrectomy Audit (British Association of Urological Surgeons 2019). ***Of these, 1,041 patients were T1b who would be potentially eligible for the study. Additionally there are complex T1a tumours who would be potentially eligible for the study.*** According to international guidelines, most patients with T1 disease should undergo PN, when possible (Ljungberg et al 2022). Comparing just the rates of RN to PN, the BAUS audit revealed that for (i) T1a (<4cm lesions), 35% had RN and 65% had PN (65%); and (ii) T1b (4-7cm lesions), 80% had RN and 20% had PN. Although there is a growing narrative in the published field about feasibility of PN for large T2 tumours, this is not

reflected in UK practice where only 3% (22/632) were undertaken in 2019, most likely in complex scenarios. In summary the national data reveals a spread of treatment approaches for T1 tumours, in keeping with uncertainty around best practice.

(ii) Unmet health needs to be addressed: There is only one randomised trial comparing PN and RN for small RCCs (<5cm) (Van Poppel, 2007). The study's limitations were its failure to meet pre-planned accrual targets (541/1300 participants) and that technical approaches to PN were still being refined. A 21% cross over occurred, mainly PN to RN, due to perceived technical challenges, affecting the intention-to-treat analysis. Currently <5% convert to from PN to RN (Arora 2018; Klein 2021; Petros 2018). Technical advances with PN have rapidly progressed with minimally invasive robotic surgery increasing its use for tumours <7cm (stage T1). This is recommended in key clinical guidelines, including the European Association of Urology (EAU 2020) and major US guidelines (Motzer 2017; Campbell 2017)). The clinical climate is now receptive to the conduct of an RCT; where previously there was a lack of clinician equipoise related to higher complication rates and concern about residual cancer.

What is the knowledge gap this research will address?

(i) Contemporary systematic review: Previous evidence synthesis exercises have relied predominantly on retrospective cohort data (Mir 2017; Pierorazio 2016). A Cochrane review identified the only RCT and acknowledged limitations, as discussed above (Kunath 2017). Given the absence of high-quality evidence, the authors recommended a methodologically rigorous study to assess the potential benefits and harms of PN, whilst accounting for baseline renal function, tumour size and patient age (Kunath 2017).

(ii) Ongoing relevant research: Currently, there are no RCTs of PN vs RN for surgical treatment of smaller renal tumours. There is an ongoing feasibility study of a cohort embedded randomised control trial comparing NEphron Sparing Treatment (NEST) for small renal masses (NIHR PB-PG-0817-20013; 2019-2022). This study is exclusively in T1a (<4cm) tumours and focuses on a different patient population and treatment options (comparing cryoablation and PN) to our proposed study, and therefore these studies are not conflicting.

(ii) Defining and addressing uncertainty in clinician and patient preferences T1 tumours: To understand the most clinically relevant issues from the commissioned NIHR brief, we undertook detailed surveys and focus groups with key stakeholders (patient, urologists and nephrologists) to defined key parameters for our study.

Patients: We conducted three focus groups for patents with lived experience of PN or RN (n = 24 in total), in collaboration with Kidney Cancer UK (KCUK) and an experienced mixed-methods researcher (Dr Mathew Breckons, co-applicant). Patients described diverse experiences in being counselled about the surgical options, with the vast majority understanding there was a choice between PN and RN for smaller tumours. Patients agreed a clinical trial is urgently required to determine which treatment in superior in terms of relative benefits and harms for intermediate sized tumours. Patients shared that main drivers in decision making were an intuitive and strong desire to maintain kidney function and also avoidance of harm by prioritising (i) being cured of cancer and (ii) returning to normal activities as soon as possible. For the proposed study, the increase level of risk in the PN group associated with intermediate sized tumours was explored, and an acceptable level of significant complication - Clavien-Dindo 3 or higher, up to 11% (Schiavina 2017) and positive surgical margin rates up to 5% with only <1% requiring further treatment and no impact on

risk of cancer death reported (Bensalah 2010). These rates were considered acceptable for potential gains in renal function. Additionally, we explored a possible reduction in cardiovascular events in the long term, which if present were highly desired. Explicitly, these patients unanimously stated acceptability of randomisation if hypothetically suitable. We also confirmed participant acceptability to the nature and burden of health related quality of life questionnaires in the trial schedule. Additionally, the focus groups revealed that a very strong driver for making a decision for RN vs PN was the recommendation of the clinician.

Urologists: To further establish the key areas of clinical uncertainty, we undertook a detailed (33 question) national survey through the *BAUS Section of Oncology* targeting all Urologists (n = 110) involved in managing kidney cancers. Key demographics - 95% discussed all T1a tumours at SMDTs, 90% undertake RN (85% >25/year), 75% of respondents undertake PN (60% performing >25/year). For the main group of interest for this study, T1b tumours, 80% would offer robotic/laparoscopic PN in suitable cases. Only 6.5% of respondents said they felt PN was not appropriate for T1b tumours with a contralateral normal kidney. The main drivers for surgeons considering PN vs RN relate to potential harms as otherwise, there was a strong conviction to save renal function where possible. The main determinants of harm (perioperative complications) relate to the anatomy of the tumour – captured and categorised by a number of renal morphometric scoring systems, such as the PADU and RENAL systems (Ficarra 2009; Schiavina 2017). Work from our group shows that depending on surgical complexity, moderate to severe complications (Clavien-Dindo 3 or higher) are seen in 4-11% of PN compared with just 2-3% in RN (2-3%) in contemporary series treated by robotic approaches (Schiavina 2017). The main variables determining complexity and risk of complication are (i) size, (ii) higher risk endophytic or favourable exophytic growth pattern and (iii) higher risk hilar locations next to main feeding vessels vs peripheral locations (Buffi 2020; Mari 2020). Our survey revealed that for small (T1a) peripheral tumours (low risk of complications), there was a strong preference for PN (93%). However, in cases of (i) small (T1a) endophytic hilar and (ii) intermediate (T1b) tumours (with the solitary exception of hilar endophytic T1b cases) there was equipoise regarding the best approach. Moreover, 78% of urologists, aligned with the patient focus groups, explicitly stated a willingness to randomise these cases and therefore this defines our trial population.

Nephrologists: We also surveyed nephrologists (n=32) from the Renal Association, the leading professional body for the UK renal community. Here, following on from our patient focus groups and a strongly expressed motivation to save renal function where possible, we were interested to learn what thresholds of renal compromise would be considered clinically meaningful. We shared key relevant data explaining that the only RCT looking at RN vs PN, showed mean eGFRs stabilised at 12 months at 52.7mls/min/1.72m^2 with RN and 66.8mls/min/1.72m^2 with PN (difference of 14.1 ml/min/1.73m^2). Reductions of renal function to this these levels are associated with a 5-year risk of (i) ESKD approaching 1% in both groups (Scosyrev 2014) and (ii) cardiovascular events of 9.9% and 15.6%, for PN and RN respectively (Tangri 2016; Capitanio 2014). Although not reproduced in the Van Poppel study, these risks of cardiovascular events are consistent with the 40% increase shown by comparing eGFR>60 vs GFR=45-59 ml/min/1.73m^2 in a longitudinal cohort study that is a seminal paper in the nephology field (Go, 2004). In our proposed study, we expect the control arm (RN) to result in an eGFR as previously described in large studies (ca. 50 mL/min/1.73m²) in patients initial eGFR of >60mls/min (normal contralateral kidney). In the nephrologist's survey, 100% chose an eGFR difference of at least 10mls/min/1.72m^2 between PN and RN as being a minimal clinically important difference (MCID) and, triangulating these findings with those

from the urologists and patients, informed the design of our study and its co-primary outcome.

1.3 Assessment and management of risk

The CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports of adverse events, to a level appropriate to the risk assessment of the study.

Trial participants will be informed of possible benefits and known risks (including known complications) of both interventions in the trial by means of a Participant Information Leaflet (PIL), discussion with the local Urologists and Research Nurses. Both surgical procedures (partial nephrectomy and radical nephrectomy) are routinely used within the NHS. We do not anticipate that participants will run additional risks by participating in the PARTIAL study. Participants will sign a consent form approved by the Research Ethics Committee. They will be consented to participating in the study with follow up, being randomised, being contacted in the future about this and other research including electronic tracing using NHS data, and data linkage with computerised NHS data sources. Participants who are not able or not willing to be randomised will not be recruited.

2. TRIAL AIM AND OBJECTIVES

2.1 Aim

The aim of this trial is to determine the trade-off between potential benefits, harms and cost between partial nephrectomy (PN) with radical nephrectomy (RN), for intermediate sized and selected small complex kidney tumours, primarily focusing on renal function and surgical complications over 2 years.

2.2 Hypothesis

Partial nephrectomy *for intermediate sized 4-7cm (T1b) and small <4cm (T1a) endophytic (deep-seated) tumours result in better renal function by at least* 10mls/min/1.72m^2 *compared to radical nephrectomy in patients with a normal contralateral kidney.*

2.3 Objectives

Primary objective: Describe benefits (potential gains in renal function preservation) and harms (surgical complications) in comparing PN and RN.

Secondary objectives: Compare partial nephrectomy with radical nephrectomy in terms of:
(i) health related quality of life (HRQoL),
(ii) cost and cost-effectiveness,
(iii) quality of recovery (capturing length of stay),
(iv) rates of positive surgical margin rates (and retreatment/surgical revision),
(v) recurrence free and overall survival (including local recurrence),
(vi) rates of cardiovascular events (heart attack and stroke),
(vii) progression to chronic kidney disease (CKD),
(viii) operative conversions,
(ix) patient acceptability (interviews in embedded mixed methods trial process evaluation; and by participant questionnaire at 3 months).

Long-term objectives:

(i) We will obtain consent from participants to allow potential future follow-up through efficient means (such as routine data) as part of a separately funded study, allowing correlations of renal preservation with cardiovascular events, survival (cancer-specific, recurrence free and overall survival) and end-stage kidney disease (ESKD) at 5–10 years.

(ii) We aim to establish a well-characterised cohort of patients with RCC including clinical data, urine, blood and tumour specimens for future studies (based on separate funding). If additional funding for this objective is obtained, we will amend the protocol and associated documentation to accommodate this.

3. TRIAL DESIGN

A pragmatic patient-randomised controlled, parallel group superiority trial, with an embedded economic evaluation comparing PN and RN for patients with suspected or confirmed renal cell carcinoma (RCC). Patients will be approached to participate following informed decision-making and electing for a surgical approach. Trial treatments will follow routine clinical management protocols. There is an embedded mixed methods evaluation of trial recruitment.

An overview of the trial design is shown in Figure 1.

3.1 Intervention to be evaluated

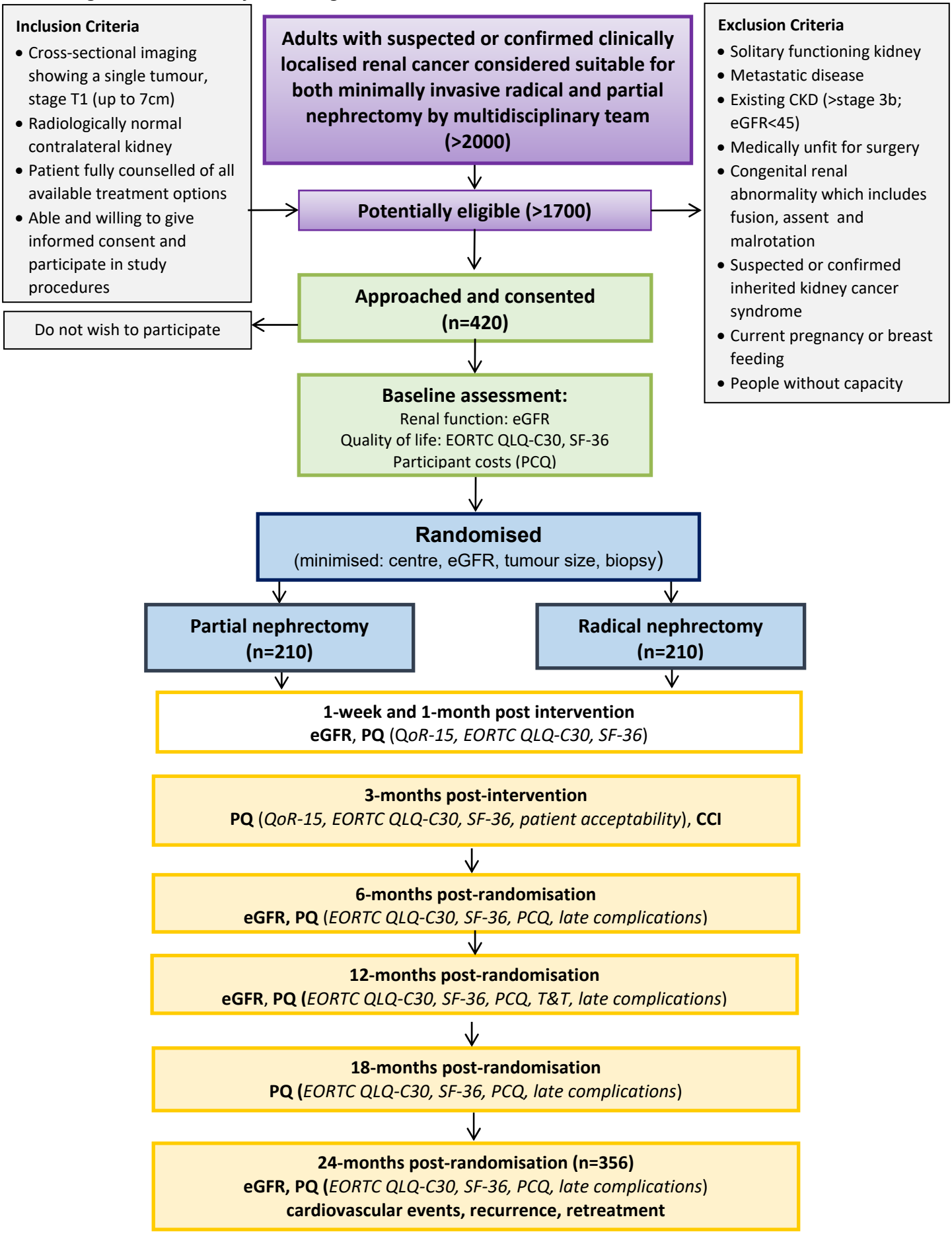
The two technologies being assessed are minimally invasive (keyhole surgery) partial nephrectomy (PN) vs radical nephrectomy (RN). The robotic approach is effectively a minimally invasive laparoscopic approach assisted by robotic technology. Open approaches are significantly more morbid that minimally invasive approaches and usually reserved for very large or anatomically complex tumours, which are outside the inclusions criteria of our study.

