CLINICAL STUDY PROTOCOL

This protocol has regard for the HRA guidance.

FULL STUDY TITLE: A randomised controlled trial of Partial prostate Ablation versus Radical Treatment in intermediate risk, unilateral clinically localised prostate cancer

SHORT STUDY TITLE: **P**artial prostate **A**blation versus **R**adical **T**reatment (PART)

Version 3.0 15 May 2024

Study website: https://part-trial.octru.ox.ac.uk/

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OCTRU
Oxford Clinical Trials Research Unit

Contents

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Funder:	The study is funded by the National Institute for Health Research (NIHR). Refer to section 27.2 (Funding and support in kind) for full details of all funding sources.
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Conflict of Interest statement:	None of the protocol authors/contributors have declared a potential conflict of interest
Confidentiality Statement:	In accordance with the NIHR Open Access policy, the protocol will be published and made freely and openly accessible to all.

3 KEY STUDY CONTACTS

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4 PROTOCOL APPROVAL/SIGNATURE PAGE

This protocol has been approved by the Sponsor, Chief Investigator and Lead Statistician. Approval of the protocol is documented in accordance with OCTRU Standard Operating Procedures.

All parties confirm that findings of the study will be made publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any important deviations and serious breaches of GCP from the study as planned in this protocol will be explained.

5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

The PART study aims to test whether treating only the part of the prostate containing the prostate cancer is as effective in curing prostate cancer as treating the whole prostate gland, and has fewer side effects. Treatment of the whole prostate gland (known as 'radical' treatment) includes surgical removal, radiotherapy, or brachytherapy.

Prostate cancer is the most common cancer in men in the UK. Treatment of the whole prostate ('radical' treatment) is normally offered, even if the cancer is only on one side of the prostate gland. New technologies can now treat the part of the prostate affected by the cancer only (known as 'partial ablation', or PA), destroying the cancer but preserving urinary and sexual functions. PA shows promising results in terms of having minimal side effects in men with low-risk prostate cancer, compared to a policy of 'active surveillance' (i.e. no active treatment). We want to test PA in men with intermediate-risk unilateral localised prostate cancer, who would usually be advised to have radical treatment.

The two types of PA in this trial will be Irreversible Electroporation (IRE) and High Intensity Focal Ultrasound (HIFU). NICE currently recommends that both HIFU and IRE as PA treatments for prostate cancer are safe, and that more evidence is needed to assess their efficacy (https://www.nice.org.uk/guidance/ipg756) (https://www.nice.org.uk/guidance/IPG768). IRE is an image-guided tissue ablation technology that induces cell death via short, strong pulsed electric fields. Due to its non-thermal nature, IRE preserves vessels, nerves and extracellular matrix, making it a suitable PA treatment modality for prostate cancer. HIFU uses ultrasound energy focused by an acoustic lens to cause tissue damage as a result of thermal coagulative necrosis and acoustic cavitation. The results of the PART study will inform recommendations for widespread use of PA throughout the NHS; currently, IRE and HIFU are available at only a few specialist centres.

We aim to recruit 800 men from 10+ hospitals in the UK. Participants will be randomly allocated to either radical treatment (choice of surgery or radiotherapy or brachytherapy, as most appropriate) or PA treatment (IRE or HIFU). All patients will be assessed regularly to check if the treatments have worked, using blood tests and (for the PA arm) repeat imaging and prostate biopsies. If there is any

sign of the disease returning or worsening, additional treatments will be discussed and offered. We will compare how well the treatments work by measuring the time it takes for additional treatment to be necessary in the radical treatment arm, or to require treatment of the whole prostate gland, or other prostate cancer-specific treatment, in the PA arm. We will also assess quality of life using questionnaires, and costs to the NHS of each treatment.

6 STUDY SYNOPSIS

Full Study Title:	A randomised controlled trial of Partial prostate Ablation versus Radical Treatment in intermediate risk, unilateral clinically localised prostate cancer
Short Title:	**P**artial prostate **A**blation versus **R**adical **T**reatment
Study Acronym:	PART
Study Design:	The PART study is a multi-centre, two arm, parallel design, randomised controlled clinical study. A QuinteT Recruitment Intervention (QRI) is incorporated into the study to identify and understand any challenges to recruitment.
Study Participants/Target Population:	The PART study will recruit patients aged 18 years and over with localised intermediate-risk prostate cancer amenable to either partial ablation of the prostate or radical treatment (radical prostatectomy, radical radiotherapy, or low dose-rate brachytherapy).
Eligibility criteria:	**Inclusion:** 1. Age ≥18 years with unilateral clinically significant intermediate-risk Gleason Grade Group 2 or 3 (3+4 or 4+3) PCa, or dominant unilateral clinically significant intermediate-risk PCa and contralateral low-risk low-volume Gleason Grade Group 1 (3+3) PCa 2. PSA ≤ 20 ng/ml within the last 120 days 3. Pre-biopsy mpMRI scan within the previous 6 months, and bilateral biopsies of the prostate (transrectal or transperineal, and targeted biopsy for visible lesions) 4. Clinically ≤T2b intermediate-risk Gleason Grade Group 2 or 3 (3+4 or 4+3) disease judged by results of digital rectal examination, imaging by Multi-parametric Magnetic Resonance Imaging (mpMRI) and biopsy (low-risk Gleason Grade Group 1 lesions on the contralateral side are acceptable) 5. Fit, eligible, with a standard-of-care recommendation for any or all of radical prostatectomy, radical radiotherapy or low dose-rate brachytherapy (LDR-B), and suitable for PA using at least one of irreversible electroporation (IRE) or high intensity focused ultrasound (HIFU)

	6. An understanding of the English language sufficient to receive written and verbal information about the study, its consent process and complete study questionnaires **Exclusion:** 1. Taking part in another therapeutic prostate cancer clinical trial or has been involved in such trials within the previous 4 months (NB. the TRANSLATE trial is a diagnostic trial and co-enrolment is permitted) 2. PSA > 20ng/ml within the last 120 days 3. Unfit for radical treatment or general anaesthesia or cannot tolerate transrectal ultrasound 4. In the opinion of the treating physician, has a contraindication to either HIFU or IRE 5. Not suitable for mpMRI or have a single or bilateral hip replacement 6. Has evidence of extraprostatic extension by mpMRI, or clinical or radiological ≥T3 disease 7. Concomitant cancer or previous active treatment for PCa 8. Evidence of metastatic disease 9. Bilateral intermediate-risk disease or higher 10. Low-risk (Gleason Grade Group 1) disease only, or high-risk (Grade Group ≥4) PCa only 11. History of acute urinary retention within the last 6 months prior to entry to the study 12. Prostatic calcification and cysts causing ultrasonic shadowing of greater than 1cm 13. History (within 3 years) of inflammatory bowel disease or any condition that may increase the risk of recto-urethral fistula formation 14. Has known hypersensitivity to pancuronium bromide, atricurium or cisatricurium, or any medical condition such that muscle relaxation cannot be administered as part of a general anaesthetic 15. Has a history of bladder neck contracture 16. Had active treatment for a malignancy within 3 years, including malignant melanoma, except other types of skin cancer 17. Has any active implanted electronic device (e.g., pacemaker) 18. Is unable or unwilling to be catheterised 19. Has had prior or current PCa therapies 20. Has had prior transurethral prostatectomy (TURP), urethral stricture surgery, urethral stent or prostatic implants 21. Has had prior major rectal surgery (except for haemorrhoids) 22. Is actively bleeding, is anticoagulated or on blood thinning medications that cannot be stopped for the peri-operative period for a PA procedure, or has a significant bleeding disorder that may affect the peri-operative period as judged by the clinical staff. 23. Unable to give consent to participate in the trial as judged by the clinical staff 24. Wishing to maintain future fertility

No. of study arms:	2	
Intervention:	Partial Ablation of the prostate (using either irreversible electroporation (IRE) or high intensity focused ultrasound (HIFU))	
Comparator:	Radical prostate cancer treatment using one of the standard NHS treatment options: Radical prostatectomy (RP) Radical radiotherapy (RRT) Low dose-rate brachytherapy (LDR-B)	
Planned Sample Size:	800 participants	
Target no. of centres:	10+	
Planned recruitment duration:	Recruitment is expected to last for 5 years.	
Planned study duration	Feb 2023 – Mar 2030	
Duration of intervention/treatment:	Participants will receive treatment for their prostate cancer in accordance with their randomised allocation, and in accordance with standard clinical care pathways. Treatment should commence within 12 months of randomisation.	
Follow-up duration:	Participants will be followed-up in the study for as long as the study remains open – for those recruited early in the study this may be for 5 years post-randomisation. The study team will also seek funding to see if longer term follow-up (up to 15 years post-randomisation) may possible. The minimum 'on study' follow-up for the last recruited patient is 12 months. All participants will continue NHS follow-up beyond the duration of the study.	
	Objective	**Outcome Measure**
Co-primary objectives and outcome measures:	To determine whether partial ablation provides effective oncological outcomes compared with radical treatment	Primary treatment failure (as defined in section 8.5)
	To determine whether partial ablation has a reduced side effect profile, and an improved patient-reported outcomes profile, compared with radical treatment	Health-related quality of life (HRQoL) as measured by the Patient Oriented Prostate Utility Scale (PORPUS-P).
Secondary objectives and outcome measures:	Refer to the main OBJECTIVES AND OUTCOME MEASURES section of the protocol for full study objectives and outcome measures.	

ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trials Unit
DSMC	Data and Safety Monitoring Committee
DVT	Deep vein thrombosis
EPIC	Expanded Prostate Cancer Index Composite
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HIFU	High Intensity Focal Ultrasound
HRA	Health Research Authority
HRQoL	Health-related Quality of Life
ICF	Informed Consent Form
IRE	Irreversible Electroporation
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LDR-B	Low Dose-Rate Brachytherapy
MDT	Multi-disciplinary team
MAX-PC	Memorial Anxiety Scale for Prostate Cancer (MAX-PC)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Models for Repeated Measures
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OCTRU	Oxford Clinical Trials Research Unit
OPCSG	Oxfordshire Prostate Cancer Support Group
PA	Partial Ablation
PART	Partial Ablation versus Radical Treatment
PCa	Prostate Cancer
PE	Pulmonary Embolism
PI	Principal Investigator
PIC	Participant Identification Centre
PIP	Participant Inormation Portal
PIS	Patient information sheet
PORPUS-P	Patient Oriented Prostate Utility Scale-Psychometric
PPI	Patient and Public Involvement
PROM	Patient-reported Outcome Measure
PSA	Prostate-Specific Antigen
QA	Quality Assurance
QALY	Quality-adjusted life year
QRI	QuinteT Recruitment Intervention

RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RITA	Radiofrequency Interstitial Tissue Ablation
RP	Radical Prostatectomy
RRT	Radical Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SITU	Surgical Intervention Trials Unit
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Response/Reaction
SWAT	Study Within a Trial
TIDieR	Template for Intervention Description and Replication
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TURP	Transurethral Prostatectomy
VTP	Vascular Targeted Photodynamic Therapy

7 BACKGROUND INFORMATION AND RATIONALE

7.1 Prostate cancer in the United Kingdom (UK)

Prostate cancer (PCa) is the most common cancer and the second most common cause of cancer-related death in men in the UK. There are >52,000 new cases diagnosed, and >12,000 PCa deaths, each year on average in the UK, and the lifetime risk of being diagnosed with PCa is around 1 in 8 men (1). PCa incidence is increasing due to wider use of Prostate Specific Antigen (PSA) testing of asymptomatic men coupled with an ageing population. The NIHR HTA ProtecT randomised controlled trial (RCT), led by the applicants, assessed the value of a single round of PSA testing in over 111,000 men in nine UK centres in the community, and compared the effectiveness of radical treatment (prostatectomy or radiotherapy) versus active monitoring in 1,643 men diagnosed with clinically localised PCa. ProtecT demonstrated that radical treatment of PSA-detected PCa halved the risk of subsequent disease progression and metastasis at a 10-year median follow-up. Moreover, PCa-specific mortality was very low at this 10-year median follow-up, with or without radical treatment. The study also defined the adverse urinary, bowel, and sexual side effect profiles resulting from the radical treatment options (2,3). Hence, most patients with low-risk (i.e. Gleason Grade Group 1), and many patients with low-volume lower-end intermediate-risk (i.e. Gleason Grade Group 2), PSA-detected localised PCa are now recommended to consider pursuing an initial policy of Active Surveillance involving regular clinical examination, PSA measurement, repeat mpMRI imaging +/- repeat biopsies, with radical treatment offered if indicated (4).