In the UK, looking at those patients with kidney cancers undergoing surgical treatment, there were 3,130 RN (73% laparoscopic, 5% robotic, 19% open, 3% n/a) and 1,562 PN (76% robotic, 9% laparoscopic 14% open, 1% n/a) as reported in the BAUS Nephrectomy Audit (British Association of Urological Surgeons 2019) capturing 79% of national activity. There is evidence that both laparoscopic approaches, with or without the robot, are broadly similar in outcomes (Li 2020).

Through the UK, robot access is increasing and the differential costs between laparoscopic and robotic costs are closing, meaning that an increasing proportion of robotic RN and PN are performed (Camp 2018). Therefore, to provide a generalisable approach to this pragmatic study, we will include both minimally invasive approaches, only excluding those for which open surgery is recommended.

Further details about the intervention are provided in section 5.

Figure 1: overview of trial design



4. TRIAL RECRUITMENT

4.1 Trial population

All adults with suspected or confirmed clinically localised renal cancer on cross-sectional imaging with a normal functioning contralateral kidney will be considered through screening in local/regional specialist MDTs (SMDT). Kidney cancer diagnosis in generalist urology set ups (such as some district general sites), without specialist expertise in PN and/or RN, should be discussed at SMDT, which should include members from specialist centres with PN capability and therefore ensure all patients have an equitable access to all appropriate options for treatment through referral.

4.2 Setting

The setting will be UK NHS secondary care medium and high-volume sites. Thirty such sites have agreed to support our study, ensuring generalisability, and we have six sites on a reserve list.

This network of sites provides a total of 1700 possible participants (British Association of Urological Surgeons 2019), accounting for approximately 85% of the national caseload, with an average of 44 (range 25–118) robotic partial nephrectomies/site/year.

These centres also include geographic populations with high disease burden (NE, NW and SW England and Wales) which have been historically underserved by research activity (NIHR Health Technology Assessment 2020).

Variations in surgeons/surgical team performance can produce wide differences in outcomes within the clinical trial setting. Surgeons and surgical teams will be competent in the delivery of robotic PNs and minimally invasive RNs and this will be assessed as part of site feasibility discussions. Surgeons for PARTIAL will have completed more than 30 robotic PNs and 50 minimally invasive (laparoscopic or robotic) RNs (as primary surgeon) and will have submitted this data to the database. Additionally, surgeons for PARTIAL will have undertaken more than 10 robotic PNs per year for the last 2 years as the primary surgeon and median length-of-stay and surgical complication rates will fall within acceptable parameters (BAUS Nephrectomy Audit 2019). It is likely that there will be more than one surgeon delivering PNs and RNs for PARTIAL in some centres. Individual surgeon data will act as surrogate measures for the entire surgical team.

4.3 Inclusion and exclusion criteria

Inclusion criteria:

- Adults ≥18 years;
- Newly diagnosed clinically localised renal cancer (suspected on cross-sectional imaging or histologically confirmed)*;
- Local multi-disciplinary review identifying those cases thought suitable for both minimally invasive RN or PN; (for minimally invasive we mean laparoscopic or robotic surgery; cases where open surgery is planned are not eligible);
- Cross-sectional imaging showing a single tumour, stage T1 (up to 7cm), where there is equipoise in the MDT and willingness to recruit into the trial;
- On imaging, evidence of a radiologically normal contralateral kidney;
- Patients that have been fully counselled of all the available treatment options (including non-surgical approaches, where appropriate);

- Able and willing to give informed consent to participate and to participate in study procedures.

Note: Biopsy proven RCC was considered as an inclusion criterion. This issue was also specifically explored in our national urologist questionnaire and patient focus groups. Although this is routinely offered in selected cases by 70% of clinicians it is not routinely taken up by patients who often elect to proceed direct to surgery having expressed anxiety about waiting for biopsy and delaying treatment. Therefore, we will* ***not* *be mandating biopsy as an inclusion criteria.*

Where biopsy is part of local standard of care, approximately 10% may have non-conclusive biopsy. For these patients, if the surgeon and patient are in equipoise in relation to full or partial nephrectomy, they are eligible for the study and can be randomised. Participants who do not have biopsy are also eligible for the study. In both these groups, if, following treatment, it becomes apparent that there was no tumour (RCC) present, the participant will remain in this pragmatic, intention to treat study. All outcomes (apart from those secondary outcomes specifically related to RCC, including local recurrence, need for re-treatment) are relevant) and will be collected from this group. We intend to explore any effect of biopsy/no biopsy, and confirmed RCC/no RCC. This will be a post-hoc sub-group analysis if numbers are sufficient in both potential subgroups or a sensitivity analysis if there are insufficient numbers to form sub-groups.(see section 11).

Exclusion criteria:

- Solitary functioning kidney
- Metastatic disease
- Existing CKD (>stage 3b; eGFR<45)
- Medically unfit for surgery
- Congenital renal abnormality which includes fusion, assent and malrotation
- Suspected or confirmed inherited kidney cancer syndrome
- Current pregnancy or breast feeding
- People without capacity

4 4 Co-enrolment

There may be satellite studies or sub-studies developed as part of the main PARTIAL trial (see protocol section 20) and participants may be co-enrolled into these.

Participants will be permitted to take part in other non-interventional studies (e.g. questionnaire studies, studies collecting blood/tissue samples or studies investigating aspects of robotic surgery).

With the exception of trials of adjuvant therapy (see below), those enrolled in the active intervention phase of another interventional trial should be excluded from PARTIAL.

It would not be ethical to deny access of PARTIAL participants to a clinical trial of adjuvant therapy (or to adjuvant therapy if it becomes part of standard of care). Equally the PARTIAL trial may suffer from recruitment challenges if in competition with trials of adjuvant therapy. Only a proportion of participants in the PARTIAL trial will also be eligible for adjuvant therapy, and those who are eligible will be permitted to participate in clinical trials of adjuvant trials subject to appropriate co-enrolment agreements.

Patients will be eligible for inclusion in PARTIAL if they are in the long-term follow-up phase of any other interventional trial.

4.5 Identifying and approaching participants

Patients will be identified following review by specialist MDT at UK hospitals. Potentially eligible patients may be identified in generalist urologist clinics in hospitals without specialist expertise in partial and/or radical nephrectomy. Such patients may be discussed at MDT meetings at specialist centres where their treatment may take place.

Local pathway and procedures at participating hospitals are different and the timing and mode of approach to eligible patients and the consent process may vary to accommodate both the local circumstances and the needs and preferences of the potential participant.

We will provide training at site initiations describing areas of uncertainty in the field, presenting contemporary evidence and a summary of our national survey to help minimise individual clinician biases. We aim to ensure that screened patients appreciate there are choices and uncertainty about treatment and respective treatment outcomes. Irrespective of becoming a participant, our decision-making tools will help provide patients information on equitable access to their preferred treatment in conjunction with treating urologist, appreciating that a referral to a specialist centre could be sought if their chosen treatment it not offered locally.

Eligible patients will be given or sent a Participant Information Leaflet (PIL) describing the study and will have the opportunity to read this before deciding whether or not they wish to take part. A member of the clinical team will discuss the surgical options and establish eligibility, and the patient will have opportunity to discuss the study with the clinical team. These consultations may occur face-to-face or virtually using locally accepted NHS platforms. Eligible patients can discuss the study with other members of the local clinical team, the Research Nurse, family and friends and their GP before deciding whether or not to take part in the study. The patient may decide to participate during an initial (or subsequent) consultation with the clinical team, or alternatively at home.

If the participant decides to participate at home, they will be sent or given (if initial consultation is face-to-face) the consent form and baseline questionnaire for completion. If the participant agrees to be contacted at home, they may receive a telephone call from the site Research Nurse to discuss any queries. Participants who decide to participate at home will send their completed documents (consent form and baseline questionnaire) through the post to the local team at their treating hospital. All participants will have the option to complete the consent form electronically rather than completing a hard copy (section 4.7.1).

Details of the consent discussion, including discussion date, will be recorded in the medical notes and on the trial inclusion form.

Eligibility will be confirmed by the PI, or by a medically qualified delegate at each recruitment site.

A paper screening log will be kept at site, with limited (non-identifiable) information uploaded onto the study website.

All people who are randomised into the study will be assigned a unique Study Number.

4.6 Non-recruited participants

The following anonymised information will be monitored and collected for all potentially eligible participants

- Year of birth
- Ethnicity (if recorded in the medical notes)
- Gender
- Date of consultation when approached about the trial
- Reason for not participating if willing to give a reason

4.7 Informed consent

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. As part of the informed consent process, potential participants will be made aware of all aspects of the trial, including the potential risks and their responsibilities. There is no minimum time that potential participants should be given to decide whether to participate in the trial. Potential participants will be given enough time, and as long as they want, to accept or decline involvement and will be given opportunity to ask questions and to have these answered before giving consent.

It will be explained that entry into the trial is entirely voluntary, and that treatment and care will not be affected by their decision, and they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected to date cannot be erased and will be used in the final analyses.

Patients who cannot give informed consent (e.g. due to their mental state) will not be eligible for participation. Following informed consent, if a participant loses capacity, the consent given when capable remains legally valid. In such circumstances, a decision needs to be made, in conjunction with the participant and any family or carers, in relation to ongoing participation in the trial.

Patients who are not able to read or write (but who have capacity and who can speak English sufficiently to understand the information being provided orally) can agree to take part in the trial. In such cases, the trial team will provide them with written literature about the trial and read and discuss this information with the potential participant. There should also be a discussion about the support networks that the patient has to facilitate their participation in the trial (for example help to complete questionnaires). If the potential participant is fully informed and wishes to take part in the trial, they will be asked to sign or make their mark on the consent form. Their agreement to take part in the trial should be witnessed by someone independent from the research team.

Procedures to seek and gain informed consent from eligible potential participants are agreed and confirmed by Research Ethics Committees with responsibility for reviewing applications for research. The application for approval is made via the NHS National Research Ethics Service.

Where informed consent is received in person, this should be received by an appropriately trained individual who is listed on the delegation log. Consent forms that are returned by post are checked, signed and dated with the date of receipt by someone who is listed on the delegation log with appropriate delegated responsibilities. The countersignature will only be recorded after discussion has taken place with the participant about the study and any

questions have been answered. Only once both patient and person receiving consent signatures are present will informed consent be considered to have been obtained.

Participants will be given or sent a copy of the completed consent form for their own records and a copy will be retained in the investigator site file (ISF). A copy of the consent form should be forwarded to the trial office for retention in the Trial Master File (TMF).

4.7.1 e-Consent

For participants who opt to consent using an e-consent form, they will do this via the secure web-based trial management system provided by CHaRT. If this option is preferred, participants will be asked to provide their email address which will be entered into the secure web-based trial management system. Participants will be sent a verification email with a link to verify their email. Once the email address is verified, participants will be automatically emailed the PIL and a link to the participant e-consent form for their unique study number. The e-consent form will be identical to the approved paper version of consent form, with the approved PIL version number and date automatically populated. The participant will be asked to provide their signature online via a signature box using a finger tracing via a touch screen or using a mouse.