Men with intermediate-risk PCa (Gleason Grade Group 2-3) requiring treatment are usually recommended to receive radical treatment with curative intent in the form of Radical Prostatectomy (RP), Radical Radiotherapy (RRT) or Low Dose-Rate Brachytherapy (LDR-B). Partial Ablation (PA) is an alternative approach that aims to reduce treatment side effects while retaining oncological benefit, but its effectiveness compared to radical treatment has not been rigorously evaluated in the context of an RCT. The aim of PA is to target and treat only the part of the gland harbouring clinically significant PCa, thus minimising the morbidity of PCa treatment by reducing the adverse radical treatment sequelae of erectile dysfunction and urinary incontinence following RP, or erectile dysfunction, bowel and urinary toxicity following RRT. Several PA techniques have been developed including High

Intensity Focused Ultrasound (HIFU), Vascular Targeted Photodynamic Therapy (VTP), cryotherapy, Radiofrequency Interstitial Tissue Ablation (RITA), laser photocoagulation and irreversible electroporation (IRE) (5). Having demonstrated the feasibility of randomising men with unilateral intermediate-risk PCa to a radical treatment option or PA in our PART Feasibility Study (6) (section 7.7), this is a full RCT of PA versus radical treatment, which will build on and complement the ProtecT study, and provide essential evidence to inform commissioning and clinical practice.

7.2 Diagnosis of prostate cancer – evolution of the diagnostic pathway

Until recently PCa did not rely consistently on imaging to detect disease and guide tissue sampling for histological confirmation. Conventional Magnetic Resonance Imaging (MRI) has been used but with accuracy ranging from 50-92% (7). More recently, multiparametric MRI (mpMRI) has demonstrated high levels of accuracy in detecting clinically-significant PCa (8,9) mpMRI has a high negative predictive value of 90-95% for lesions >0.5 ml in volume, accepted as constituting clinically significant disease (10,11) , and this has now transformed clinical practice. The contemporary diagnostic pathway for PCa now involves PSA-testing followed by a pre-biopsy mpMRI, following recent evidence from the PROMIS and PRECISION RCTs (12,13). Incorporating pre-biopsy mpMRI into the PCa diagnostic pathway has demonstrable benefits in allowing targeted biopsies of visible lesions seen on imaging, leading to an improved detection rate of "clinically significant" PCa, particularly unilateral intermediate-risk tumours that might be suitable for PA.

7.3 Radical treatment options for localised prostate cancer

In 2017 approximately 78% of men diagnosed with PCa in England were under 75 years old (Office for National Statistics), and around 7,500 would have been suitable for potentially curative therapies. Conventional radical treatments for localised PCa (RP and RRT) appear to have similar oncological outcomes at a median of 10 years' follow-up (2). Low dose-rate brachytherapy [LDR-B] (placement of radioactive seeds directly in the prostate) is also a recognised standard-of-care option for some men with suitable intermediate-risk disease (NICE, 2021). Radical treatment has the potential for significant short, medium and long-term side effects such as erectile dysfunction following both RP and RRT, urinary incontinence following RP, and bowel and urinary dysfunction following RRT.

7.4 Alternative to conventional radical treatment: partial ablation

The National Institute for Health and Care Excellence (NICE) in the UK recommends that PA treatments should only be used with special arrangements for clinical governance, consent and audit or research (15,16)Click or tap here to enter text., but demand for PA in intermediate-risk PCa is expanding. The lack of RCT-based evidence means that NICE and similar bodies globally are unable to make robust recommendations, highlighting the urgent need for this RCT. It is imperative to investigate whether PA can offer comparable oncological outcomes to radical treatments, with fewer potential side effects.

The PART Feasibility Study (6), along with other recently published evidence, has demonstrated that the side effects (in terms of erectile dysfunction and urinary incontinence) following PA are low after short-term (median 12-24 months) follow-up (17,18). Only 5% of PA-treated men had significant residual cancer following PA (18).

The PART Feasibility Study also established that mpMRI followed by systematic +/- targeted biopsies is required prior to minimally invasive PA to assess whether the disease is amenable to PA and has demonstrated that men can be recruited to such an RCT without necessarily needing an extended or template biopsy protocol.

Several PA technologies have been described and are summarised in a HTA synthesis review (5). These include HIFU, cryotherapy (19,20), RITA, interstitial laser photocoagulation, VTP and IRE. Having demonstrated their ability to ablate prostate tissue safely, PA technologies are currently being introduced and taken up in clinical practice without robust evidence of their utility, cost-effectiveness or medium- or long-term functional and oncological outcomes (16,17). We used HIFU as the PA technique in the PART Feasibility Study but encountered some practical limitations regarding the use of HIFU as the sole PA modality: 1) it required expensive equipment available only in a minority of UK NHS Trusts and some private providers; 2) the equipment was not readily available, and its lease from the manufacturers incurred a large expense which could not be covered by the Clinical Commissioning Groups. However, following recent developments, some of these limitations have been overcome, and in addition we have now added IRE as a PA modality in this main PART trial. AngioDynamics Inc. have agreed to partner with the PART study team by providing IRE equipment (AngioDynamics, Inc., NanoKnife System, Latham, NY USA) and training to any recruiting centre that requests it. EDAP TMS have also agreed to partner with the PART study team by providing their HIFU equipment and training to any recruiting centre that requests it. In addition, any site offering HIFU using the Sonablate system may also treat patients within PART. This will allow these well-tested PA technologies to be utilised in the PA arm of the trial.

An essential consideration for a PA strategy to be successful in treating intermediate-risk PCa is the ability to image and map the disease accurately, and this is now possible through use of mpMRI, as recently demonstrated by the PROMIS and PRECISION trials (12,13). In this proposal, PART participants will have undergone, as part of routine care, a pre-biopsy mpMRI and subsequent transrectal ultrasound guided (TRUS) biopsies, local anaesthetic transperineal (LATP) biopsies or transperineal template mapping biopsies as necessary. Repeat imaging will be used to follow-up men in the PA arm after treatment. The PA modalities included in PART are described below.

7.5 High Intensity Focused Ultrasound (HIFU)

HIFU uses ultrasound energy focused by an acoustic lens to cause tissue damage as a result of thermal coagulative necrosis and acoustic cavitation. The procedure is performed using a transrectal approach and is generally performed under general anaesthesia as a day case procedure. A transrectal probe incorporating an ultrasound scanner and a HIFU treatment applicator is inserted. The probe emits a beam of ultrasound, which is focused to reach a high intensity in the target area. Absorption of the ultrasound energy creates an increase in temperature, which destroys tissue. A cooling balloon surrounding the probe protects the rectal mucosa from the high temperature. HIFU continues to be a treatment option listed by NICE guidelines in 2019 ‘requiring further evaluation’, and a recent NICE draft recommendation (October 2022) continues to support the rationale of the PART study, by stating that although there is sufficient evidence of safety with HIFU, evidence of treatment efficacy is lacking, and further research is needed, in particular RCTs. Several reviews of HIFU treatment of PCa have been published, and a recent meta-analysis and systematic review concluded that prospective RCTs of partial-gland HIFU were needed (21–23).

7.6 Irreversible Electroporation (IRE)

Irreversible Electroporation (IRE) is an image-guided tissue ablation technology that induces cell death via short, strong pulsed electric fields. Due to its non-thermal nature, IRE preserves vessels, nerves and extracellular matrix, making it an effective treatment modality for prostate cancer. IRE was cleared by the US FDA in 2011 for the surgical ablation of soft tissue. As of late 2022, 1,626 men with prostate cancer treated with partial ablation using IRE have been reported in 22 published studies

(24,25), with a favourable oncological (26,27) and safety profile (28–30). Interest in the IRE technology for PCa is increasing in the UK amongst clinicians and patients, and a number of patients have recently been treated at UCL in London. IRE is UKCA marked in the UK.

7.7 The PART feasibility study

In the PART Feasibility Study, 41 participants were randomly allocated to surgery (RP) and 41 to HIFU (as the PA treatment modality) (6). Analyses were performed using data from 71 participants. Participant characteristics were similar at baseline. The return rate for clinical CRFs and PROMs were 95% and 91% respectively. HRQoL outcomes relating to urinary and sexual function were better in the PA group (6) compared with RP, but no significant differences were observed in overall HRQoL between the two groups. Analysis of EuroQoL EQ-5D-5L utility scores was limited by small numbers but highlighted potential health gains for patients receiving PA compared to RP, with evidence suggesting that HIFU is unlikely to result in a loss in health benefit relative to RP. Five SAEs were reported, two of which were SUSARs and were reported to the REC.

Although the PART Feasibility Study was not powered to assess effectiveness of HIFU treatment compared to RP, the HRQoL outcomes are concordant with previous observational studies, which suggested that over the short- to medium-term HRQoL outcomes are better in patients treated with PA than RP. An indication towards better HRQoL and utility with PA added to the clear need to undertake a full RCT to quantify the level of benefit, and to determine overall clinical and cost-effectiveness, hence the full PART study.

7.7.1 Recruitment in the PART feasibility study

Recruitment is often challenging because of difficulties in explaining and justifying the concepts inherent in the trial design (such as randomisation and uncertainty) to patients (31). The QuinteT Recruitment Intervention (QRI) methodology was first developed to address such problems encountered with recruitment to the ProtecT trial, and QRIs have since been successfully integrated within 30 RCTs (32). We included an integrated QRI in the PART Feasibility Study to understand the recruitment process in the clinical centres and gathered evidence about the origin of difficulties as they occurred (using standard and novel qualitative research methods), and then produced rapid plans to address the recruitment difficulties in close collaboration with the Chief Investigator (CI), Trial Management Group (TMG) and Clinical Trials Unit (CTU). This process enabled the research team to understand and then overcome recruitment challenges (33).