Completed e-consent forms will be checked, and electronically counter-signed by someone listed on the delegation log with appropriate delegated responsibilities. The countersignature will only be recorded after discussion has taken place with the participant about the study and any questions have been answered. Only once both participant and person receiving consent signatures are present will informed consent be considered to have been obtained. Any e-consent obtained will be verbally confirmed by the site at any future communication. Participants will be sent a copy of the e-consent form for their own records and a copy will be retained in the ISF and TMF.

Should participants who are sent the study information choose not to take part in the study their email address will be deleted (as an automated process) from the trial management system after 3 months.

The trial management system used to record e-consent has a clear audit trail with tracking of all inserts or updates made. Database interactions logged against a user and date/time and the audit trail can be downloaded and analysed at any time by authorised users.

4.8 Randomisation and allocation

Eligible and consenting participants are randomised using the proven 24-hour web-based randomisation application hosted by CHaRT.

Participants will be randomly allocated 1:1 to either PN or RN using a remote central, computer generated randomisation schedule, minimised by previously reported major confounders: of centre, pre-operative eGFR (45-59; ≥60) and tumour size (T1a; T1b), pre-randomisation biopsy (yes; no).

4.9 Blinding

Blinding for participants is not possible. Similarly, the immediate clinical, nursing and research teams cannot be blinded. However, the primary outcome kidney function, is determined objectively.

4.10 Code break/Emergency unblinding procedures

This is no blinding within the study and therefore emergency unblinding procedures are not required.

4.11 Administration arrangements post recruitment

Following trial entry, the trial office will:

- Notify the GP in writing that a participant has joined the trial.

The site research team should:

- File a copy of the consent form in the hospital/primary care notes along with information about the trial.
- File a copy of the GP letter into the hospital notes (if required by the site).
- Enter trial data regarding the participant into the bespoke trial website.
- Ensure participant is added to the appropriate surgical list.
- Maintain trial documentation at site.
- Return a copy of the signed consent form to the Trial Office in Aberdeen.

5. TRIAL INTERVENTION

Total (Radical) Nephrectomy – Minimally Invasive Technique (Robotic/Laparoscopic)

This procedure is undertaken in patients with diagnosed/suspected localised kidney cancer.

It is undertaken under general anaesthesia. The patient is secured in a lateral position. Small incisions are made in the abdominal wall to inset ports (4-6) for laparoscopic /robotic instruments.

The kidney is dissected from adjoining abdominal organs and colon while keeping Gerona's fascia intact. Dissection is carried out to identify ureter and renal vessel (artery and vein).

Renal vessels and ureter are clipped and cut and the kidney with perinephric fat is placed in a secure bag and removed through and Pfannenstiel or extended port incision.

Wound drains may or may not be used for the renal bed. The extracted wound and port incisions are closed with sutures/clips.

Partial Nephrectomy – Minimally Invasive Technique (Robotic/Laparoscopic)

This procedure is undertaken in patients with diagnosed/suspected localised kidney cancer.

It is undertaken under general anaesthesia. The patient is secured in a lateral position. Small incisions are made in the abdominal wall to inset ports (4-6) for laparoscopic /robotic instruments.

The kidney is dissected from adjoining abdominal organs and colon. Dissection is carried out to identify ureter and renal vessels (artery and vein). The tumour is identified and marked with intraoperative ultrasound (if available).

Blood flow is stopped to the kidney by applying vascular clamps to the artery/vein. The tumour is dissected and haemostasis is secured in some cases by renography (suturing) of the base. However, this step may not be universally applied. The cut edges (may or may not

be) approximated with an additional suture layer. Vascular sealant may or may not be applied during this process to improve the haemostasis. Blood flow to the kidney is restored by removing the vascular clamps and further measures (suturing /sealant) may be applied for enhanced haemostasis after release of clamps.

Peri nephric fat is sutured over the kidney. The tumour is secured in bag and removed through one of the extended port incisions.

Wound drains may or may not be used for the renal bed. The extracted wound and port incisions are closed with sutures/clips.

6. OUTCOME MEASURES

6.1 Primary outcome measures

(i) *Gains* in preserving renal function over two years (eGFR at baseline, 1 week and 1 month post-intervention, and 6, 12 and 24 months post-randomisation using NICE recommend Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation): We will determine if PN results in better maintenance of renal function compared with RN (>10 mL/min/1.73 m^2 differential reduction in eGFR; see section 10.1 for further details) in individuals with contralateral normal kidneys at 2 years. Renal function initially falls but compensations can occur with within the first 9 months after surgery and stabilises beyond the first 12-18 months following both PN and RN (Scosyrev 2014; Leppert 2018).

(ii) *Harms* captured by Comprehensive Complication Index (CCI) over the peri-operative period: Most complications for both PN and RN occur acutely in the post-operative window, such as bleeding and urine leaks. Based on work from our group (as part of a global network), expected rates of significant complications (Clavien-Dindo grade 3 or more) is up to 4-11% of more surgical complex PNs and 2-3% of RNs (Schiavina 2017). Acceptable thresholds of complication are not well described, and most studies fail to provide information about the cumulative severity of complications, or inform only on the most severe event, ignoring events of lesser severity. The CCI is based on the Clavien-Dindo classification (reporting on the most severe event) and is calculated as the sum of all surgical complications that are weighted for their severity (Slankamenac 2013) and will allow us to more comprehensively compare relative harms – including all incurred complications and re-operation rates, within 90 days of surgery. This tool is validated in renal surgery and estimated CCI scores for RN and PN are 2.6 ± 7.9 and 8.4 ± 14.7, respectively (Kowalewski 2020; Kowalewski 2021). However, more precise measures are first required before we can explore trade-off with potential gains.

6.2 Secondary outcome measures

(i) HRQoL – EORTC QLQ-C30 and SF-36 (Acute version – 1 week recall): The most dynamic phase in HRQoL will be in the weeks and months after surgery, relating to hospital stay and complications (Poulakis 2003) and serial assessment will allow AUC analysis extended up to 24 months (measured at baseline, 1 week and 1, 3 months post-intervention and 6, 12, 18 and 24 months post-randomisation). These data will complement and extend the acute measure of harm collected using the CCI.

(ii) Cost-effectiveness (QALY and costs): we will capture a full assessment of care pathway costs (including complications) and HRQoL over the trial follow-up. The harms and gains for

each retreatment strategy will be traded off mainly as QALYs (based on the SF-6D in for the base case, EORTC QLQ-C30 for a sensitivity analysis), and cost-consequence. (see section 12).

(iii) QoR-15 quality of recovery questionnaire (including length of stay): As in most cases hospital admissions last just a few days without significant complication, to further assess more subtle harms in the acute perioperative timeframe from the patent perspective we will deploy the QoR-15 questionnaire. It is a patient-reported outcome instrument that measures the quality of recovery after surgery and anaesthesia and has been validated in clinical trials (Kleif 2018)

(iv) Positive surgical margins, local recurrence, need for retreatment: Over two years we will capture positive margin rates and their consequence. From current series, positive surgical margin rates of up to 5% for PN are reported (Delto 2018). However, in many cases this may not represent a true case of residual disease (the periphery of the excision margin may be damaged by surgical excision) as only <1% require further treatment and there appear to be no impact on risk of cancer death (Bensalah 2010). In our patient focus groups, higher rates of surgical margin were acceptable if re-treatment rates remained low, and survival unaffected. However, this comes with a burden of increased anxiety for patient, thinking the cancer could come back, and increased intensity and cost of follow up imaging. In our patient focus groups, being cured of cancer was the main concern. These oncological outcomes will be correlated with HRQoL with a focus on capturing anxiety and cost relating to surveillance/investigation and possibly further treatments.

(v) Recurrence free and overall survival (cancer specific survival and all-cause mortality): As outlined above, low rates of local recurrence can occur within the kidney, but also metachronous metastatic recurrence can occur, affecting both PN and RN. The incidence of RCC recurrence has been reported to be 7% with a median time of 38 months for T1 tumours. Relative rates of extra-renal recurrence, renal cancer death and all-cause mortality will be captured, and in time will be linked into the proposed long-term study (see below).

(vi) Cardiovascular events (non-fatal heart attack, non-fatal stroke and cardiovascular death): One of the main clinical drivers to consider a nephron-sparing approach is based off observational studies correlating renal function with cardiovascular events and death (Go 2004; MacLennan 2012a; MacLennan 2012b; Kim 2012; Capitanio 2015; Leppert 2018; Breau 2020). Even with moderate levels of CKD (<60 ml/min/1.73m^2), there is an associated 40% increased risk of cardiovascular events and 20% increase in all-cause mortality (Go 2004). However, the effect of surgical reduction of renal function has been contended (Lane 2012). Additionally, the randomised data from the EORTC study (Van Poppel 2007) comparing PN vs RN for small renal masses showed no benefit for PN, in fact it showed increased deaths in the PN arm (24% vs 19% 10-year all-cause mortality and 9.3% vs 7.3% cardiovascular mortality for PN vs RN, respectively). Limitations of this study are discussed above and a new contemporary high-quality study is required. Relative rates for PN and RN will be captured and in time follow-up will be extended to the proposed long-term study where we will also account a number of confounding interactions (see below).

(vii) Progression to chronic kidney disease (CKD) stages 3, 4, 5 (end stage) by eGFR: A major motivation for patients choosing PN in our focus group was the need to preserve kidney function because of the potential renal disease in the future, even if they had a normal contralateral kidney. We will measure eGFR throughout routine follow-up (pre-operation

baseline, at 1 week and 1 month post-intervention and then at 6, 12 and 24 months post-randomisation). Again, we will explore longer term data linkage (including The UK Renal Registry which collects data on ESKD).

(viii) Operative conversion to RN: Contemporary practices, using the robot, only <5% convert to RN from PN (Arora 2018; Klein 2021; Petros 2018). There was demonstrable equipoise in our clinician survey, regarding the best approach for the small T1a hilar endophytic tumours. Especially in these cases, there is a risk to the blood supply/surgical complication and a resultant conversion to RN.

(ix) Patient acceptability: In the EORTC RCT of PN and RN, there was 21% cross over (Van Poppel 2011) suggesting that treating clinicians and possibly participants lacked equipoise. We surveyed urologists and patients and learnt that patients strongly trust the recommendation of the clinician. We have carefully selected tumour criterion that clinicians showed an agreement for randomisation (78%). Nevertheless, we will monitor patient acceptability from screening logs to reveal preferences and pre-operative post-randomisation cross over. In order to understand patient (and clinical preferences) and develop solutions to address misunderstandings and enhance recruitment a mixed methods trial process evaluation will also be undertaken as part of the pilot (see below).

We will also investigate intervention acceptability to patients (in both trial arms) at 3 months using a theory informed questionnaire to assess the acceptability of healthcare interventions based on work by Sekhon et al 2022).

(x) Core Outcome Sets in renal cancer: There is an ongoing core outcome set (COS) in development for localised renal cell carcinoma (www.comet-initiative.org/Studies/Details/1406). Our group already has existing collaborations with the lead (Dr Steven MacLennan, University of Aberdeen). The COS will be completed (but not published) during the lifetime of this trial. In order to accelerate the COS development and maximise benefit for PARTIAL, the interviews proposed with patients as part of the embedded mixed methods evaluation (appendix 1) will also collect information on outcomes of importance for people living with renal cancer. These will also feed into the COS development at no additional cost to the trial. We will communicate regularly to ensure any outcomes identified from the developing COS and incorporated (where able) into PARTIAL. A similar process has been conducted in another ongoing NIHR HTA trial (CGALL – 14/192/71).

6.3 Long term outcomes

(i) As part of a separately funded study, we will measure at 5-10 years cardiovascular events (heart attack, stroke and cardiovascular death), survival (CSS/OS) and longitudinal eGFR (including rates of ESKD). Glomerular filtration rate loss related to renal cancer surgery, whether due to partial or radical nephrectomy, influences the risk of CKD; however, its impact on survival remains debated (Van Poppell 2011; Lane 2012). In contrast, age and the preoperative glomerular filtration rate, which reflects general health status, appear to be more robust predictors of non-renal cancer mortality, at least in patients with good preoperative function or mild CKD (Zabell 2018). Therefore, in light of the debate in the literature, we will collect data to model interactions between age, established medical conditions, preoperative and post-operative renal function on cardiovascular events and mortality.

(ii) Well-characterised cohort of patient tissue including clinical data, urine, blood and tumour specimens will allow future measures of biomarker for detection, surveillance, prognosis, and inform best treatment strategies (based on separate funding).