In the PART Feasibility Study, five centres opened to recruitment between January and November 2015. In total, 236 patients (out of 329 screened individuals) were identified as eligible to participate by 31st March 2017, and 82 patients agreed to be randomised by 4th May 2017. The QRI findings showed that there was strong support for PART among recruiters. However, many had not previously been involved in RCTs, and in the early part of the PART Feasibility Study they found it challenging to explain aspects of the study, with some holding preconceptions about which treatment was preferable for patients and therefore finding it difficult to maintain equipoise. This meant that some clinicians were not comfortable approaching all eligible patients, and when the study was discussed, biases were conveyed through the use of particular terminology, poorly balanced information and treatment recommendations. The issues identified are common within many RCTs (31). Following the identification of these recruitment issues, the QRI team developed tailored strategies to optimise recruitment, including group training, individual feedback and 'tips' documents. The recruitment rate increased from 15/75 eligible (20%) (January-November 2015) to 67/161 (42%) (December 2015 to March 2017), and recruitment was achieved in four centres (with a clear understanding as to why it was not possible in the one other centre).

A QRI is integrated into this definitive trial to continue to support recruitment (see section 10). This will build on the findings from the PART Feasibility Study and will aim to understand the recruitment process as it occurs in the clinical centres/sites, to quickly gather evidence about the origin of difficulties (using standard and novel qualitative research methods), and then to produce a plan to address the difficulties in close collaboration with trial staff.

8 OBJECTIVES AND OUTCOME MEASURES

8.1 Aim

The aim of the PART study is to determine whether partial ablation for unilateral intermediate-risk prostate cancer provides effective oncological outcomes compared with radical treatment, with the added benefits of reduced side effects, and an improved patient reported outcomes profile.

8.2 Primary objective and outcome measure

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)
To determine whether partial ablation provides effective oncological outcomes compared with radical treatment	Primary treatment failure (as defined in section 8.5)	After a minimum of 3 years median follow-up post-randomisation, with at least 12 months post-randomisation follow-up of the last recruited participant
To determine whether partial ablation has a reduced side effect profile, and an improved patient-reported outcomes profile, compared with radical treatment	Health-Related Quality of Life (HRQoL) as measured by the Patient Oriented Prostate Utility Scale (PORPUS-P)	Baseline, 6wks post-treatment and 3mths, 6mths, 12mths post-randomisation, thereafter every 12 months until the end of the study.

8.3 Secondary objectives and outcome measures

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)
1. To compare the effect on HRQoL of both treatment arms	HRQoL using standard, validated patient-reported outcome measures (PROMs) questionnaires: IPSS, EQ-5D-5L, EPIC and MAX-PC (Modified 18 item)	Baseline, 6wks post-treatment and 3mths, 6mths, 12mths post-randomisation, thereafter every 12 months until the end of the study.
2. To compare the effect on health care resource	Health care resource utilisation and cost-effectiveness in terms	Baseline, 3mths, 6mths, 12mths post-randomisation,

utilisation of both treatment arms	of cost per quality-adjusted life year (QALY)	thereafter every 12 months until the end of the study.
3.To compare the short and medium term serious adverse events related to treatments in both treatment arms	Short, medium and long-term serious adverse events related to treatments	Short term: 31 days Medium term: 3 years
4.To determine the proportion of patients needing repeat partial ablation treatment	Proportion of patients needing repeat PA treatment in the PA group	Documentation of the need for repeat PA treatment in the PA group – at 1 year post-treatment and 3 years post-treatment (for those that reach this time point in the study's lifetime)
5.To evaluate the accuracy of current mpMRI imaging and biopsy protocols in determining suitability of patients for PA	The proportion of prostatectomy patients who develop high-risk disease or bilateral intermediate disease	After histopathological evaluation (only in men who have had RP, including salvage RP)
6.To determine disease progression beyond the prostate, including local spread and development of metastases	Time to disease progression (including local and distal recurrence)	At a minimum 12 months post-randomisation follow-up of the last recruited participant, but will be longer for those recruited early in the study.
7.To determine medium-term disease-specific and overall mortality	Time to disease-specific and overall mortality	At a minimum 12 months post-randomisation follow-up of the last recruited participant, but will be longer for those recruited early in the study.

8.4 Tertiary objectives and outcome measures (subject to additional funding)

Objective	**Outcome measure**	**Time point(s) of evaluation of this outcome measure (if applicable)**
1.To compare the long-term serious adverse events related to treatments in both treatment arms	Long-term serious adverse events related to treatments	Up to 15 years post-randomisation
2.To determine disease progression beyond the prostate, including local spread and development of metastases	Time to disease progression (including local and distal recurrence)	Up to 15 years post-randomisation

3.To determine long-term disease-specific and overall mortality	Time to disease-specific and overall mortality	Up to 15 years post-randomisation

8.5 Definition of primary treatment failure

Primary treatment failure will be determined by repeat prostate biopsies (either as part of the routine protocol-defined time point), or "for cause", or clinical appearance of symptoms demonstrating disease progression, or radiological concerns on repeat imaging, or due to clinical concern. Primary treatment failure is defined according to the treatment received:

Treatment Arm	Treatment received within arm	Definition of primary treatment failure
Partial Ablation	HIFU or IRE	Any of the following: a) persistent intermediate-risk PCa in a treated area after one repeat PA treatment b) repeat PA treatment requiring more than 75% of the prostate to be treated, and/or indication for radical treatment c) positive biopsies demonstrating high-risk PCa (Gleason Grade Group 4-5) at any time d) extra-prostatic disease progression defined by imaging, clinical examination, or biopsy findings e) the development of systemic disease requiring long-term androgen deprivation therapy
Radical Treatment	Radical prostatectomy (RP)	Any of the following: a) a rising serum PSA reaching ≥0.2 ng/ml following initial reduction to <0.1 ng/ml after surgery b) a failure of serum PSA to fall below 0.1 ng/ml after surgery c) clinical progression to local recurrence/systemic disease d) the need for long-term androgen deprivation therapy
	Radical radiotherapy (RRT) or low dose-rate brachytherapy (LDR-B)	Defined using the RTOG-ASTRO Phoenix criteria (48) as: a) a rise of post-treatment PSA ≥2.0 ng/ml above the post-treatment nadir or b) clinical progression to systemic disease with the need for long-term androgen deprivation therapy

Further information regarding diagnosis and management of primary treatment failure can be found in section 16.4.

8.6 The QuinteT Recruitment Intervention (QRI) – "The Information Study"

The PART study includes an integrated QuinteT Recruitment Intervention (QRI) which will be referred to as "The Information Study" to potential study participants. The aim of the QRI is to

understand/assess the recruitment process and how it operates in each recruiting site, so that sources of recruitment difficulties can be identified and suggestions made to change aspects of design, conduct or training that could then lead on to improvements in recruitment and informed consent.

Further information about the QRI can be found in section 10.

8.7 Use of core outcome sets

Maclennan (34) established a Core Outcome Set (COS) for trials of effectiveness in localised prostate cancer; outcomes reported in this COS are all being recorded for this study.

9 STUDY DESIGN AND SETTING

The PART study is a multi-centre, two arm, parallel design, randomised controlled clinical study. An embedded QuinteT Recruitment Intervention will be used to understand, monitor and address barriers to participation.

The study will recruit 800 men (400 in each of the 2 study arms) with PCa from approximately 10 sites in the UK. Participants will be randomised to receive partial ablation (HIFU or IRE) or radical treatment (radical prostatectomy (RP), radical radiotherapy RRT) or low dose-rate brachytherapy (LDR-B)).

A study flow chart is provided in

APPENDIX 1 .

Within the radical treatment arm, the type of treatment the participant receives (i.e. radical prostatectomy, radical radiotherapy, or low dose-rate brachytherapy) will be determined through joint decision-making between the participant and clinical team, based on current guidelines. Within the PA arm, clinical factors such as the location of the tumour within the prostate gland will be assessed at the treatment planning stage in order to make a specific recommendation regarding which PA option (IRE and/or HIFU) is necessary on a case-by-case basis for PA treatment.

All participants randomised to PA will have their medical case reviewed by a "Partial Ablation Treating Planning Team" (see section 9.5) who will recommend the use of either IRE or HIFU (or in some cases either option), largely based on tumour location in the prostate gland, along with treatment planning aspects. As part of this process, patients may be referred for their PA treatment (IRE or HIFU) at another PART centre delivering that PA modality. In order to facilitate this expert review of PA cases ahead of treatment for participants randomised to PA, and/or as part of the treatment process, patient information (including clinico-pathological data and radiological images) may be transferred securely between NHS centres involved in PART, as is the case in standard-of-care when patients' care is transferred from one NHS Trust to another.

Follow-up will be conducted using standard NHS care protocols for the radical treatment group, and a combination of mpMRI and repeat targeted and/or systematic prostate biopsies in the PA group. Following treatment for PCa, participants will be actively followed-up/monitored for treatment failure in accordance with usual NHS care. All participants will undergo regular blood tests for PSA levels, and for participants randomised to the PA arm, follow-up will also consist of mpMRI and prostate biopsies in accordance with the schedule of study assessments; in-person clinic visits are required for these.

The number of visits per participant will vary and will be dependent on which treatment they are allocated to.

Participants will be followed-up in the study for as long as the study remains open – for those recruited early in the study this may be for 5 years post-randomisation. All participants will have a minimum of 12 months follow-up. Additional funding for longer-term follow-up will be sought in a new funding application in due course. All patients will continue with standard-of-care NHS follow-up beyond the time duration of the study. Any patients with less than 3 years 'on study' follow up will continue to receive necessary PSA tests, MRI and other imaging, and prostate biopsy as necessary, and/or any additional investigations or treatment, in NHS standard of care pathways beyond the timescale of this study.

9.1 Recruiting sites/site types

Approximately 10 urology centres (within NHS secondary care hospitals in the United Kingdom) who see patients with PCa will recruit participants into the PART study.

In order to take part in the study, recruiting centres need to be able to offer radical treatment +/- PA* to PCa patients.

*PA therapy does not need to take place in each recruiting centre; if the method of PA treatment recommended by the PA Treatment Planning Team is not available locally within the recruiting centre, the participant will be referred to an appropriate nearby centre delivering this therapy within a model of PART centre co-operation.

Participants may receive some of their treatment at other NHS sites; such treatment will be arranged in accordance with usual care practice by the recruiting site e.g. participants randomised to radiotherapy treatment will have their radiotherapy scheduled in accordance to the usual care arrangements for that recruiting site. The recruiting site will be responsible for completion of the case report form; any sites undertaking treatment that is standard of care or within usual care competence will be required to transfer data to the recruiting site as required for completion of the CRF. An appropriate agreement will be put in place for these sites.

9.1.1 Participant Identification Centres

Participant Identification Centres (PICs) will not be used in this study. The identification of participants will be done by the recruiting centres, including at regional prostate cancer multi-disciplinary team (MDT) meetings, as described below in Section 12.1.

9.2 Collection of outcome data and follow-up assessments

Participants will undergo research specific visits and receive communications from the PART study team to collect outcome data.

Participants will subsequently be followed up in clinic approximately **six weeks post-operatively** and **three-monthly** post-treatment in the first year, and then approximately every **6 months** as per routine NHS care for up to 5 years post-randomisation depending upon when they are recruited into the study. If, at any point, disease progression is suspected, the patient will be re-staged as per NHS standard care.