7. DATA COLLECTION AND PROCESSING

7.1 Measuring outcomes

Table 1 summarises what outcomes are assessed at each of the timepoints. Further details about collection of outcome data are provided elsewhere in this section.

Table 1

	Baseline	Surgery	Post intervention			Post randomisation			
			1 week	1 month	3 months	6 months	12 months	18 months	24 months
Baseline characteristics	RA								
Renal function: eGFR[1]	SoC		SoC[2]	SoC		SoC	SoC		SoC
Quality of life: EORTC QLQ-C30, SF-36	PQ		PQ	PQ	PQ	PQ	PQ	PQ	PQ
Participant cost questionnaire	PQ					PQ	PQ	PQ	PQ
Participant time and travel							PQ		
Comprehensive complication index (CCI)					MR				
Quality of recovery (QoR-15)			PQ	PQ	PQ				
Late complications						PQ	PQ	PQ	PQ
Cardiovascular events									MR
Recurrence[3]									SoC
Further treatment									MR
Surgical details & resource use		MR							
Pathology and positive surgical margins		MR							
Patient acceptability					PQ				

RA, Research Assessment; SoC, Standard of Care; PQ, Participant questionnaire; MR, medical records

[1] measurement of eGFR is standard of care for participants with suspected or confirmed RCC during their pre-operative work-up. Post surgery, measurement of eGFR is standard of care for those with confirmed RCC but the timepoints at which it is measured may not coincide with the study timepoints. The eGFR may be done at hospital outpatient clinics or in primary care. Therefore results of all eGFR tests post randomisation will be recorded from laboratory records as part of study data. In patients who do not have confirmed RCC, regular eGFR may not be standard of care, and in such cases, participants will be invited to attend for study specific follow-up with the aim of achieving eGFR measurements within 1 week, and at 1 month after surgery and 6, 12 and 24 months after randomisation. At the point of analysis, in consultation with the PMG, the statistician will allocate each eGFR measurement to the appropriate time-point or use the actual date of test for an area under the curve analysis.

[2] The first post-operative eGFR is usually done within 48 hours of surgery, and this will be used as the 1 week measure.

[3] Recurrence is only possible in patients who had confirmed RCC. Standard of care for patients with confirmed RCC is a six-monthly scan for 5 years. Recurrence will be determined from routine scans up to and including 24 months. This outcome will not be collected in patients who do not have confirmed RCC.

7.2 Baseline

At baseline, the local research team will complete a baseline case report form, which will capture information to characterise the study population in relation to demographic and clinical factors. We will collect age, sex, ethnicity, height, weight, postcode (for area level deprivation), medical history (including hypertension and diabetes), radiological tumour size and location (for PADUA classification; Ficarra 2009), pre-randomisation biopsy status and smoking status. As part of standard of care, renal function (eGRF) should be measured, and this will be captured on the baseline CRF.

Participants will be asked to complete a questionnaire including EORTC QCQ-C30 and the acute version of the SF-36. They will also be asked to complete a cost questionnaire reflecting recent use of health services.

7.3 Follow-up

Surgery

The local research team will collect information about the surgical procedure from medical records or in real time, including American Society of Anesthesiologists (ASA) physical status classification, and grading of intraoperative complications (ClassIntra; Dell-Kuster 2020). The surgical CRF will be supplemented with information about pathology and positive surgical margins when this information is available.

Harms

Three months after surgery, the local research team will complete the Comprehensive Complication Index (CCI) to record any complications following surgery.

Kidney function

In patients who do not have confirmed RCC, regular eGFR may not be standard of care, and in such cases, participants will be invited to attend for study specific measurement of eGFR.

In patients who have confirmed RCC, measurement of eGFR is standard of care but the timepoints at which it is measured may not coincide with the study timepoints.

For all study participants, the key measurements of eGFR for the purposes of the study will be within one week of surgery, and at 1, month post intervention, and at 6, 12 and 24 months post-randomisation. The preferable window for the 1 month measurement is +/- 1 week. The preferable window for the 6 and 12 month measurements is +/- 1 month. The preferable window for the 24 month measurements is +/- 3 months. However, an out-of-window measurement is preferable to no measurement at any timepoint.

In addition, the results of **all eGFR tests post-randomisation up to 24 months post-intervention**, including out of window observations, will be recorded by the research team from laboratory records as part of study data. The statistical analysis plan will document how out-of-window measurements will be incorporated into the analysis.

The trial office will monitor the accumulating eGFR data and ask sites to prioritise measurements in patients within one week and 1 month post-intervention, and 6, 12 and 24 months post-randomisation. Missing eGFR measurements will be identifiable within the trial dataset and not recorded as protocol deviations.

Major Adverse Cardiovascular Events (MACE)
At 24 months post-randomisation, the local research team will review the participant's medical notes to identify any MACE that have occurred since randomisation. For the purposes of the study, MACE will include non fatal stroke, non fatal myocardial infarction, and cardiac death.

Further treatment
At 24 months post-randomisation, the local research team will review the participant's medical notes to identify any further treatment related to their kidney that has occurred since randomisation.

Recurrence
As noted above, recurrence is only possible in patients who had confirmed RCC following surgery. Standard of care for such patients includes a six-monthly/regular scan for 5 years. At 24 months post-randomisation, the local research team will review the participant's medical notes to identify any recurrence from routine scans up to and including 24 months.

Participants who do not have confirmed RCC following surgery cannot have a recurrence, and so this outcome will not be collected in patients who do not have confirmed RCC.

Patient reported outcomes
Participants will be asked to complete a questionnaire including EORTC QCQ-C30, the acute version of the SF-36 and the Quality of Recovery instrument at 1 week, 1 month and 3 months post-intervention.

At 6, 12, 18 and 24 months post-randomisation, participants will be asked to complete a questionnaire including EORTC QCQ-C30, the acute version of the SF-36, participant costs, and to report any late complications.

At 12 months post-randomisation, they will also be asked about their time and travel costs associated with accessing care.

Any trial participants who do not progress to surgery will not be eligible to complete the questionnaires at post-intervention time points (1 week, 1 month and 3 months post-intervention) but will be eligible to complete the post-randomisation timepoints (6, 12, 18 and 24 months post-randomisation).

At baseline, participants will be asked for their contact preferences for questionnaires. Those selecting email as their preference will have a link to the questionnaire emailed to them. Those selecting postal as their preference will have the questionnaire posted to them. Those selecting text messaging as their preference will have a link to the questionnaire texted to them. First reminders will be emailed, posted or texted to participants (according to their stated preference). A second reminder (by telephone) will be attempted but if there is no response by telephone, a final postal reminder will be sent.

Questionnaires will be administered to all participants who were randomised in the study, regardless of whether or not they had the surgery they were randomised to receive, unless they have opted out of questionnaire follow-up.

If questionnaires are returned as non-deliverable, attempts will be made by site staff or staff at the Trial Office to trace the participant.

7.4 Capture of data from medical records (if appropriate)

As noted above, the results eGFR tests done as standard of care will be captured from medical records. The secondary care medical notes of all participants will be reviewed at 24 months after randomisation for cardiovascular events, further treatment, late complications and recurrence.

7.5 Change of Status/Withdrawal procedures

Participants remain in the trial unless they choose to withdraw consent. Participants are free to withdraw from the trial at any timepoint. All changes in status, with the exception of complete withdrawal of consent, means the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal is retained and used in the analysis.

Following informed consent, if a participant loses capacity, the consent given when capable remains legally valid. In such circumstances, a decision needs to be made, in conjunction with the participant and any family or carers, in relation to ongoing participation in the study.

Participants who do not receive their allocated treatment or receive the other (non-allocated) intervention are not considered withdrawals and will be followed-up for all trial outcomes unless they request otherwise.

Participants who request that no further questionnaires are issued (i.e. completing questionnaires) will be followed up for other trial outcomes unless they are complete withdrawals.

Participants for whom any outcome data are available are included in an intention to treat analysis.

7.6 Data processing

Research Nurses will enter locally collected data in the centres. Staff in the Trial office will work closely with local Research Nurses to ensure the data are as complete and accurate as possible. Postal questionnaires will be entered into the study website by trial office staff.

7.7 Long term follow-up

We plan to seek funding to follow-up participants in the longer-term using data from NHS and other government central registries, and primary care and hospital notes (see section 6.3 for further details). We seek informed consent for this at the outset of the trial.

7.8 Participant samples

We plan to seek separate funding to establish a well-characterised cohort of patient tissue including clinical data, urine, blood and tumour specimens which will allow future measures of biomarker for detection, surveillance, prognosis, and inform best treatment strategies. If funding is secured, an amendment to this protocol (with associated patient facing documentation) will be made to establish the cohort of patient tissue.

8. SAFETY

8.1 Safety-related outcomes collected within PARTIAL

Harms captured by Comprehensive Complication Index (CCI) over the peri-operative period (up to 3 months post-surgery) are a primary outcome of the PARTIAL study and will be collected as part of the CRF. Participants will be asked to report any late complications of surgery as part of the follow-up questionnaires. We will also collect these from medical records at 24 months post-randomisation. Secondary outcomes include cardiovascular events and chronic kidney disease, again which will be captured as part of the case report form.

Both surgical procedures (PN and RN) are routinely used within the NHS and safety is well characterised. The PARTIAL study is highly unlikely to reveal any new safety information relating to either partial or radical nephrectomy. The recording of selected adverse events (AEs) will not impact the safety of participants in the trial, or the integrity of the trial itself.

As such, the following will **not** be classed or reported as AEs (but where appropriate, will be recorded as part of the case report form):

- *Intraoperative complications (complication recorded as part of the surgery CRF)*
- *Surgical complications (any complication recorded as part of the CCI, with or without hospitalisation or prolongation of existing hospitalisation)*
- *Late complications following surgery (for example incisional hernia, ongoing pain around the incisional sites, need for dialysis; which will be captured in the participant questionnaires and from the review of medical records at 24 months).*
- *Prolonged hospitalisation without an associated adverse event*
- *Additional medication required above that normally expected*
- *Emergency presentations and admissions*
- *Routine admissions for pre-planned events*

In addition, any AE that would already be captured as a secondary outcome for the study would not be reported separately as an AE for PARTIAL:

- Positive surgical margins (retreatment/ surgical revision)
- Recurrence or metastasis of renal cell carcinoma
- Death (any cause)
- Cardiovascular event
- Progression to chronic kidney disease

All AEs (except those listed above) that meet the criteria for a Serious Adverse Event (SAE) will be documented from the date protocol defined treatment commenced (entering the anaesthesia suite) until the participants exits from the study (24 months post randomisation or withdraws from collection of data). Any SAEs that are not included in the list above which are assessed to be at least possibly related to the intervention must still be reported in an expedited manner irrespective of how long after intervention the event occurred.

8.2 Standard Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical event affecting a clinical trial participant.

Term	Definition
Serious Adverse Event (SAE)	Where an AE • results in death; • is life threatening (i.e. 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; • is a congenital anomaly or birth defect, • is otherwise considered medically significant by the investigator

Adverse events are not:

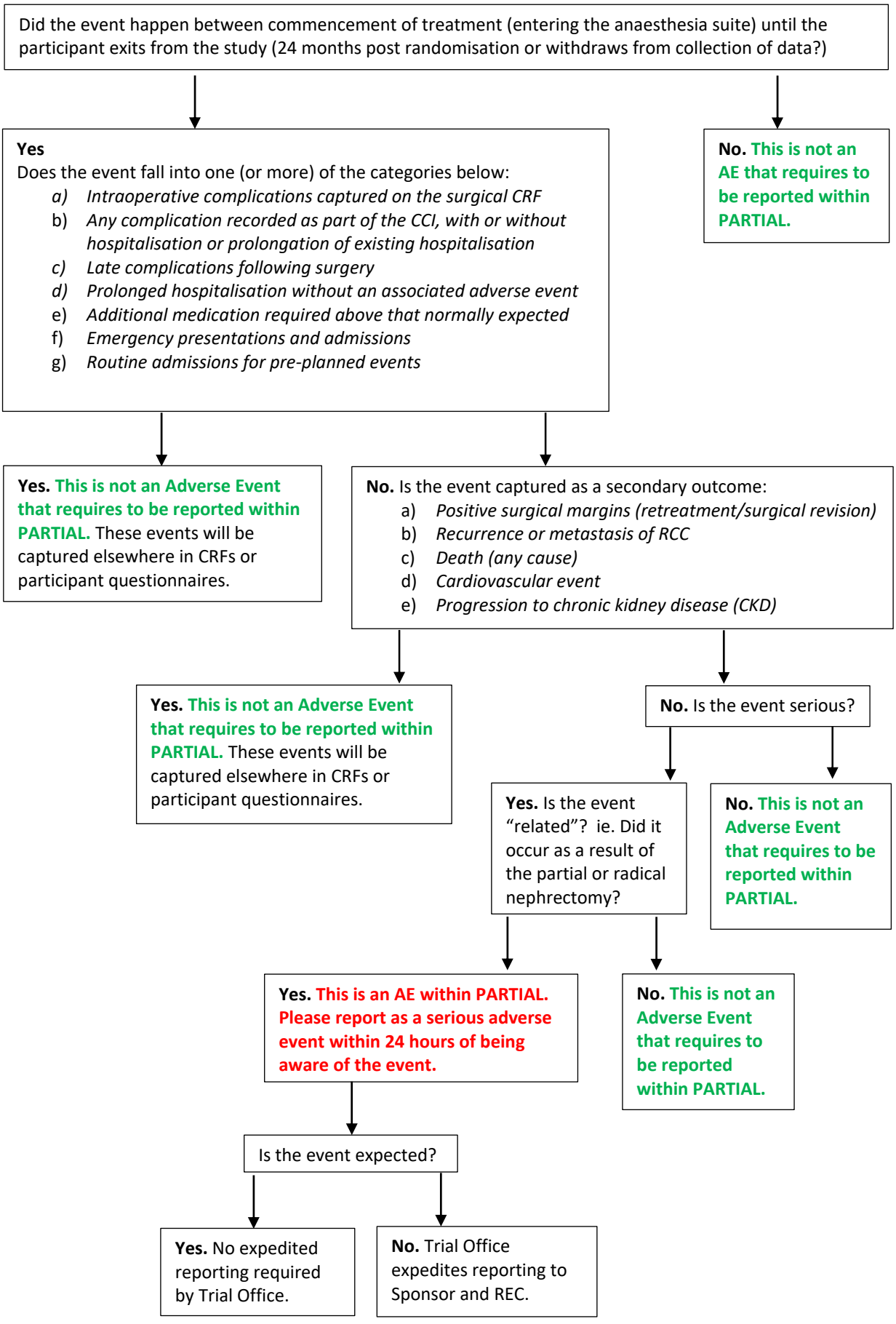
- continuous and persistent disease or symptom, present before the trial, which fails to progress;
- signs or symptoms of the disease being studied; or
- treatment failure (for example conversion from partial nephrectomy to radical nephrectomy).

Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate.

8.3 Trial specific considerations

Section 8.1 outlines the trial specific considerations in relation to safety reporting. These are summarised in Figure 2.

Figure 2. Summary of safety reporting procedures in PARTIAL



8.4 Procedures for detecting, evaluating, recording, & reporting AEs and SAEs

8.4.1 Detecting AEs and SAEs

All AEs and SAEs meeting the criteria for recording within the PARTIAL trial (see sections 8.1-8.3) are recorded from the date that protocol defined treatment commenced (entering the anaesthesia suite) until the participants exits from the study (24 months post randomisation or withdraws from collection of data). The Investigator asks about the occurrence of relevant AEs/SAEs (i.e. those that meet the criteria for recording within the PARTIAL trial) at every visit, and within follow-up questionnaires.

8.4.2 Evaluating AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event.

Consideration of whether the AE/SAE requires to be recorded within PARTIAL

The investigator should refer to section 8.1 of the protocol and figure 2 to determine whether or not the event requires to be recorded within PARTIAL.

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 8.2.

Assessment of Relatedness (causality)

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related:** resulted from administration of any of the research procedures required by the protocol, whether or not it is either a) the specific intervention under investigation or b) it is administered outside the study as part of normal care.
- **Unrelated**: where an event is not considered to be related to the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness

Expectedness will be assessed for events that meet the criteria for serious and related.

8.4.3 Recording SAEs

The Investigator (or delegate) should then record all relevant SAEs on the SAE form.

8.4.4 Reporting SAEs

Reporting responsibilities of sites

Once the Investigator becomes aware that an event has occurred in a trial participant that requires to be recorded as an SAE in PARTIAL, (see figure 2) they must report the information to the Trial Office within 24 hours. The Trial Office will report to the Sponsor within 24 hours of becoming aware of the event.

The SAE form must be completed as thoroughly as possible with all available details of the event and signed by the Investigator or designee.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

To report an SAE to the trial office, site staff can either complete a hard copy of the SAE form and email it to the trial office or create the SAE form directly into the trial website. If the SAE form is created directly onto the trial website, the trial manager will be automatically notified.

Reporting responsibilities of the Trial Office
If the event is *serious, related* (required by the protocol (i.e. partial or radical nephrectomy)), *and unexpected*, the Trial Office will notify the Sponsor within 24 hours of receiving the signed SAE notification.

The sponsor will provide an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties and documented in the TMF.

If the event is *serious but not related*, or *serious, related and expected*, expedited reporting to Sponsor is not required. Rather these events will be summarised and reported to Sponsor, REC, Funder, TSC and DMC in their regular progress reports.

8.4.5 Regulatory reporting requirements
The CI or delegate reports any events that are *serious, related and unexpected* to the REC within 15 days of the CI becoming aware of it using the HRA SAE form.

The CI is responsible for submitting annual reports to the REC on the anniversary of the approval.

All related SAEs are summarised and reported to the Ethics Committee, the Funder, the Trial Steering Committee and the Data Monitoring Committee in their regular reports.

8.4.6 Follow up procedures
After initially recording and reporting an SAE, the Investigator is required to follow each participant as indicated by clinical practice. Follow up information on an SAE should be reported to the Trial Office as described above in the Section on 'Reporting responsibilities of sites'. The Trial office will notify the Sponsor about any follow-up information.

8.5 Pregnancy
Pregnancy is not considered an AE or SAE. Participants who become pregnant will be treated in line with local clinical practice. We will not collect information on pregnancy within PARTIAL.

9. EMBEDDED MIXED METHODS TRIAL PROCESS EVALUATION
See Appendix 1 for details.

10. SAMPLE SIZE AND PROPOSED RECRUITMENT RATE

10.1 Sample size

Our sample size is based on the primary outcome of kidney function, which is also adequate for a 90% power non-inferiority test on the CCI, we will have precision to describe, positive surgical margins and quality of life:

(i) For kidney function we have used the width of the confidence interval between the groups in eGFR at two years: We estimate from systematic reviews that the absolute difference between PN and RN groups in arresting kidney function decline from baseline will be an eGFR of at least 10 mL/min/1.73m^2, with a standard deviation of 16 (Capitanio 2015; Mir 2017; Jiang 2019). This is a minimal clinically important difference (MCID) informing international guideline recommendation for PN (EAU /AUA/NCCN guidelines 2020). Based on the only randomised data available for PN vs RN, we predict a difference of at least 15 mL/min/1.73m^2 at two years (Van Poppel 2007; Scosyrev 2014). As we require the confidence interval around the estimated difference to rule out a MCID of 10 mL/min/1.73m^2 we've used a confidence interval of width 7. For us to be 90% sure our two-sided 95% confidence interval is at most 7 requires outcome data on 178 participants in each arm, or 356 participants in total. We will gain extra precision by using participants' baseline eGFR in analysis.

We have inflated the sample size to account for a 15% potential attrition at two years to 420 randomised participants in total.

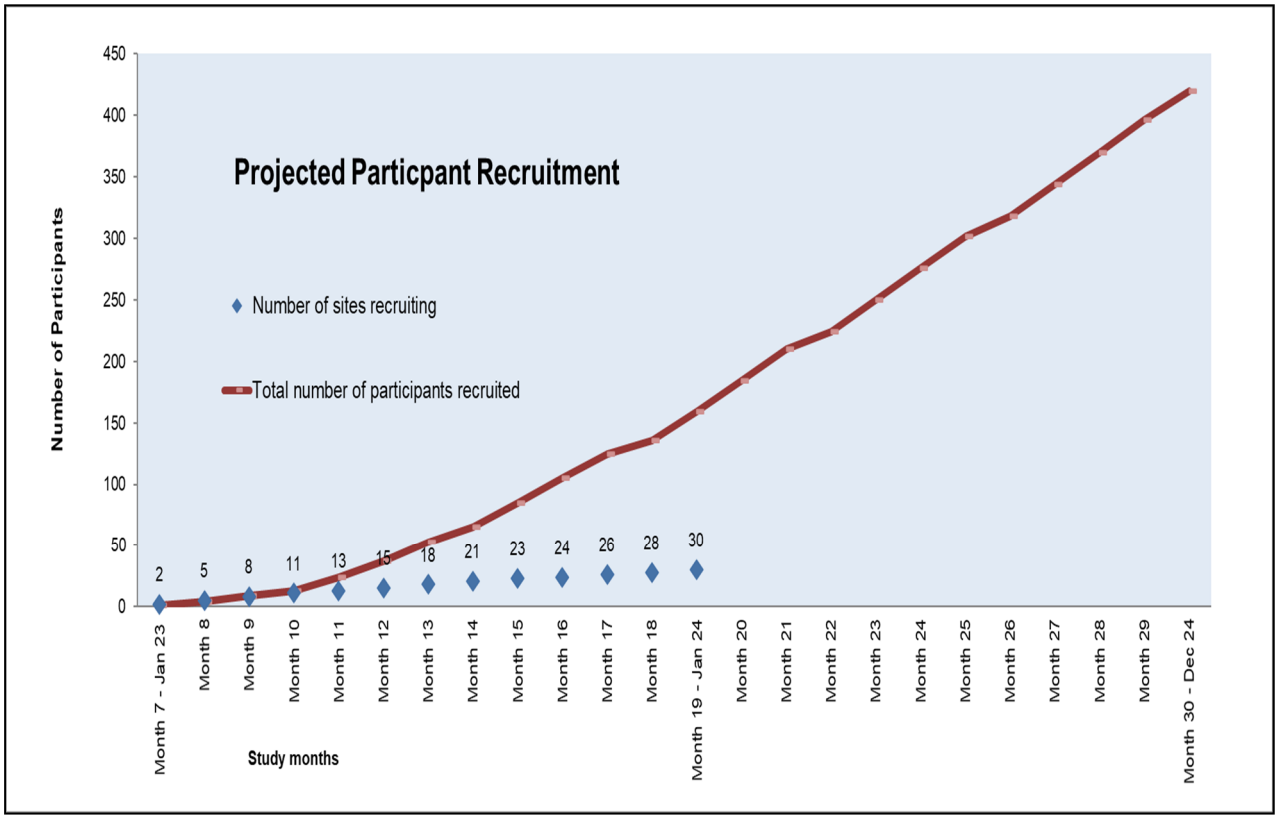
(ii) We require CCI outcome data on 380 procedures for 90% power to rule out a 4-point non-inferiority margin (i.e., we would tolerate up to 4 points higher CCI in the PN group) using the upper bound from a one-sided 97.5% confidence interval around the difference in means between the groups. The 4-point margin was derived using expert opinion and PPI input on a non-inferiority margin for major complications, and from data on a minimally important different in the CCI (Kowalewski 2021).

(iii) With 420 procedures we will have adequate precision to describe rates of positive surgical margin over a range of scenarios. Positive surgical margin rates up to 5% may be expected, with only <1% requiring re-treatment (Bensalah 2010).

(iv) Our sample size also gives adequate power/precision to compare quality of life (expressed as AUC analysis between randomisation and 24 months), with ~90% power to detect a third of standard deviation.

Based on Mayo Scoring System, rates of metastatic recurrence over three years for low risk (most T1a/T1b) tumours is 2.1% (Leibovich 2005). In a contemporary series comparing PN with RN for T1b, 5-year metastases rates were 8.2% and 12.8%, respectively (Shapiro 2020). Nevertheless, survival rates for localised T1b renal cancer remain high with over 5-year CSS rates for PN = 2.4% and RN = 4.5% (Shapiro 2020). Also, two-year OS rates in the Van Poppell study was >95% for both PN and RN (Van Poppell 2011). Therefore, we do not anticipate any emerging patterns of differential outcome on the main measures of interest due to few events at two years.

10.2 Recruitment rates



10.3 Internal pilot study

We plan an internal pilot phase to establish whether recruitment is achievable. We have set two targets: one to assess the opening of centres and the other the recruitment of participants. We propose one decision point at month 9 of the recruitment phase. At the end of month 9 we would expect to have 23 centres set up and 85 participants randomised. The progression criteria are laid out in table 2 below.