Participants receiving PA will be required to attend in-person follow-up clinic visits for mpMRI at 1 week, 6 months, 12 months and 36 months[#] post- treatment and for prostate biopsies at 12 months and 36 months[#] (targeted and/or systematic, depending on mpMRI result).

Participants will be sent HRQoL questionnaires (PORPUS, IPSS, EPIC, EQ-5D-5L, and MAX-PC (modified 18 item)), and health care use questionnaires to complete electronically (a postal option will also be made available where required) at 6 weeks post-treatment and at 3 months, 6 months, 12 months, 24 months[#] and 36 months[#] post- randomisation.

Treatment complications and unexpected serious adverse events related to the study intervention will be collected using a combination of medical notes review, Health Care Use Questionnaire review and asking patients at follow-up appointments, and/or when a member of the research team becomes aware that a serious adverse event has occurred.

For participants who have undergone treatment using PA, additional imaging and repeat biopsies could also be triggered by a rise in PSA of at least 50% over a period of 12 months, or due to clinical concern.

Refer to section 16 for full details of outcome data collection and follow-up assessments.

[#]24-month and 36-month follow-up of all 800 participants is subject to receipt of additional funding for longer-term follow-up, and may not be collected for all participants. These participants will continue with standard-of-care NHS follow-up beyond the time duration of the study. Any patients with less than 3 years 'on study' follow up will continue to receive necessary PSA tests, MRI and other imaging, and prostate biopsy as necessary, and/or any additional investigations or treatment, in NHS standard of care pathways beyond the timescale of this study.

9.3 Duration of participant involvement

Participants will be in the currently-funded study for approximately 3 years median from commencement of the randomised treatment allocation, and for a minimum of 12 months follow-up 'in study' for the last recruited patient.

9.4 Post-study treatment/care and follow-up

At the end of the study participants will receive standard care as per that provided by their NHS site.

9.5 Partial Ablation Treatment Planning Team

All participants randomised to PA will be reviewed by a **PA treatment planning team** consisting of a clinician with expertise in PA delivery, and a radiologist. The PA treatment planning team will review the diagnostic biopsy report and MRI imaging of trial participants, and will recommend the use of IRE or HIFU (or either), largely depending on the tumour location in the prostate gland, along with other relevant clinical factors, along with treatment planning aspects.

9.6 Use of NHS Digital data (including data from registries)

Subject to additional funding, Hospital Episode Statistics (HES) and national mortality records data will be used to monitor long-term outcomes (anticipated up to 15 years). Participants will be asked to consent to the collection of their NHS/CHI number and use of other details for this purpose.

9.7 Health economics analysis

A health economic evaluation will assess the health care resource utilisation, cost impact and cost-effectiveness in terms of cost per QALY of treating PCa patients using PA compared with radical treatment.

Using an NHS perspective for the baseline analysis, data will be collected on health care resource use via a questionnaire to be completed by participants. Costs will be estimated using a standardised approach. Data will also be collected on HRQoL using the EQ-5D-5L questionnaire. A "within-trial" cost-utility analysis will be conducted comparing the implementation of PA therapy with standard radical treatment for PCa participants.

10 THE QUINTENT RECRUITMENT INTERVENTION (QRI) – "THE INFORMATION STUDY"

The Quintet Recruitment Intervention ("Information Study") will be led by researchers at the University of Bristol and will be undertaken in two iterative stages as detailed below. The objectives of the QRI are detailed in Table 1.

Table 1: QRI study objectives and outcome measures

Objectives	Outcome Measures	Time point(s)
To understand the recruitment process in the PART study (Internal Pilot Phase I)	The QRI team will present a summary of anonymised findings emerging from the QRI, based upon: 1. Analysis of interviews and audio recordings with the TMG, recruiters and potential participants for PART. 2. Results from the mapping of recruitment processes at PART study sites.	Depending on the rate of data collection, it is anticipated that preliminary findings will be obtained within the first three to six months of recruitment.

	3. Review of information given to the participant in information sheets and through the recording of informed consent discussions.	
To develop strategies to optimise recruitment and informed consent (Phase II)	Suggestions will be made to change aspects of design, conduct, or training.	Phase II will continue for the duration of recruitment until the target of 800 men is reached.

10.1 QRI PHASE I: Understanding recruitment

The aim of the first phase of the QRI is to understand the process for recruiting patients into the PART study and how this is conducted in the recruiting sites taking part in the study. A multi-faced, flexible approach will be used to investigate site-specific or wider recruitment obstacles.

The following research methods will be used in this phase of the QRI:

1) Interviews with all parties involved in recruitment into the study.

Semi-structured interviews will be undertaken with three groups:

1) Members of the Trial Management Group (TMG) and the Study Office
2) Members of the research team involved in study recruitment at participating sites
3) Potentially eligible participants who have been approached about the study at participating sites

Interviews with members of the TMG and members of the research team at participating sites will explore their perspectives on PART, and experiences of recruitment. Key topics that will be explored will include perspectives on the study design and protocol; views about the evidence on which the trial is based; perceptions of uncertainty/equipoise in relation to the RCT treatment arms; views about how the treatment arms and protocol are delivered in their clinical centre; methods for identifying eligible patients; views on eligibility; and examples of actual recruitment successes and difficulties.

Interviews with patients approached about the study at participating sites will explore views on the presentation of study information, understandings of study processes (e.g. randomisation), and reasons underlying decisions to accept or decline the study. Patients will be purposefully sampled for maximum variation based on age, study centre, and the final decision about trial participation (i.e. accept or decline), and treatment selected.

Interviewees will be contacted by a researcher from the University of Bristol if they have consented to this part of the Information Study. Interviews will be arranged for a time and place convenient to the interviewee and may be in person or using other remote means of communication (whichever is preferable).

A purposeful sampling strategy will also be used to ensure that views of PART and recruitment are captured from a range of health care professional's perspectives. This will include sampling by professional role (e.g. surgeons, research nurses) and recruitment site, and recruitment rate (i.e. high to low recruitment). RCT participant characteristics will be assessed as the study progresses, and individuals or groups that were under-represented will be targeted. It is anticipated that approximately 20 healthcare professionals and 20 participants will be interviewed, although the

number of participants will ultimately be guided by saturation (whereby data collection continues until no new themes are emerging).

2) Audio-recording discussions between the site research team and patients about study participation

Consent will be sought from potential study participants to record any discussions they have with the local site research team regarding them taking part in the study before full study information is given to them. Following appropriate consent, scheduled appointments during which the study is discussed will be audio-recorded. This will also include any follow-up telephone conversations. The audio recordings will be used to explore information provision, recruitment techniques, management of participant treatment preferences, and randomisation discussions, to identify recruitment difficulties and improve information provision. An encrypted audio recording device for recording recruitment discussions will be supplied by the researchers at the University of Bristol.

3) Mapping of eligibility and recruitment pathways

Detailed eligibility and recruitment pathways will be compiled for participating sites, noting the point at which patients receive information about the study, which members of the clinical team they meet, and the timing and frequency of appointments. The QRI researcher will also work closely with the PART study office to review logs of potential participants as they proceed through screening and eligibility phases, to help identify points at which patients do not continue with recruitment to PART. Logs of eligible and recruited patients will be assembled using simple flow charts and counts to display numbers and percentages of patients for each stage of the eligibility and recruitment processes. These figures will be compared across sites and considered in relation to estimates. The screening log data used during this process is not identifiable.

4) Observation of TMG and Investigator Meetings

The QRI researcher will regularly observe TMG meetings (which may be conducted remotely or in person) to gain an overview of trial conduct and overarching challenges (logistical issues, etc.). Observation of these meetings can elucidate new lines of enquiry and add new dimensions to challenges that have emerged through other data collection methods.

10.2 QRI PHASE 2: Feedback and implementation of strategies to improve recruitment

The QRI research team will present summaries of anonymised findings to the CI and the Trial Management Group, identifying the factors that appear to be hindering recruitment with supporting evidence. The QRI team will then suggest a potential plan of action to improve recruitment, based on the findings from the QRI Phase 1, the PART QRI Feasibility Study, and experience from other RCTs for generic issues. The aspects that the QRI team will be able to work on with the PART study team are likely to include: providing feedback and training on generic recruitment issues, such as how to present the study design more clearly to improve levels of understanding during appointments; how to approach patients' treatment preferences; and facilitating discussions around issues of clinical pathways and eligibility assessment, equipoise, and team-working. The responsibility for deciding on the details of the plan of action and implementing changes and facilitating the QRI team's work will lie with the CI.

10.3 QRI Inclusion Criteria

- Patients approached for participation in the PART study
- Healthcare professionals involved in management, operation or recruitment for the PART study

10.4 QRI Exclusion Criteria

- Patients who do not wish to have consultations recorded and/or participate in interview
- Healthcare professionals who do not wish to have consultations recorded and/or participate in interview.

11 PARTICIPANT ELIGIBILITY CRITERIA

11.1 Timing of eligibility assessment

Eligibility will be assessed upon initial entry into the study and checked at the point of randomisation. Following randomisation, study treatment will be planned as per the randomised allocation. Participants will be placed on NHS waiting lists for the study intervention in accordance with usual NHS policies. All study participants will be assessed immediately prior to receiving the study intervention as per standard of care prior to any procedure/treatment within the NHS, and any participants found to be unsuitable for the planned study intervention at this point will be withdrawn from the study.

11.2 Overall description of study participants

The PART study will recruit patients aged 18 years and over with localised intermediate-risk PCa amenable to either PA of the prostate or radical treatment (radical prostatectomy, radical radiotherapy, or low dose-rate brachytherapy).

Written informed consent must be obtained before any study specific procedures are performed. Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator (PI) based on the criteria described below.