Table 2: Stop/Go criteria at month 9 of recruitment

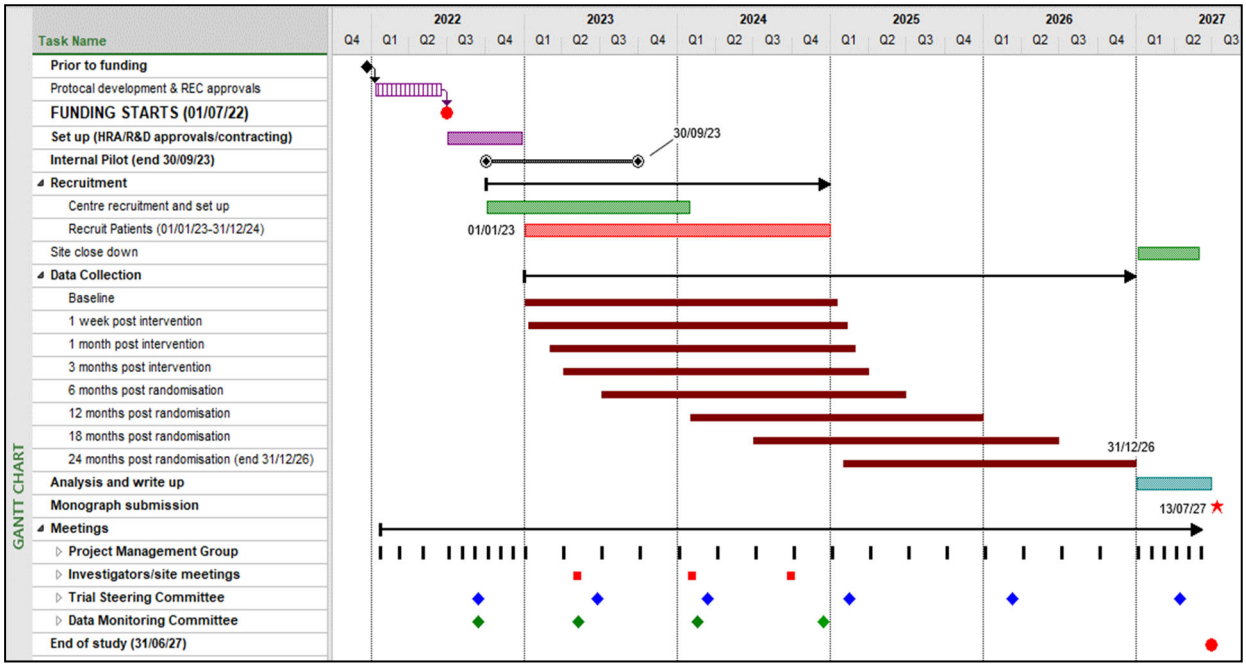
	GREEN	AMBER	RED
Centre recruitment	100% (23 centres)	60-100% (≥ 14 centres)	< 60% (< 14 centres)
Participant recruitment	100% (85 participants)	60-100% (≥ 51 participants)	< 60% (< 51 participants)
Action	Proceed whist considering opportunities to enhance recruitment from embedded mixed methods trial process evaluation	Consider Recruitment strategies based on 'fixable faults' findings from embedded mixed methods trial process evaluation and blockages (if centres are not open), including trouble shooting, revised training and support	Discuss urgently with the TSC and funder, considering all options including discontinuation. Consider which 'fatal flaws' uncovered during the embedded recruitment evaluation are amenable to change.

10.4 Project timetable and milestones

The Gantt chart (Figure 3) below shows the project timetable. The funding start date for the study is 1 July 2022: the study duration is 60 months.

Milestones: prefunding: REC and HRA approval; Months 1 – 6 (July 2022 – December 2022): set-up, R&D authorisations; Month 7: first participant recruited (2 sites set up); Months 7 – 30 (January 2023 – December 2024; with stop-go criteria at month 9 of recruitment): patient recruitment; Months 31–54 (January 2025 – December 2026): complete follow-up to 24 months post randomisation; Months 55 – 60 (January 2027 – June 2027): data analysis, interpretation of results, report writing and dissemination; Submission of monograph to the HTA (July 2027).

Figure 3: Gantt chart



11. STATISTICAL ANALYSIS

All analyses will be based on the intention-to-treat principle. The primary outcome, differences in kidney function decline, will be analysed using a generalised linear model that includes a random effect for centre, with fixed effects for treatment and design covariates and adjusted for baseline eGFR. A second analysis of this outcome will use a repeated measures model on a kidney function measures at all time points to explore the trajectory of decline between groups. The CCI at 90 days will be compared between groups initially using linear regression, using the bounds of the 95% CI around the difference to test non-inferiority. However, there is potential for the CCI distribution to violate the assumptions of linear regression - if that occurs, we will use a more appropriate analysis method, e.g. beta regression on CCI scores transformed to the (0,1) interval. Positive surgical margins will be analysed as a binary outcome using logistic regression model including a random effect for centre, with fixed effects for treatment and design covariates. Treatment effects for positive surgical margins will be summarised using absolute percent differences. Pre-planned subgroup analysis includes pre-operative eGFR, any comorbidity (diabetes affects 20%, hypertension affects 60% and cardiovascular disease affects 20% (Palacios 2021)), smoking status, age, and size of tumour.

Pre-operative renal biopsy is not a standard of care across the UK and is not mandated for recruitment into the trial.

Regardless of whether pre-operative biopsies are routinely undertaken or not at a site, if a patient has a pre-operative biopsy, randomisation should be undertaken after the outcome of the biopsy is known. Patients who do not have a pre-operative biopsy will be randomised on cross sectional imaging and this group of patients may subsequently be found to have non-cancerous renal mass. Such patients will remain in the trial. The effect of this will also be explored by a post-hoc sub-group analysis if the numbers in both confirmed RCC and no RCC are sufficient. If one of the groups is too small for a sub-group analysis, a sensitivity analysis will be undertaken.

The HR QoL outcomes (EORTC QLQ-C30 and SF-36 (Acute version – 1 week recall; physical and mental component summaries and the sub-domains)) will analysed in two ways – an analysis of the AUC and a repeated measures analysis using a time-by-treatment-interaction. Other secondary outcomes will be analysed in a similar way with generalised linear models appropriate for the distribution of the outcome. Treatment effects will be summarised with treatment estimates and 95% confidence intervals. The sensitivities of all treatment effect estimates to missing outcome data will be explored. Patterns of missing data will be described, and multiple imputation (under missing at random assumption) and pattern mixture models will be used.

All statistical analyses will be pre-specified in a comprehensive Statistical Analysis Plan (SAP) which will be agreed with TSC and DMC. There will be one analysis of effectiveness outcomes at the end of the trial after all follow-up is complete. There will be no planned interim analysis for efficacy or futility. Safety data will be monitored throughout the trial by an independent DMC.

12. ECONOMIC EVALUATION

The study will include a within trial and model based economic evaluation. Full details of the health economics analyses will be set out in the Health Economics Analysis Plan (HEAP). This plan will be written to be consistent with the SAP.

The within trial analysis will be conducted on an intention to treat principle. Results will be presented as a cost-consequence analysis (CCA) and a cost-utility analysis (CUA) from the NHS and personal social services (PSS) perspective for the 2-year trial follow-up. For the within trial analysis, a broader perspective incorporating costs to patients and their families will form part of sensitivity analysis.

The model-based analysis will be informed by the trial data and will be presented as the incremental cost per QALY gained over the estimate patient lifetime from the NHS a personal social services (PSS) perspective.

For both the within trial and the model based analyses, costs and effects occurring after 1-year will be discounted at the recommended rates, currently 3.5% per annum. A CUA has been adopted in order to aggregate the benefits, harms and costs into a single “trade-off” metric. The cost-consequence analysis will support this as effects, presented in their natural units, will highlight any trade-offs between different outcomes.

12.1 Collection of resources use and data, including participant costs

Intervention costs will be derived from a micro-costing conducted at individual study centres (see section 12.4 below). Centre level data will be supplemented with participant level data e.g. procedure time, collected using case report forms (CRFs). Most PNs are delivered using robotic surgery and whilst this equipment is costly, the difference between robotic and laparoscopic costs may be closing. Our base case analysis will adopt standard purchasing approaches used in existing economic evaluations (Ramsay 2012), but we will also explore alternative equipment costing assumptions (e.g. how equipment is procured and managed, whether costs are irreversible or not).

Complication rates may be higher in PN, so reducing HRQoL and causing additional costs. These additional costs will relate to initial management (e.g radiological imaging, blood tests, blood transfusions, visits to theatre etc), management of long-term sequalae and patient costs (travel, time off work) and social care. CRFs will be used to collect secondary care services use. Use of primary care services e.g. general practice visits and use of PSS, will be collected using a participant cost questionnaire (PCQ) administered at baseline, 6, 12, 18 and 24 months post randomisation. Participants' use of private health care will also be collected with the PCQ. Time and travel costs borne by participants in accessing and using services will be estimated from responses to a time and travel questionnaire (TTQ) administered at 12 months.

The unit costs of NHS and PSS resource use will be estimated from study specific estimates and routine data sources (Curtis 2020; NHS Reference costs). Unit costs will be combined with information on the use of services to estimate a cost for each participant. For patient costs, the time and travel costs of accessing care will be estimated using the responses to the TTQ and data on the use of services. To this will be added the monetary cost of any private health care. For each randomised arm a mean cost will be calculated.

12.2 Quality of Life

Participant quality of life data is being collected as described in section 7. The relative changes in HRQoL resulting from the physical and psychological benefit together with any harms associated with each surgical strategy will be captured by the SF-36 administered at baseline, 1 week and 1, 3 months post-intervention and 6, 12, 18 and 24 months post-randomisation. Responses to the SF-36 will be converted to SF-6D scores (Deverill 2002) and QALYs estimated using the AUC approach (Matthews 1990) and a mean QALY per arm calculated.

As part of sensitivity analysis we will map the EORTC QLQ-C30 (administered at the same time points as the SF-36) on to the EQ-5D valuation set and these used to estimate QALYs. As this is an evolving area, the choice of mapping algorithm will be informed by a review mapping algorithms performance.

12.4 Any other relevant Health Economics data collection

At a site level information will be elicited on the mix of theatre staff typical for each procedure, the standard operating kit (including both reusable and disposable equipment). Also elicited will be the price of equipment. Information will also be sought on the operating costs of theatres (excluding the items listed above) to capture the opportunity cost of theatre time associated with each procedure. Initially, detailed information will be elicited from a single site

(the host site for the CI) and then used as a template to for data collection at other sites. The precise methodology will be set out in the HEAP.

12.5 Cost effectiveness

Estimation of incremental cost per QALY gained

An appropriate regression model (e.g. a general linear model) will be fitted to estimate marginal costs and QALY gains; controlling for baseline covariates (e.g., age, sex, SF-6D score, pre-randomisation use of health services, socio-economic status). Data will be presented as point estimates and bootstrapping techniques characterise imprecision (Barber 2000). The results will be presented as cost and QALY plots and as cost-effectiveness acceptability curves (CEACs) (Fenwick 2004).

Within Trial Cost-consequence analysis

The CCA will be presented as a balance sheet to illustrate the trade-offs between different health outcomes. The consequences will be those reported above. Costs will be reported as surgical intervention, subsequent costs and costs falling on participants.

Model based analysis cost-utility analysis

The 2-year follow-up of the trial may will not capture all of the costs and health outcomes associated with the interventions, as some events will be incurred over a longer timeframe. Therefore, an economic decision model will extrapolate costs and outcomes over the lifetime of the patient. The economic model will describe cancer outcomes, with persisting impacts of any complications and the impacts of renal function (and its deterioration with ageing) over the patient lifetime. We anticipate the model will be a microsimulation model. Previous modelling work (Klinghoffer 2013) have used a simple structure. Therefore, we will work with our PPI and clinical team to design a model reflecting the patient journey. The model will be constructed following guidelines for best practice in economics modelling (Caro 2012). The use of services both for the treatment and management of disease will be modelled using data obtained from the trial. Further data will be systematically derived from the literature and from expert clinical input (e.g. the Centre for the Evaluation of Value and Risk in Health (CEVR) Cost Effectiveness Analysis (CEA) Registry, etc).

The model will be used to produce estimates of costs, QALYs (from the SF-6D and mapped EQ-5D utility scores). Cost-effectiveness will be reported as incremental cost per QALY gained (at both 2 years and over the patient's lifetime). The model will be probabilistic, and distributions; the choice of which will depend upon the data available and recommendations for good practice in modelling. The results will be presented as point estimates of costs, QALYs, incremental costs, QALYS, and measures cost-utility. They will also be presented as plots of costs and QALYs and cost-effectiveness acceptability curves. The model will be developed in a suitable software package (e.g. R).

Sub-group and Sensitivity analysis

For the economic evaluation we expect to replicate the sub-group and sensitivity analyses proposed in section 11(Statistical Analysis) where these are relevant to the estimation of costs and QALYs.

For all analyses deterministic sensitivity analysis will be combined with the combined with the trial based stochastic or model based probabilistic analysis to explore other forms of

uncertainty (e.g different cost assumption, inclusion of participant costs, QALYs based on EORTC QLQ-C30 responses, etc).

13. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 Trial office in Aberdeen

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT will take responsibility for the day-to-day transaction of trial activities, for example approvals, site set-up and training, oversight of recruitment and follow-up rates etc. The data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal) and raising data queries on data collected and entered at the recruitment sites.