11.3 Inclusion Criteria for entry into the main study

A patient will be eligible for inclusion in this study if all of the following criteria apply:

1. Age ≥18 years with unilateral clinically significant intermediate-risk Gleason Grade Group 2 or 3 (3+4 or 4+3) PCa, or dominant unilateral clinically significant intermediate-risk PCa and contralateral low-risk low-volume Gleason Grade Group 1 (3+3) PCa:
2. PSA ≤ 20 ng/ml within the last 120 days
3. Pre-biopsy mpMRI scan within the previous 6 months, and bilateral biopsies of the prostate (transrectal or transperineal, and targeted biopsy for visible lesions)
4. Clinically ≤T2b intermediate-risk Gleason Grade Group 2 or 3 (3+4 or 4+3) disease judged by results of digital rectal examination, imaging by Multi-parametric Magnetic Resonance Imaging (mpMRI) and biopsy (low-risk Gleason Grade Group 1 lesions on the contralateral side are acceptable)
5. Fit, eligible with a standard of care recommendation for any or all of radical prostatectomy, radical radiotherapy or low dose-rate brachytherapy (LDR-B), and suitable for PA using at least one of irreversible electroporation (IRE) or high intensity focused ultrasound (HIFU)
6. An understanding of the English language sufficient to receive written and verbal information about the study, its consent process and complete study questionnaires

11.4 Exclusion Criteria for entry into the main study

A patient with not be eligible for the study if **ANY** of the following apply:

1. Taking part in another therapeutic PCa clinical trial or has been involved in such trials within the previous 4 months (N.B. the TRANSLATE trial is a diagnostic trial and co-enrolment is permitted)

2. PSA > 20 ng/ml within the last 120 days
3. Unfit for radical treatment or general anaesthesia or cannot tolerate transrectal ultrasound
4. In the opinion of the treating physician, has a contraindication to either HIFU or IRE
5. Not suitable for mpMRI or have a single or bilateral hip replacement
6. Has evidence of extraprostatic extension by mpMRI, or clinical or radiological ≥T3 disease
7. Concomitant cancer or previous active treatment for PCa
8. Evidence of metastatic disease
9. Bilateral intermediate risk disease or higher
10. Low-risk (Gleason Grade Group 1) disease only, or high-risk (Grade Group ≥4) PCa only
11. History of acute urinary retention within the last 6 months prior to entry to the study
12. Prostatic calcification and cysts causing ultrasonic shadowing or greater than 1cm (for HIFU)
13. History (within 3 years) of inflammatory bowel disease or any condition that may increase the risk of recto-urethral fistula formation (for HIFU)
14. Has known hypersensitivity to pancuronium bromide, atracurium or cistracurium, or any medical condition such that muscle relaxation cannot be administered as part of a general anaesthetic
15. Has a history of bladder neck contracture
16. Had active treatment for a malignancy within 3 years, including malignant melanoma, except other types of skin cancer
17. Has any active implanted electronic device (e.g., pacemaker)
18. Is unable or unwilling to be catheterised
19. Has had prior or current PCa therapies
20. Has had prior transurethral prostatectomy (TURP), stricture surgery, urethral stent or prostatic implants
21. Has had prior major rectal surgery (except haemorrhoids)
22. Is actively bleeding, is anticoagulated or on blood thinning medications that cannot be stopped for the peri-operative period for a PA procedure, or has a significant bleeding disorder that may affect the peri-operative period as judged by the clinical staff.
23. Unable to give consent to participate in the study as judged by the clinical staff
24. Wishing to maintain future fertility

11.5 Rationale for inclusion and exclusion criteria

Patients with suitable disease characteristics (i.e. previously untreated unilateral intermediate-risk PCa), suitable for at least one of the radical whole gland treatments, and for at least one of the PA treatments, are included. It is also necessary to exclude patients with certain clinical factors that may make PA unsuitable for safety reasons.

11.6 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a research study. There will be no waivers regarding eligibility i.e. each participant must satisfy all the eligibility criteria. Changes to the approved inclusion and exclusion may only be made by a substantial amendment to the protocol.

Before entering a patient into the study the Principal Investigator or designee will confirm eligibility. If unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion investigators must contact the Study office, who will contact the CI or designated clinicians as necessary. If in any doubt the CI must be consulted before entering the patient. Details of the query and outcome of the decision must be documented in the TMF and site files.

11.7 Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact the Study Office for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the Study Office. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all study investigators for information as necessary. For urgent safety measures or changes that require a protocol amendment see Urgent safety measures section.

12 SCREENING AND RECRUITMENT

12.1 Participant Identification

Participants will be recruited from Urology centres within NHS hospitals in the United Kingdom.

Potentially eligible patients will be identified via several routes, including by a member of their usual care team through a search of clinic records/hospital databases at participating centres, or at patient consultations, and through identification of potentially eligible patients at regional MDT meetings (where patients from several individual NHS Trusts may be discussed at that MDT, via standard-of-care pathways, and thus may be identified).

Potentially eligible patients will be provided with a Patient Information Sheet (PIS) by a member of their usual care team and/or by a member of the research team. Where their usual care clinician is not a member of the research team, potential participants will be asked if it would be acceptable for their name and contact details to be passed to the research team who will make contact with them (this may be in person in a clinic or via telephone or video call in accordance with local site practice). Alternatively, potential participants may be given the PIS and asked to call the number on it if they wish to find out more about the study. When a potential participant is approached for permission for their details to be passed on to the local research team, if this permission is given, this should be recorded in their clinical notes.

Patients will be informed about the “Information Study” which involves the audio-recording of all subsequent discussions about their treatment options (until they have chosen whether to join the PART study), and it will be explained that this is being done to understand how information is communicated to patients and how patients make decisions about whether to take part in research. The doctor or nurse will briefly explain the purpose of the audio-recording and ask for verbal consent to proceed, informing the patient that the Information Study PIS explains why in more detail and asks for their written consent to participate and for the recording to be analysed. Providing they are happy to proceed, recruitment discussions will be audio recorded. Consent to take part in the “Information Study” is optional and does not affect the patient joining the main PART study if they choose not to take part in this. Where patients feel they require more time to consider participation, this will be accommodated before being re-approached about the study. Audio files will not be shared with the University of Bristol team until written consent is obtained. If written consent is not obtained, the audio files will be deleted immediately upon the patient declining participation.

Each patient will be seen by a urologist who will give an overview of the PART study, answer any questions and confirm the patient’s eligibility. During the consultation, potential participants will be fully appraised of the potential risks, benefits and burdens of the study. The patient will be given the opportunity to deliberate and will be offered a second consultation if they wish to consider and discuss the PART study again. If the patient decides to participate, the Research Nurse, the Consultant

Urologist responsible for the patient, or another delegated clinical member of the research team will obtain informed consent for the PART main study.

The study team will work closely with the research nurses and clinicians to ensure that the strategies for recruitment and consent are robust, while also being easy to accommodate within existing clinical practices. All individuals taking informed consent will have relevant training for their role and will be appropriately delegated to do so by the Principal Investigator. It will be clearly stated that the participant is free to withdraw from the study at any time without prejudice to future care, and with no obligation to give the reason for withdrawal. In such an event, the choice of treatment will be a matter for decision between the patient and their clinical team. Patients will have ample time to discuss the study with family, friends, their GP and the Research Nurse. If a patient is not eligible for the PART study, they will be informed by their treating clinician, who will go through their treatment options with them.

12.2 Use of screening logs

A screening log (within the REDCap study database) must be kept of all patients considered for the study including any that are subsequently excluded; the reason for exclusion must be recorded. All patients with localised intermediate-risk PCa who may be amenable to either PA of the prostate or radical treatment (RP, RRT or LDR-B) should be screened for study participation and entered onto the screening log in advance of discussion at the uro-oncology MDT meeting.

The screening log will be used to record information about the number of patients considered and/or approached for the study and if provided, the reasons for declining participation.

All patients meeting the following criteria should be entered onto the screening log:

- Age ≥18 years with unilateral clinically significant intermediate-risk Gleason Grade Group 2 or 3 (3+4 or 4+3) PCa, or dominant unilateral clinically significant intermediate-risk Gleason Grade Group 2 or 3 (3+4 or 4+3) PCa and contralateral low-risk low-volume Gleason Grade Group 1 (3+3) PCa
- PSA ≤ 20 ng/ml within the last 120 days
- Clinically ≤T2b intermediate-risk Gleason Grade Group 2 or 3 (3+4 or 4+3) disease judged by results of digital rectal examination and imaging by mpMRI (within the last 6 months) and biopsy (low-risk Gleason Grade Group 1 lesions on the contralateral side are acceptable).

13 TREATMENT ARMS

13.1 Partial Ablation (intervention)

Participants randomised to PA will undergo either irreversible electroporation (IRE) or high intensity focused ultrasound (HIFU).

13.1.1 Choice of partial ablation

Patients allocated to PA will receive an appropriate PA treatment modality (IRE or HIFU). PA treatment planning meetings, attended by, as a minimum, a clinician who administers PA and is able to advise a suitable PA option, along with a uro-radiologist as necessary, will guide recommendations regarding which PA modality, i.e. IRE or HIFU, or in some cases either, may be used on a case-by-case basis, for patients randomised to the PA arm, based on factors such as prostate size and tumour location. Treatment will be co-ordinated by local investigators and research nurses, and by cooperation between recruitment and treatment centres in PART, with some patients receiving their allocated

treatment at a PART centre that was different to their recruitment centre (for example, to enable PA treatment with the necessary treatment modality). PA will either be performed by the recruitment centre (if it is available locally), or at an alternative centre within PART. See section Recruiting sites/site types for further details.

13.1.2 High-intensity focussed ultrasound (HIFU)

HIFU treatment will be scheduled by the recruiting site for participants randomised to the PA arm of the study, and where the PA treatment planning team have selected this to be the most appropriate treatment for the participant.

HIFU will be performed using either the Focal One® medical device (manufactured by EDAP TMS) or Sonablate® device (manufactured by Sonacare Medical). Both devices are CE marked and will be used in accordance with their indicated use. The device used will be determined by local availability. HIFU treatment will be performed in accordance with the relevant manufacturer's User Manual. Only trained HIFU clinicians will carry out the procedure on PART study participants (see section 13.3 Training)

HIFU treatment uses ultrasound energy focused by an acoustic lens to cause tissue damage as a result of thermal coagulative necrosis and acoustic cavitation. The HIFU procedure is performed using a transrectal approach under general anaesthesia, usually as a day case procedure, or in some cases requiring an overnight inpatient stay. A transrectal probe incorporating an ultrasound scanner and a HIFU treatment applicator is inserted. The probe emits a beam of ultrasound, which is focused to reach a high intensity in the target area. Absorption of the ultrasound energy creates an increase in temperature, which destroys tissue. A cooling balloon surrounding the probe protects the rectal mucosa from the high temperature.

HIFU will require hospital admission and will be performed under general anaesthesia with the patient placed in a relaxed lithotomy position. The procedure will be conducted in accordance with NHS standard of care for this procedure and the user manual for the relevant HIFU device being used.

A phosphate enema will be administered before surgery to ensure an empty rectum and participants undergoing HIFU will have a urinary catheter, which usually stays in place for a minimum of 48 hours after the procedure.

TED stockings and Flowtron boots will be fitted to the patient's legs for prophylaxis against any potential thrombo-embolic event. In accordance with local hospital policy sub-cutaneous heparin may be administered peri-operatively. Unless there are any contra-indications a dose of intravenous Gentamicin (or other suitable antibiotic) will be given as antibiotic prophylaxis.

A probe is introduced in the rectum and the imaging transducer starts the gland scanning to plan the treatment. The treatment transducer then emits high intensity focused ultrasound in the prostate gland. At the point where the ultrasound waves are focused, the absorption of the ultrasounds beam created a sudden temperature increase (around 85°C) which destroys the tissue in the targeted zone.

Three-dimensional ultrasound images will be taken to allow registration with MRI both pre-treatment and post-treatment in order to evaluate whether the treatment protocol was effective in ablating the lesion. The HIFU probe and machine will be prepared and used as per the manufacturer's instructions.

Please refer to the manufacturer's HIFU User's Manual relating to the HIFU treatment/re-treatment strategy and training of HIFU clinicians.

It is anticipated that most subjects will be discharged from the treatment facility the day of, or the day after, the procedure.

13.1.3 Irreversible electroporation (IRE)

IRE treatment will be scheduled by the recruiting site for participants randomised to the PA arm of the study and where the PA treatment planning team have selected this to be the most appropriate treatment for the participant.

IRE will be performed using the NanoKnife® medical device (manufactured by Angiodynamics). NanoKnife® is a CE marked device and will be used in accordance with its indicated use. IRE treatment will be performed in accordance with the manufacturer's User Manual. Only trained IRE clinicians will carry out the procedure on PART study participants (see section 13.3 Training)

IRE treatment consists of the application of an electrical field to cells in order to increase the permeability of the cell membranes through the formation of nanoscale defects (openings called nanopores) in the lipid bilayer. IRE of the prostate is typically performed with the subject in the lithotomy position under general anaesthetic, with 2-6 monopolar probes placed through the perineum using a brachytherapy grid and ultrasound guidance, usually as a day case procedure, or in some cases requiring an overnight inpatient stay. IRE supplies the targeted tissue with high voltage (2-3 kV) direct current pulses lasting up to 100 microseconds through the electrode probes.

The patient will have the procedure under general anaesthesia. The patient will be placed in a relaxed lithotomy position. TED stockings and Flowtron boots will be fitted to the patient's legs for prophylaxis against any potential thrombo-embolic event. In accordance with local hospital policy sub-cutaneous heparin may be administered peri-operatively. Unless there are any contra-indications a dose of intravenous Gentamicin (or other suitable antibiotic) will be given as antibiotic prophylaxis. A urethral catheter will be inserted prior to the IRE treatment. This catheter will stay in place for a minimum of 48 hours after the procedure.

The area of the prostate that was positive for cancer based on the mpMRI and transperineal or transrectal prostate biopsy will be targeted for PA via the NanoKnife System. Only the PCa will be targeted for ablation, however, a treatment margin of greater than or equal to 5 mm around the Gleason 3+4 or 4+3 (intermediate-risk) lesion should be included.

An MRI/transrectal ultrasound (TRUS) fusion device or standard TRUS probe may be placed in the rectum to visualise the prostate in both sagittal and axial views. The ultrasound grid which was used during the mapping biopsy will be oriented using anatomical landmarks and used to identify the location of the positive biopsy cores. The NanoKnife Single Electrode Probes will be surgically inserted into the prostate through the perineum using MRI/TRUS fusion guidance and the ultrasound grid for guidance. The location of the probes will be documented via ultrasound imaging and notation in the Case Report Form (CRF).

It is anticipated that most subjects will be discharged from the treatment facility the day of, or the day after, the procedure.

13.1.4 Repeat HIFU or IRE treatments

Repeat treatment will be considered in two instances:

1. the finding of a new intermediate-risk PCa suitable for PA on the contralateral side to the original treated malignancy; and/or
2. the finding of intermediate-risk cancer in the previously treated area (ipsilateral side).

One repeat IRE or HIFU treatment of a previously PA treated region of the prostate gland will be allowed as indicated following repeat imaging and biopsies as per protocol. A repeat PA treatment in PART can be with the other modality compared to the first modality - i.e. a patient who initially had HIFU can have IRE next time around (as long as <75% of the gland in total across two treatments), and vice versa. Repeat treatment of a previously treated area will be performed using either HIFU or IRE. A previously untreated region of the prostate can be treated with either HIFU or IRE if necessary, up to a total of 75% of the gland based on the two PA treatments. If the prostate demonstrates the presence of intermediate-risk PCa in the same region of the prostate gland following a repeat HIFU or IRE treatment, PA will be deemed to have failed (see section 8.5).

13.2 Radical Treatment (usual care/comparator)

Participants randomised to radical treatment will receive one of the following usual care treatment options which will be carried out as per local hospital policy:

- Radical prostatectomy (RP)
- Radical radiotherapy (RRT)
- Low dose-rate brachytherapy (LDR-B)

13.2.1 Choice of radical treatment

Patients randomised to radical treatment will be able to select which treatment (RP or RRT or LDR-B) they receive following full discussion with their local urologist and oncologist, where all treatment options may be applicable (i.e. participant of appropriate fitness / performance status / age), through shared decision-making. Where a particular radical treatment option is preferred or recommended by the treating clinician (e.g. radiotherapy, based on age or fitness issues, rather than radical surgery), patients may still be recruited to PART, with a recommendation for a particular radical therapy option if randomised to that arm of the study. Treatment will be co-ordinated by local investigators and research nurses.

13.2.2 Radical Prostatectomy (RP)

Patients randomised to the radical treatment group for whom the preferred treatment option is surgery will undergo open, laparoscopic or robot-assisted RP according to local centre expertise, patient preference and clinical judgement. Centres included in PART all have cancer network recognised MDTs and cancer centre status. Robot-assisted laparoscopic surgery is recommended, but centres that perform open RP can also participate; this reflects current practice in that a small number of NHS centres continue to perform open surgery, and for clinical reasons some patients may require open surgery. Recent cohort studies confirm similar side effect profiles from both procedures ((35,36)). Routine histopathology evaluation of the surgical resection specimens will be performed by local pathology departments. As per NHS standard care, if disease progression is suspected as per the definition of a post-RP PSA rising to ≥0.2ng/ml then the patient will be re-staged with imaging. Patients will be fully informed about their disease grade, clinical stage and the various treatment options, risks and possible outcomes.

13.2.3 Radical Radiotherapy (RRT)

Patients randomised to the radical treatment group and selecting RRT will undergo external beam RRT according to local centre expertise, clinical judgement, and current practice. RRT will be delivered with or without concomitant androgen deprivation therapy according to a defined local centre clinical protocol, which will document the details of planning, dose delivery and quality assurance, as per NHS standard care at that treatment site. Patients will undergo routine clinical follow-up according to local protocols following RRT as per NHS standard care. If disease progression is suspected as per the definition of a PSA rise of ≥2.0 ng/ml above the post-therapy nadir then the patient will be re-staged with imaging as per NHS standard care.

13.2.4 Lose Dose Rate Brachytherapy (LDR-B)

Patients randomised to the radical treatment group and selecting LDR-B will undergo this according to local centre expertise and clinical judgement. LDR-B will be delivered according to a defined local centre clinical protocol, which will document the details of planning, dose delivery and quality assurance, as per NHS standard care at that treatment site. Patients will undergo routine clinical follow-up according to local protocols following LDR-B as per NHS standard care. If disease progression is suspected as per the definition of a PSA rise of ≥2.0 ng/ml above the post-therapy nadir then the patient will be re-staged with imaging as per NHS standard care.

13.3 Training

Training is required for clinicians taking part in the PART study and delivering the PA modalities (HIFU and/or IRE). HIFU training/proctoring will be undertaken by clinicians with expertise in this PA modality. IRE training will be provided by Angiodynamics and by clinicians with expertise in this PA modality. Many of the clinicians receiving training to deliver PA treatment will already have regular experience of use of a transperineal brachytherapy/biopsy "stepper", and for needle-based targeting of MRI-visible lesions in the prostate through procedures such as targeted biopsy. The ability to independently deliver a PA treatment to PART study participants will be based on a "competency" basis, and the expert proctor will "sign off" PART clinicians in each of the HIFU and IRE procedures based on demonstrable "competency" following "hands on" proctoring and training within PART.

The IRE manufacturer (AngioDynamics) have committed to delivering and ensuring appropriate training with proctoring for optimal administration of treatment. The learning curve will be monitored by the designated proctors to ensure competency in centres delivering PA.

14 INFORMED CONSENT

14.1 Consent for the QRI Information study (pre-study consent)

Patient participants: A separate QRI-specific PIS and ICF will be prepared and may be sent to patients prior to their clinic appointment, or if this is not possible, given to them at the time of their out-patient appointment by members of the clinical care teams. Patients will be asked to consider consent for the QRI – to either take part in an interview, an audio recording of their PART consultation, or both, in clinic, by a member of the local research team if they agree to being approached once the study has been mentioned by a member of the clinical care team. It will be clearly stated in the Information Study PIS for patients that they are free to withdraw from the study at any time and without giving a reason. For the QRI, where possible, patients will be given a reflection period of at least 24 hours to consider whether to participate. Where the period of reflection is less than 24 hours, patients will only be enrolled if they confirm that they feel they have had enough time to consider their participation and fully understand the QRI and its requirements. Staff at site will make this judgement on a case-

by-case basis. A copy of the signed Information Study ICF for patients will be given to the participant. The original signed ICF will be retained at the study site, a copy will be filed in the patient medical record, and participant QRI consent will be recorded in the PART study database.

Staff participants: Consent from staff to audio record their consultations will be discussed and sought as part of the site set up processes. Staff may consent to an interview only, to be audio recorded only, or to both. They may also decline to participate in the QRI. Where the recruiting member of staff has not consented to participate in the QRI audio-recordings, their patients will not be invited to take part in the Information Study. It will be clearly stated in the Information Study PIS for HCPs that they are free to withdraw from the study at any time and without giving a reason. Where possible, HCPs will be given a reflection period of at least 24 hours to consider whether to participate. Where the period of reflection is less than 24 hours, HCPs will only be enrolled if they confirm that they feel they have had enough time to consider their participation and fully understand the QRI and its requirements. The member of staff (central study team) receiving consent will make this judgement on a case-by-case basis. A copy of the signed Information Study ICF for HCPs will be given to the participant. The original signed form will be retained at the study site.

14.2 Consent Procedure for the main PART study

Prior to any study related procedures or data being collected the participant and the individual delegated to take consent at site must personally sign and date the latest approved version of the Informed Consent Form (ICF).

Informed consent will be obtained by a member of the study team listed on the delegation log from each participant before they undergo any study-specific interventions (including physical examination and history taking) related to the study.

Potential participants will be given a current, approved version of the patient information sheet and will also receive clear verbal information about the study from a member of the local research team detailing no less than: the nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal.

Patients will be given as much time as they wish to consider the information and will have the opportunity to ask any questions to the Investigator, their GP or other independent parties to decide whether they wish to take part in the study.

The Investigator who obtains consent must be suitably qualified and experienced. All delegates must be authorised by the site Principal Investigator to obtain consent. The Investigator is responsible for ensuring that the study consent procedures comply with current applicable GCP, regulatory and ethical requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator must be satisfied that the patient has made an informed decision before taking consent.

14.3 Completion of the Informed Consent Form

The Informed Consent Form will usually be offered to participants in clinic as an electronic form on a tablet device (with the consent form being filled in directly on the study database, REDCap), however paper consent forms will also be made available for use in situations where electronic consent is not possible or suitable.

Consent may be obtained in person in clinic, or remotely. The Informed Consent Form will be offered to participants in clinic as an electronic form on a tablet device (with the consent form being filled in directly on REDCap), or on paper if specifically requested. Where it is not possible for a consent form to be completed in clinic (For example; If a participant has only had telephone appointments), remote electronic informed consent may also be obtained by means of an eConsent form emailed to the participant as a link via the study database, REDCap. This emailed link will direct the participant to an electronic consent form on REDCap, which is identical to the electronic consent form used in clinic on a tablet device.

A copy of the fully signed consent form will be given to the participant; where electronic consent is used and the participant has an email address they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the participant does not have/does not provide an email address the local team will be able to print a copy of the signed ICF and provide this to the participant. Consent forms will be e-mailed securely to the participant. The original signed consent form (paper consent only, for electronic consent this will be downloaded from the study database) should be placed in the Investigator Site File and a copy in the participant's medical record.

14.4 Patients lacking capacity to consent

Not applicable. Patients lacking capacity to consent to study participation will not be eligible to enter the study.

14.5 GP notification

Participants will be made aware as part of the informed consent process that if they consent to take part in the study their GP will be informed of their participation. An approved GP letter will be sent by the local site research team to the participant's GP informing them of their participation in the study together with study information.