The Trial Office Team will meet formally at least monthly during the course of the trial to ensure smooth running and troubleshooting.

13.2 Local organisation in sites

The PI and Research Nurse(s) in each site are responsible for all aspects of local organisation including identifying potential recruits, consenting, arranging any study-specific follow-up, and completing and maintaining appropriate documentation. The site agreement documents the full list of responsibilities for sites. Appropriate members of the local team are knowledgeable about the Protocol and will have appropriate Good Clinical Practice (GCP) training if applicable. A trial-specific delegation log is prepared for each site, detailing the responsibilities of each member of staff working on the trial. The local team is also responsible for notifying SAEs to the Trial Office (see section 8).

13.3 Project Management Group (PMG)

The trial is supervised by its Project Management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. We will meet/teleconference approximately every 3 months.

The research team has the expertise to cover the clinical, surgical and methodological aspects of the research.

13.4 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members, oversees the conduct and progress of the trial. The TSC Charter documents the terms of reference of the TSC, the template for reporting and the names and contact details of members of the TSC. This Charter is filed in the Trial Master File (TMF).

13.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) oversees the safety of subjects in the trial. The DMC Charter documents the terms of reference of the DMC and the names and contact details of members of the DMC. This Charter is filed in the TMF.

13.6 Patient and Public Involvement (PPI)

Mr Di Mambro is leading our PPI. He has lived experience of kidney cancer and will play an active ongoing role in further developing the full application/protocol and will serve on the PMG – advising on recruitment, data collection, analysis, producing study materials to sharing findings and aid dissemination.

Patients and KCUK have provided invaluable insights into the co-production of this application and will continue to be important in its delivery. Our PPI group (co-applicant Mr di Mambro, PAG and KCUK) will provide advice about the conduct of the trial from a patient perspective and support the research team in development of patient-facing resources and activities to foster participant connectedness with the study.

Members of the PPI group will be an integral part of the TMG, and will also provide regular updates to the broader PAG. Results of the study will be distributed to patients and families affected with kidney cancer through bespoke plain English summaries generated in conjunction with our PPI group through lay media outlets, social media and charity run patient portals (e.g. KCUK, CRUK).

As part of the health economics component, we will work with our PPI and clinical team to design a model reflecting the patient journey. This will form the basis of our model based economic evaluation (see section 12.6).

The PPI group will contribute to the process evaluation – particularly the interpretation of findings, development of potential solutions and action plans to target recruitment and retention.

An independent PPI representative will be a member of the Trial Steering Committee.

At the end of the study, with our PPI team we will produce lay summaries and disseminate to (i) those patients who participated, (ii) patient organisations (KCUK and The Urology Foundation (TUF) websites), and (iii) social media. We will inform policy makers shaping NHS practice, such as NICE, NHS England and international guideline writing committees (EAU).

The PPI activities will be facilitated by the HSRU PPIE coordinator.

14. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

14.1 Research Governance

CHaRT (https://www.abdn.ac.uk/hsru/what-we-do/trials-unit/index.php) is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This aids compliance with Research Governance and the principles of GCP, and provides centralised trial administration, database support and statistical analyses. CHaRT SOPs are followed. The Health Economics is being undertaken outwith CHaRT, but the CHaRT SOPs will be followed as far as possible. During set-up there will be agreement as to which Sponsor SOPs are relevant for the study.

The CI and Sponsor ensure that adequate systems are in place for monitoring the quality of the trial and that reports are prepared to a level appropriate to the risk assessment of the trial.

14.2 Data protection

Data collected during the course of the research is kept strictly confidential and accessed only by members of the trial team. Data may be looked at by individuals from the Sponsor organisation or NHS sites where it is relevant to the participant taking part in this trial.

The CI and trial staff involved with this project will comply with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The HRA recommended wording to fulfil transparency requirements under the GDPR for health and care research has been included in the PIL.

Trial staff based in Scotland will also adhere to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality.

Access to collated participant data will be restricted to the CI and appropriate trial staff.

Computers used to collate the data will have limited access measures via usernames and passwords.

Remote access to the network will be subject to robust authentication, and VPN (Virtual Private Network) connections to the network are only permitted for authorised users, ensuring that use is authenticated, and data is encrypted during transit across the network. No personal data will be downloaded or stored on local hard drives. All data input/access will be via the VPN and/or secure website.

Published results will not contain any personal data that could allow identification of individual participants.

The CHaRT senior IT development manager (in collaboration with the CI) manages access rights to the data set. Participants are allocated an individual trial number which is used to identify questionnaires and case report forms.

We anticipate that anonymised trial data may be shared (on reasonable request to the CI) with other researchers to enable international prospective meta-analyses or other analysis.

14.3 Sponsorship

The Newcastle upon Tyne Hospitals NHS Foundation Trust is the Sponsor for the trial.

15. ETHICS AND REGULATORY APPROVALS

Research Ethics Committee approval from the South West - Central Bristol Research Ethics Committee REC and any appropriate NHS R&D approvals will be obtained prior to the commencement of recruitment. The trial will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines and any appropriate NHS R&D approval(s) will be obtained. Annual progress reports, end of Trial declaration, and a

final report are submitted to the Sponsor and the South West - Central Bristol Research Ethics Committee REC within the timelines defined in the regulations.

15.1 Protocol compliance and amendment

The Investigators will conduct the trial in compliance with the Protocol given favourable opinion by the South West - Central Bristol Research Ethics Committee REC. Any amendment to the Protocol or other approved documents will be reviewed by Sponsor (and funder where appropriate) before application to REC and R&D unless in the case of urgent safety measures when the Sponsor is notified as soon as possible. Sponsor will advise if an amendment is substantial / non-substantial and which review bodies need to receive it. Any deviations from the Protocol will be fully documented.

16. MONITORING AND AUDIT

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the trial. Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

16.1 Risk assessment

An independent risk assessment has been carried out by the Sponsor. CHaRT have contributed to this risk assessment.

17. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme. The necessary trial insurance is provided by Newcastle Hospitals.

18. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial will be provided to the Sponsor and REC within one year of the end of the trial. An end of trial report should also be issued to the funders at the end of funding.

19. DATA HANDLING, RECORD KEEPING AND ARCHIVING

19.1 Source data

The source of outcome data is summarised in table 3 below:

Table 3: Source data

Outcome	Source
eGFR	Laboratory report
CCI	Medical notes
HRQoL (including EORTC QLQ-C30, SF-36)	Patient completed questionnaires
Cost effectiveness	QALY – from SF-36/EORTC QLQ-C30 Costs – care pathway costs from medical notes and patient completed questionnaires
QoR	Patient completed questionnaires
Positive surgical margins, local recurrence, need for re-treatment	Pathology reports, medical notes
Recurrence free and overall survival	Medical notes
Cardiovascular events	Medical notes
Progression to CKD	eGFR, medical records
Operative conversion to RN	Medical notes
Patient acceptability	Patient completed questionnaires

The PARTIAL trial inclusion form will be completed as a paper CRF before entering onto the study website. This permits signature from a medical doctor to confirm eligibility of the participant. For other CRFs, site staff can either complete a paper copy of the CRF before entry onto the eCRF on the study website, or bypass the paper CRF and enter the data directly onto the eCRF.

- If hard copy CRFs are completed, these are considered to be the source document. These will then be entered by the local study team onto the study website.
- If the data is entered directly into the study website, the electronic record is considered to be the source document. In order to maintain a copy of the data that is independent from the sponsor copy, sites will be encouraged to print or save a copy of the electronic data. The study website will provide this facility.

For all case report forms, there is an electronic record (as part of the study website) which indicates whether the case report form was completed online (no paper copy) or not. This will allow identification of the source document.

Participants will complete questionnaires at baseline and at 1 week and 1, 3 months post-intervention, and 6, 12, 18 and 24 month post-randomisation. The hard copy of these questionnaires will be considered the source document.

19.2 Data management

Clinical data will be entered into the study database by the designated team members working in each recruitment site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local site team members to ensure that the data are as

complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

Each website user will have their own user account and password. These will not be shared. The study website has a full audit trail and every data entry made (or changed) is logged to the specific user.

19.3 Archiving

Responsibilities for archiving are documented in the site agreement. All essential data and documents (electronic and hard copy) are retained for a period of at least 5 years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. Electronic data will be archived by UoA.

20. SATELLITE STUDIES

It is recognised, that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the PMG and, if appropriate, with the TSC. Depending on the nature of the satellite trial, the Sponsor may consider this to be a non-substantial or a substantial amendment to the REC approval for the PARTIAL study, or to require REC approval as a project in its own right. R&D management approval may also be required. In such situations, the sponsor will be contacted for advice.

21. AUTHORSHIP AND PUBLICATION

Please refer to the Appendix 2 (authorship policy) for full details on authorship.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG and TSC.

21.1 Other Dissemination

Once the main trial findings have been published, a lay summary of the findings will be sent to participants.

Trial findings will also be disseminated to professionals involved in the trial, including GPs of participants, PIs at sites, site staff, etc.

More detailed plans for this dissemination will be considered and developed with input from PPI partners through the duration of the trial and will be finalised as part of the close-out plans.

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APPENDICES

Appendix 1: Embedded mixed-methods trial process evaluation

Background and overview of mixed methods evaluation

It is well documented that surgical trials face a number of challenges, particularly around feasibility and acceptability of randomisation, from both the potential participant and surgeon perspective. This is something we have previously experienced first-hand in our own NIHR funded study (SURAB feasibility RCT; Soomro 2017) looking at randomising treatments for small renal masses (Soomro et al, 2017). An embedded evaluation will focus on overall trial acceptability and how this impacts on decisions to participate and ultimately trial recruitment.

The main aim of the embedded process evaluation is to identify significant challenges during the internal pilot relating to design or conduct that can be addressed and modified before progression to full trial. This may include changes to the way trial information is presented, recruitment consultations are framed or requirements for staff training. This pragmatic, proportionate, approach to the design and analysis of the embedded evaluation allows feedback to be delivered to trial sites in a timely manner with potential for impact and demonstrable change based on the findings of the mixed-method process evaluation.

Much of this work will be modelled on the Quintet Recruitment Intervention (Donovan et al, 2016). However, we will also augment the QRI approach with the application of behavioural science to inform key components of data collection, analysis, and development of feedback. Clinical trials depend on behaviours: they rely on people (patients, clinicians, trial staff) performing actions (such as receiving or delivering a trial intervention, attending a clinic, returning a questionnaire, or approaching eligible participants) that they would not do otherwise. Emerging evidence suggest behavioural science has the potential to add value with regard to improving the conduct of trials (Gillies et al, 2021).

The process evaluation team will identify and address the key challenges to trial recruitment and retention from the perspective of overall acceptability and will be managed across two phases:

- Phase 1 focused on identifying and understanding the 'problem' for trial recruitment and/or retention using multiple methods and data sources.
- Phase 2 sought to develop solutions to the 'problem' identified in Phase 1 through the development and delivery of interventions, with the wider trial team, to target the conduct challenges.

Methods

Phase 1: identifying and understanding challenges for trial recruitment and retention

Phase 1 will focus on the collection and analysis of data from three main data sources: 1. Participant flow at sites; 2. Analysis of trial consultations; and 3. Interviews with patients and site staff.

<u>1. A Participant flow at sites</u>

Data collection

An in-depth analysis of participant flow using the SEAR framework at each recruiting site will be conducted (Wilson et al, 2018). Data on the number of participants screened, eligible, approached and randomised will be extracted taken from screening logs and the trial website for all recruiting centres. Supplementary data on participant eligibility (including whether they met the protocol inclusion/exclusion criteria, or any reason they were deemed ineligible); whether eligible participants are approached about the trial (if not, why); and, whether participants were randomised and if not-why not and which treatment they chose. Reasons for participants declining participation, specifically patient or surgeon preference for surgery or medical management will be collected from the trial website.

Data analysis

Analysis of patient recruitment pathways using the Screened, Eligible, Approached, Randomised (SEAR) framework will be applied to identify and assess areas of complexity and protocol compliance (Donovan et al 2016). Simple counting of data collected in SEAR logs can provide useful information about the complexity of the recruitment process; differences between centres or over time can give indications of difficulties that can be investigated further. Data will be compared across study sites to illustrate any variation between centres and again identify areas of good practice that can be shared. Data will be used to guide decisions about prioritisation of feedback to sites by comparing activity across sites to identify core problem areas e.g. sites that have much lower (proportionally) approached to randomised rates, etc.

The SEAR data will also help inform the analysis of the recruitment consultations and critical aspects for enquiry in the interviews.