14.6 Re-consenting

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

14.7 Participants who lose capacity during the study

Participants that lose capacity during the study will be withdrawn from the study.

15 RANDOMISATION AND BLINDING

15.1 Timing of randomisation

Randomisation will take place once informed consent has been given, eligibility has been confirmed and baseline questionnaires have been completed.

15.2 Randomisation procedure

Participants will be randomised by the local research team via a centralised validated computer randomisation program through a secure (encrypted) web-based service, RRAMP (https://rramp.octru.ox.ac.uk), provided by the Oxford Clinical Trials Research Unit (OCTRU), accessed via the PART REDCap study database.

Participants will be randomised in a 1:1 ratio to one of the following treatment arms:

Arm	Treatment

Partial Ablation (intervention)	Participants will undergo partial ablation using either HIFU or IRE.
Radical Treatment (control arm)	Participants will undergo radical treatment by one of the following: 1) radical prostatectomy 2) radical radiotherapy 3) low dose-rate brachytherapy

Upon randomisation of a participant the central study office and a member of the local study team will be notified. This will take place via an automated email.

15.3 Randomisation methodology

Consenting participants will be allocated randomly (1:1) to either PA or radical treatment.

Randomisation will be performed using a minimisation algorithm (or randomisation schedules) to ensure balance between the two treatment groups using the following minimisation factors:

- Age (<65 years, 65-75 years and >75 years)
- Baseline Gleason Grade Group (Gleason grade group 2, Gleason grade group 3)
- PSA level (<10ng/ml, 10-≤20ng/ml)
- Whether the disease is entirely unilateral clinically significant intermediate-risk prostate cancer (i.e. Gleason Grade Group 2 or 3 disease), or dominant unilateral clinically significant intermediate-risk prostate cancer (i.e. Gleason Grade Group 2 or 3 disease) in the setting of contralateral low-volume low-risk (Gleason Grade Group 1) disease.

The first few participants will be randomised using a simple randomisation schedule, prepared by the trial statistician, to seed the minimisation algorithm, and a non-deterministic probabilistic element will be included to prevent predictability of treatment allocation. The randomisation schedule will be designed by the study statistician and full details will be detailed in a randomisation and blinding plan.

15.3.1 Justification for minimisation factors

Patient age, baseline Gleason Grade Group, PSA level, and whether the disease is entirely unilateral clinically significant intermediate-risk prostate cancer (i.e. Gleason Grade Group 2 or 3 disease), or dominant unilateral clinically significant intermediate-risk prostate cancer (i.e. Gleason Grade Group 2 or 3 disease) in the setting of contralateral low-volume low-risk (Gleason Grade Group 1) disease, will be used as minimisation factors, to ensure that the cohorts in each of the Radical Treatment and PA arms are equally matched for these important oncological and clinical variables.

15.4 Back-up randomisation procedure

There is no back-up randomisation procedure. In the unlikely event that the randomisation system cannot be accessed, the Study Office should be informed. Where delays to randomisation are anticipated as a result of any system outage, participants should not be randomised into the study if this is expected to delay their usual treatment pathway.

15.5 Blinding

Table 2 provides an overview of the blinding status of all individuals involved in the conduct and management of the study.

Table 2: Blinding status of those involved in study conduct and management

Role in study	Blinding status	Additional information
Participants	Not blinded	It is not possible to blind due to nature of the intervention. Participants will be told their treatment allocation immediately after randomisation.
Site research staff including Principal Investigator (may need to be broken down further if different levels of blinding/unblinding with the team)	Not blinded	Not possible due to the nature of the intervention. Following randomisation, an email will be sent to the PI (unblinded for participants they randomise only) and/or member of the site research team performing the randomisation (as delegated) confirming treatment allocation.
Chief Investigator	Not blinded	It is not possible to blind the CI as they may be the primary clinician for those participants recruited at their site and may be involved in treatment planning for participants randomised to PA. In instances where serious adverse events are reported, the CI will also be unblinded to complete the full causality assessment.
Database programmer	Not blinded	The database programmer is responsible for the management of RRAMP randomisation system and the REDCap database and will have access to all unblinded datasets within both systems.
PART Study Management staff within SITU	Not blinded	Study Management staff within SITU will not be blinded to treatment allocations as site staff may require support for randomisation, or participants may contact the study team directly. Serious Adverse Event reports will also be handled by the study management team which will contain allocation information.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the study randomisation system and database to ensure data quality and undertake central monitoring activities.
Study statistician and Senior Study Statistician	Not blinded	The study and senior study statisticians will have access to treatment allocations or data needed for generating the Data Safety Monitoring Committee (DSMC) closed reports and the final analysis.
Health Economist	Not blinded	The Health Economists will have access to data within the healthcare use questionnaire that may unblind them to the study intervention.
PA treatment planning team	Not blinded	The PA planning team will be reviewing clinical notes to recommend treatment options within the PA arm and this will not be blinded to treatment allocation.

TSC	Blinded	Will review accruing data and safety overall only, not separated by treatment groups. Full details will be specified in the TSC charter.
DSMC	Not Blinded	DSMC will review accruing data and safety by treatment groups. Allocation may be blinded (arm A or B). Full details will be specified in the DSMC charter and DSMC Report template

15.6 Code break/unblinding

Not applicable for this study.

16 STUDY ASSESSMENTS/PROCEDURES

The study flow chart can be found in Appendix 1 of this protocol.

16.1 Overview

Table 3 shows scheduled assessments including sampling requirements for the study. Following randomised PCa treatment (PA or radical whole treatment), only the timepoints where mpMRI and biopsies are taken require study-specific hospital/in-person visits. All other study assessments will either be undertaken during a routine clinic visit, or electronically/over the telephone.

Table 3: Schedule of assessments

	Day/Week (W)/Month (M) post-randomisaton	Screening, consent & eligibility	Baseline (pre-treatment)	Treatment start***	Day 7	6W ±2 wks**	3M ±4 wks	6M ±4 wks	9M ±4 wks	12M ±4 wks	24M# ±8 wks	36M ±8 wks	Annually until trial ends
	Initial eligibility screen	X											
	Consent for "Information Study"**	X											
	QRI audio recordings of study discussions with potential participants	X											
	Informed consent for main PART study		X										
	Eligibility assessment		X										
	PSA blood test		X*			X	X	X	X	X	X	X	X
	Randomisation		X										
	Baseline data collection/CRF completion		X										
RADICAL TREATMENT ARM ONLY	Choose radical treatment (RP, RRT o LDR-B)		X										
	Radical treatment			X									
PARTIAL ABLATION ARM ONLY	Choose partial ablation modality (HIFU or IRE)		X										
	Partial ablation treatment			X									
	mpMRI ***				X					X		X	
	Prostate biopsy ***									X		X	
	Repeat PA treatment				Repeat PA upon prostate biopsy showing intermediate-risk disease								
	Outcome data collection/CRF completion by local research team		X	X		X	X	X	X	X	X	X	X
				Safety reporting will continue throughout in accordance with section 18									
	HRQoL questionnaires		X			X	X	X		X	X	X	X
	Health care use questionnaire		X				X	X		X	X	X	X

*blood test for PSA will be performed to confirm eligibility if no PSA test has been taken in the previous 90 days. **OPTIONAL consent. # assessments will be performed annually to end of study. ***assessments are from start of treatment, all other follow-up time points are post-randomisation.

16.2 Selection of appropriate partial ablation or radical whole treatment

Upon randomisation, for those participants randomised to receive PA, the participant's clinician will send the participants MRI images to the Partial Ablation Treatment Planning Team who will select the PA modality best suited to the participant. Transfer of mpMRI images and any other clinical data used for treatment decision making will be in accordance with NHS policies between NHS clinicians. Patients randomised to radical treatment will be able to select which treatment (RP or RRT or LDR-B) they receive following full discussion with their local urologist and oncologist

16.3 Blood tests for PSA level

Following initial treatment, all participants will have their PSA levels checked at the following approximate time-points post-treatment: 6 weeks, 3 months, 6 months, 9 months and at 12 months, and annually thereafter. A blood test will be taken to monitor the PSA level in accordance with local site practice.

16.3.1 Prostate Biopsy (partial ablation arm only)

Participants undergoing PA will have biopsies at the following approximate time-points: 12 months and 36 months after receiving treatment.

Additional biopsies may be performed as a result of rising PSA levels (at least 50% increase over 12 months) or where there is clinical concern. Such biopsies will be performed in accordance with usual care.

The results of the biopsies will be used to determine the need for repeated PA treatment or treatment failure. See section 16.4.

16.4 Additional treatment/treatment failure

Partial Ablation Arm

Where a positive biopsy result is returned for intermediate-risk PCa during the study follow-up period, either in the previously treated area or in a previously untreated area (demonstrating new intermediate-risk disease), participants will be offered ONE repeat PA treatment of the positive biopsy area.

Primary treatment failure following PA will be determined by repeat prostate biopsies – per protocol or "for cause" or clinical appearance of symptoms/signs/imaging demonstrating disease progression, or due to clinical concern. Biopsies will result in one of four pre-defined scenarios:

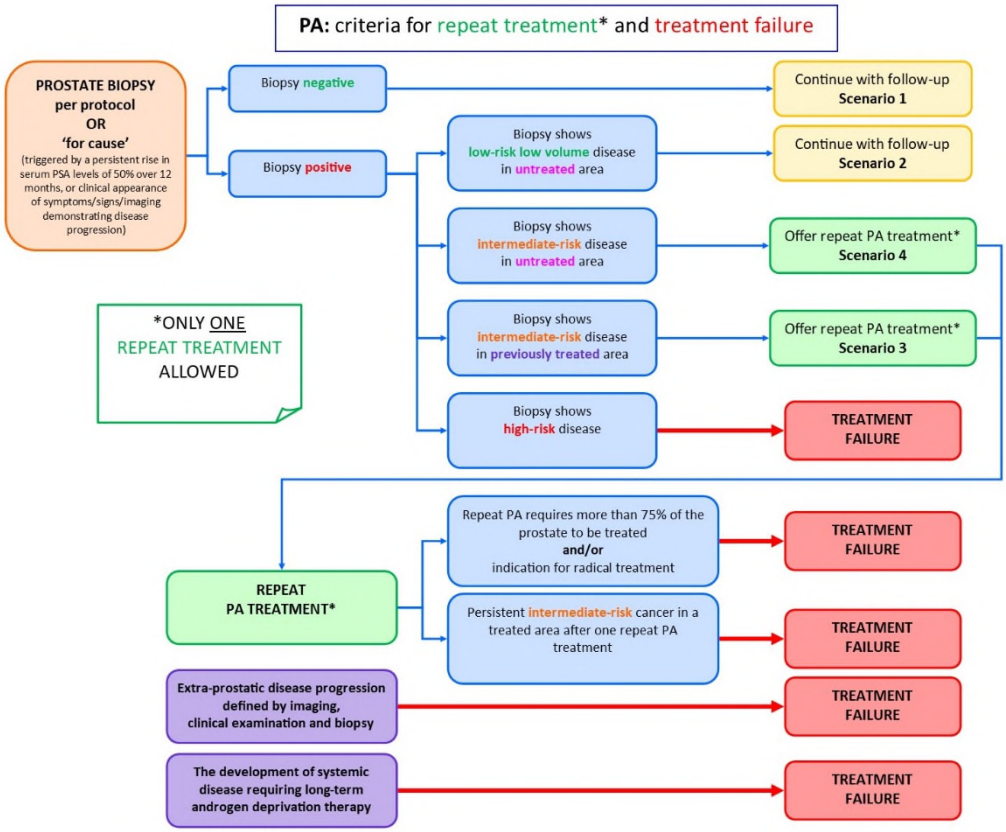
Scenario 1: Negative biopsies, in which case the patient will continue to be followed-up as described.