<u>1.B. Audio-recording of discussions about trial participation</u>

The aim of audio-recording the recruitment consultation is to explore trial decision-making by potential trial participants and clinical site staff (consultant, member of the surgical team or Research Nurse) involved in the trial. This will enable the trial team to systematically assess the content and presentation of study information by recruiters, the interactions between participants and recruiters, and provide evidence on which to develop appropriate recruitment strategies. This will also provide evidence about how potential participants can be better supported and informed when making a decision about participation in the PARTIAL trial. The audio-recordings will contribute to determining models of 'good practice' for consent discussions which can be used for site training.

Sampling and recruitment

All staff involved in discussing the PARTIAL trial with potential participants will be asked to routinely record consultations in which the trial is discussed. As part of the PARTIAL trial, potential participants will receive a participant information leaflet (PIL) explaining the trial in detail. To facilitate the audio recording study, a separate PIL will be given to participants at the same time, but before any discussion of the trial is initiated, explaining the purpose and the specific request to audio-record their recruitment consultations. Patients will not be obliged to participate in the audio-recording study and the decision will not affect their invitation to take part in PARTIAL. Similarly, patients may agree to take part in the audio-recording study but then decline to take part in the main PARTIAL trial. Recruitment consultations will be recorded after an initial greeting and introduction to the consultation. If a participant consents to the recording, the recording would continue and there will be a record of verbal consent. If a participant declined, the audio recording was stopped, and the file deleted. With regard to staff

consent, staff information sheets about the recording process will be distributed and a one-off written consent from all staff involved in audio-recording (that covers all subsequent recordings captured throughout the study period) will be sought.

Data collection
All recruiting sites will be asked to audio-record consultations in which the PARTIAL trial is discussed and for those participants who consent to audio-recording. Sites will be provided with devices to record and conversation. The audio recordings of recruitment consultations will be uploaded to a secure area of the study website. If for any reason the upload function is unavailable, a secure file transfer system, such as the University of Aberdeen ZendTo service, will be used. Anonymised transcripts and audio recordings will be held securely for 5 years in accordance with Sponsor requirements and data legislation.
All conversations within the recordings related to PARTIAL trial will be transcribed for the purpose of analysis. Only conversations related to the PARTIAL trial (where recruiters explain the design and details of the PARTIAL RCT, and patients decide whether or not to take part) will be transcribed for the purpose of analysis and discussion by a Sponsor approved third party professional transcription service or an HSRU member of staff. At least 10 consultations per site will be collected before site specific analysis is conducted.

Sample characteristics information will be collected for each of the audio recordings, including (but not limited to) information on: who was involved in the discussion (i.e. consultant, Research Nurse), duration of consultation, whether the participant consented, which treatment they were allocated to (as applicable), etc.

Data analysis
The transcripts of the consultations will be analysed using content and thematic analysis to elucidate reasons for imbalances in presentation, style and content of information provided by the recruiter, participation and engagement of the patient, and indications of the presence and origin of 'hidden challenges'. The analysis will focus on modifiable aspects of recruitment consultations e.g. eligibility of participants, exploration of preferences, discussion of uncertainty and balancing of options. Audio-recordings will also be analysed for discussions relating to trial follow-up procedures (i.e. completion of patient questionnaires) and the importance placed on commitment to the trial across the entire timeline. Feedback will be provided to the site on how to improve aspects of the informed consent process based on targeted analysis described above. Whilst we will continue to collect audio-recordings of consultations at these sites, the analysis of these will be triggered based on key diagnostics identified using the SEAR framework.

In addition, a novel mixed-methods approach combining appointment/consultation timings (time spent explaining aspects of the RCT) and qualitative interpretation of the conversation- 'quanti-qualitative appointment timing' (Q-QAT) may be used for the purpose of analysis as appropriate. This will provide useful information regarding the order of presentation (balanced/unbalanced presentation of the RCT information to potential participants which may inspire or hinder recruitment) and degree of balance between the RCT interventions, the time the RCT is first mentioned and how long is devoted to it.

Sample characteristic information will be presented using frequencies.

As audio-recordings are generated for each site they will be listened to and sent for targeted transcription (i.e. only transcribing sections relevant to improve trial process). Analysis will proceed alongside data collection. Analysis will focus on modifiable aspects of consultations e.g. eligibility of participants, exploration of preferences, discussion of uncertainty and balancing of options. Audio-recordings will contribute to determining models of 'good practice' for consent discussions which can be used for individual(s) and overall site training. With regard to exploring aspects of trial retention, audio-recordings will also be analysed for discussions relating to trial follow-up procedures (i.e. clinic visits and completion of patient questionnaires) and the importance placed on commitment to the trial across the entire timeline. Feedback will be provided to the site on how to improve aspects of the informed consent process based on targeted analysis described above.

1.C Interviews with patients and site staff

In-depth, semi-structured interviews will be conducted to understand perspectives of trial acceptability and decisions about participation with a range of individuals:

1. Participants eligible for the RCT and who accept trial participation (n=15); and
2. Participants eligible for the RCT but who decline trial participation (n=15); and
3. Clinical and recruitment staff at participating centres (2-3 staff from 7 sites, n=15).

Sampling and recruitment

Potential participants of the interview study (which includes those that have consented to the main PARTIAL trial and those that have refused consent) will be provided with a separate PIL in the clinic or by post or email if conducted remotely. Enclosed with the PIL will be a reply-slip to complete and return to the researcher (in a reply paid envelope) if they would like to discuss participating in the Interview study. Those participants who do not return the reply slip will not be contacted further.

Following receipt of the completed slip, the researcher will telephone the interested participant and ensure they are clear about what the study entails and arrange a suitable time for the interview. Interviews will be planned to be as close as possible to the initial decision to participate, or not, in PARTIAL.

For site staff interviews, clinical and recruitment staff (consultants, Research Nurses) involved in trial recruitment at sites will be invited to participate in in-depth, semi-structured telephone interviews to explore their understanding of the trial (specifically with regard to eligibility criteria, beliefs about equipoise, and process). Site staff will be emailed an invitation letter outlining the study and inviting them to contact the research team (by email or telephone) if interested in participating in the interview study. Once contact is made with the researcher, potential participants will have the opportunity to ask any further questions before making a decision to participate.

To enable all willing participants to be involved in the interview study, and maximize sample variability, telephone or online (eg Microsoft TEAMS) interviews will be utilised and verbal consent will be sought. As with all research studies, participants will be able to withdraw consent at any time. If the number interested exceeds the sample required, participants will be sampled purposively to ensure a wide variety of experiences is included in the sample. Similarly for trial participants, it will be based on participant characteristics (gender, age, ethnicity, previous surgical treatment, etc) and trial characteristics (e.g. if consenters, which treatment allocation).

Data collection and analysis
Approximately 15 interviews will be conducted for each group by sampling informed by Francis et al (2010). To provide 15 participants for the patient group who have refused consent to the PARTIAL trial, it is anticipated that a total of 60 interview study PILs will require to be distributed (anticipate participation rate of ~20%).

Interview topic guides will be developed for each group, covering aspects of trial rationale, design and conduct with a specific focus on illuminating the influences on trial recruitment and processes linked to the pathway (specifically exploring barriers and facilitators within local contexts). For those participants who declined trial participation we will investigate whether there were specific aspects of trial design or conduct that led to their decision to not to be involved. Data collection and analysis will be informed by the Theoretical Domains Framework (TDF) and/or the Theoretical Framework of Acceptability (TFA), which has been applied in existing studies exploring trial feasibility in other contexts (Sekhon et al, 2017).

Analysis for interviews in this context (i.e. to inform ongoing delivery of the trial) will be conducted pragmatically with a focus on key aspects of trial process that are amenable to change so as to determine problem areas or identify aspects of good practice. We will aim to conduct the majority of the interview phase during the internal pilot.

Phase 2: Development and delivery of interventions to target recruitment and retention challenges
Results from the process evaluation will be fed back (as anonymised summaries) to (i) site staff in real time and (ii) the Project Management Group (PMG) and PPI group during and at the end of the internal pilot (month 9). Potential solutions in the form of action plans will be developed by the process evaluation team and PMG /PPI groups in tandem, implemented and evaluated (through improvements in recruitment and retention) on a rolling case basis. The nature of the data collected allows for both aggregate and individual level feedback, which may be more effective than generalised trial feedback. Moreover, the iterative nature of the feedback allows for constant improvements in practice to be made, leading to overall improvements in efficiency. Exact plans will be determined based on the findings generated and the problems identified. However, they are likely to follow mechanism of feedback employed in other trials such as:

- Overall feedback at site investigator meetings;
- Generic or site specific email feedback on recruitment activity (to include behaviour change techniques and considered as an audit and feedback intervention);
- Infographics for staff highlighting key findings;
- Amendment sot trial PIL or other patient facing documents (such as cover letters etc)

4. Study Management

PARTIAL-QUAL will be led by experienced qualitative/mixed methods researchers with input and guidance from the Trial Project Management Team. The Research Fellow will conduct the interviews and lead data analysis. Specifically, they will be responsible for organising transcription, ensuring secure transfer of digital audio files to the transcriber and subsequent anonymisation of transcripts. File transfer will be conducted according to the current guidelines laid out in the University of Aberdeen's operating procedures. The qualitative/mixed methods researchers will also be responsible for organising appropriate storage of the digital files and transcripts, which will be stored on password protected University computers that are backed up on a secure SQL server. In addition, the audio recording of the consultation will be managed (including managing recording device and upload recordings to PARTIAL-QUAL study folder) by a Research Nurse.

5. Timeline

Following ethical approval, the invitation of potential trial participants and staff interviews will align with the internal pilot.

6. Ethical considerations

The study will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Some aspects of this process evaluation evaluation, as proposed initially, have raised ethical concerns such as the processes of contacting participants who have refused to take part in PARTIAL to invite them to participate in an interview. Efforts have been made to ensure participants invited to interview feel able to make an informed, voluntary, decision about their participation.

7. References

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Appendix 2: Authorship Policy

Authorship policy for the PARTIAL trial

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria[1]:

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT trials should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to "The PARTIAL trial group" or "Jane Doe, John Doe, John Smith, Ann Other and the PARTIAL trial group". The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. For some journals the journal will provide instructions on how to ensure the names of the collaborators appear on PubMed or equivalent.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors

but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group')[2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a trial's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

4. DISCLAIMERS

All papers arising from CHaRT must include the full title of the Health Services Research Unit (HSRU) and the appropriate disclaimer specified by the Chief Scientist Office (CSO). For the current disclaimer please see Q-Pulse.

Authors should also ensure they include the trial funder's disclaimer: refer to the funders website for details. **Be aware that other disclaimers may also be required and ensure these are included** (for example NIHR infrastructure funding, roles on NIHR committees).

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the PARTIAL trial, including conference abstracts, outputs describing methodological aspects of the trial, and any outputs describing results from the trial,

should be peer reviewed by the Project Management Group. The Project Management Group will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the trial team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

REFERENCES

1. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Developed by members of the ICMJE, the document is revised regularly and the current version (updated Dec 2021) is available at (www.icmje.org/#authors)
2. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*, **104**, 269-274.
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Based on CHaRT authorship policy v 5, 01/22

Appendix 3: COVID-19 mitigation

These arrangements are put in place to minimise risk to participants and research staff during the COVID-19 pandemic to ensure the PARTIAL study can proceed. Appropriate COVID-19 precautions will be taken in line with any national, regional or local guidelines (for example PPE, social distancing, hand hygiene, etc).

The pragmatic approach used in the PARTIAL study, will continue during the COVID-19 pandemic. The main protocol will be followed as far as possible, in line with the approved remote procedures, during any restrictions due to the pandemic.

1. Interactions with COVID-19 vaccinations

No known / reported interactions between the trial interventions and the COVID-19 vaccines.

2. Recruitment

If the potential participant agrees to be contacted at home after reading the PIL, they will receive a telephone or video call from the local Research Nurse or a member of the local clinical team to discuss any queries. Patients may make a decision to participate at home following this telephone / video counselling, or during a subsequent visit to hospital (e.g. a clinic appointment or a pre-assessment visit).

Telephone, postal and e-consenting procedures approved for PARTIAL (described in section 4.7) can continue to be used in line with current COVID-19 restrictions, allowing remote consent of participants to the study as far as possible. Remote consent options will remain in place for the duration of the project.

3. Interventions

Both of the interventions are surgical (partial nephrectomy, radical nephrectomy). Participants will receive their surgery in line with local procedures during the pandemic. The pandemic may result in some delays to the waiting list; however participants are on the cancer pathway. Across the UK, there are NHS England mandated cancer wait targets for time to diagnosis (31 days) and time to treatment (62 days).

4. Follow up

Clinical follow up will coincide with routine follow-up for these participants. Other follow-up is by postal questionnaires.

5. Embedded mixed methods trial process evaluation

It is anticipated that this component will be completed remotely; if and when current restrictions on social distancing are lifted, face to face activity may commence.