Scenario 2: Positive biopsies in a previously untreated or treated area of the prostate demonstrating low-risk low-volume disease, in which case the patient will not require additional treatment and follow-up will continue.

Scenario 3: Positive biopsy for intermediate-risk PCa in the previously treated area, in which case the patient will be offered one repeat PA treatment of the positive biopsy area.

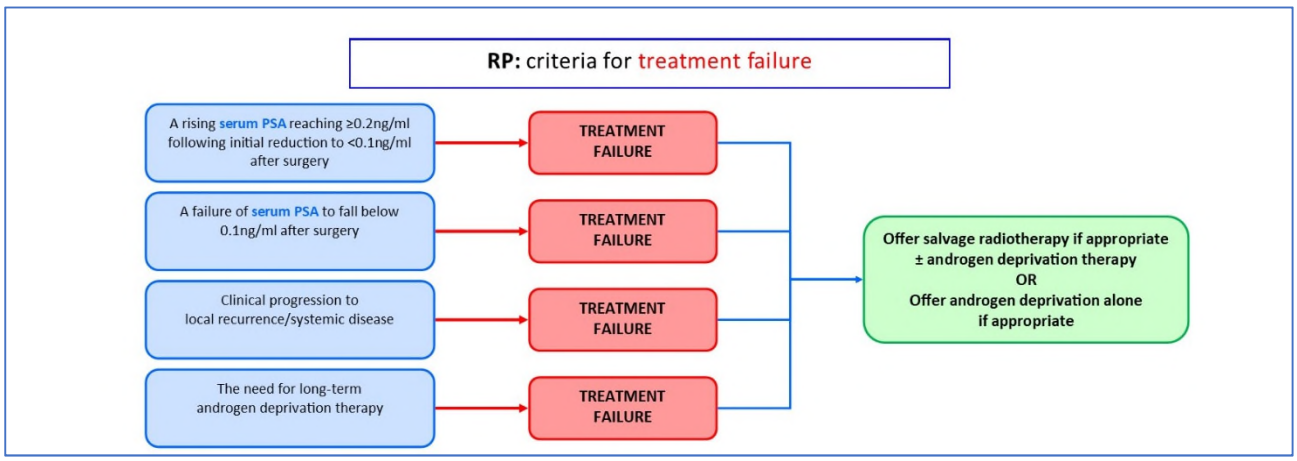
Scenario 4: Positive biopsy for intermediate-risk PCa in a previously untreated area, demonstrating new intermediate-risk disease, in which case the patient will be offered one repeat PA treatment.

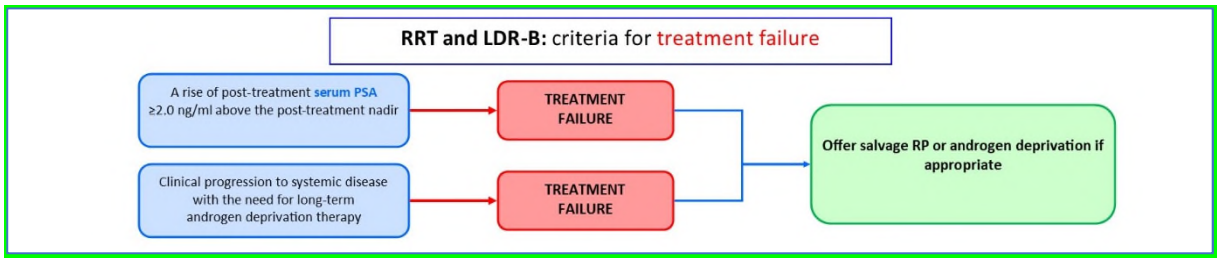
Refer to the flow chart below.



Radical treatment arm

For participants in the radical treatment arm receiving RP additional treatment, options will be discussed with the participant, as per standard NHS care. This is usually salvage radiotherapy post-RP with or without androgen deprivation therapy, or androgen deprivation alone. Salvage RP or androgen deprivation will usually be offered where appropriate if post-RRT or LDR-B treatment failure occurs, as per NHS standard care. Refer to flow charts below.





Management of primary treatment failure

Where treatment failure is diagnosed, the patient will be re-staged as appropriate with cross-sectional imaging, and additional appropriate treatment options will be discussed with the participant, as per standard NHS care. For participants in the PA arm these may include salvage RP, external beam RT, or long-term androgen-targeted therapy +/- chemotherapy. For patients in the radical therapy arm this may include an appropriate salvage therapy, or long-term androgen-targeted therapy +/- chemotherapy.

Details of further treatment received by all participants will be collected on the case report form. Participants will continue to be followed-up for the duration of the study.

16.5 Health-related quality of life questionnaire and health care use questionnaires

Health-related quality of life will be evaluated using validated questionnaires (PORPUS, IPSS, EQ-5D-5L, EPIC and MAX-PC (modified 18 item)) completed 6 weeks post-treatment and at 3 months, 6 months, 12 months post-randomisation and annually thereafter. Information about health care use will also be collected using a health care use questionnaire completed by study participants at the same time points, except 6 weeks.

Participants will be e-mailed a link to complete their study questionnaires electronically where possible (participants will be asked at their baseline visit whether they wish to complete follow-up questionnaires electronic or on paper with postal return). Paper questionnaires may also be used if requested. A health care use questionnaire will also be sent to participants at the same time points to identify and record items relating to utilisation of relevant health care resources. Where paper-based questionnaires are used, data will be entered into the study database by the local site research team.

Participants may be sent up to two reminder messages and/or where possible may be asked to complete questionnaires during a routine clinic visit. Participants that fail to complete study questionnaires may be telephoned by either the site research team or the central study team at the University of Oxford to collect the data or request return of the questionnaire.

16.6 Data Collection

Baseline

Sourced/collected by local study team	Direct patient report
• Participant demographics • Contact details of participant • Medical history • Details of prostate cancer diagnosis • Results of diagnostic tests (including radiology/biopsy/PSA level)	• Health-related quality of life o PORPUS (unmodified) o IPSS (unmodified) o EPIC (unmodified) o EQ-5D-5L (unmodified) o MAX-PC (modified 18 item) • Health care use questionnaire

Treatment Start

Sourced/collected by local study team	Direct patient report
• Partial ablation treatment • Radical treatment • Treatment complications (intraoperative)	• N/A

Day 7 post- commencement of the randomised allocated treatment

Sourced/collected by local study team	Direct patient report
• Radiology results (PA arm only)	N/A

6 weeks post-treatment

Sourced/collected by local study team	Direct patient report
• Treatment complications (up to 31 days post-procedure) • PSA level • Treatment information • Participant status including: o Treatment failure o Disease recurrence requiring repeat PA o Repeat PA treatment received	• Health-related quality of life o PORPUS (unmodified) o IPSS (unmodified) o EPIC (unmodified) o EQ-5D-5L (unmodified) o MAX-PC (modified 18 item)

3 months post-randomisation

Sourced/collected by local study team	Direct patient report
• Treatment complications • PSA level • Participant disease status including: o Treatment received o Treatment failure o Disease recurrence requiring repeat PA o Repeat PA treatment received	• Health-related quality of life o PORPUS (unmodified) o IPSS (unmodified) o EPIC (unmodified) o EQ-5D-5L (unmodified) o MAX-PC (modified 18 item) • Health care use questionnaire

6 months post-randomisation

Sourced/collected by local study team	Direct patient report

• Treatment complications
• PSA level
• Participant disease status including:
  o Treatment received
  o Treatment failure
  o Disease recurrence requiring repeat PA
  o Repeat PA treatment received
	• Health-related quality of life
	  o PORPUS (unmodified)
	  o IPSS (unmodified)
	  o EPIC (unmodified)
	  o EQ-5D-5L (unmodified)
	  o MAX-PC (modified 18 item)
	• Health care use questionnaire

9 months post-randomisation

Sourced/collected by local study team	Direct patient report

• Treatment complications
• PSA level
• Participant disease status including:
  o Treatment received
  o Treatment failure
  o Disease recurrence requiring repeat PA
  o Repeat PA treatment received
	N/A

12 months post-randomisation

Sourced/collected by local study team	Direct patient report

• Radiology (PA arm only)
• Biopsy (PA arm only)
• Treatment complications
• PSA level
• Participant disease status including:
  o Treatment received
  o Treatment failure
  o Disease recurrence requiring repeat PA
  o Repeat PA treatment received
	• Health-related quality of life
	  o PORPUS (unmodified)
	  o IPSS (unmodified)
	  o EPIC (unmodified)
	  o EQ-5D-5L (unmodified)
	  o MAX-PC (modified 18 item)
	• Health care use questionnaire

24 months post- randomisation (when timepoint met within current funding window of study)

Sourced/collected by local study team	Direct patient report

• Treatment complications
• PSA level
• Participant disease status including:
  o Treatment failure
  o Disease recurrence requiring repeat PA
  o Repeat PA treatment received
	• Health-related quality of life
	  o PORPUS (unmodified)
	  o IPSS (unmodified)
	  o EPIC (unmodified)
	  o EQ-5D-5L (unmodified)
	  o MAX-PC (modified 18 item)
	• Health care use questionnaire

36 months post-randomisation (when timepoint met within current funding window of study)

Sourced/collected by local study team	Direct patient report

• Radiology (PA arm only)
• Biopsy (PA arm only)
• Treatment complications
• PSA level
• Participant disease status including:
  o Treatment failure
  o Disease recurrence requiring repeat PA
  o Repeat PA treatment received
	• Health-related quality of life
	  o PORPUS (unmodified)
	  o IPSS (unmodified)
	  o EPIC (unmodified)
	  o EQ-5D-5L (unmodified)
	  o MAX-PC (modified 18 item)
	• Health care use questionnaire

Ad Hoc Data

Sourced/collected by local study team	Direct patient report
• Withdrawal • Death • SAEs	N/A

16.7 Qualitative assessments

Researchers at the University of Bristol will collect data for the QuinteT Recruitment Intervention as detailed in sections 10 and 21.6.

16.8 Withdrawal

Withdrawal of consent means that a participant has expressed a wish to withdraw from the study altogether, or from certain aspects of the study only. The type of withdrawal will be collected on the CRF labelled 'Withdrawal'.

Participants may also be withdrawn from the study (or aspects of the study) by their clinician if they believe the participant needs to be withdrawn.

The Withdrawal CRF should be completed to document the reasons for withdrawal, and state who made the decision to withdraw. Discussions and decisions regarding withdrawal should be documented in the participant's medical notes. Investigators should continue to follow-up any SAEs and should continue to report any SAEs to resolution in the CRF in accordance with the safety reporting section.

Where a participant expresses a wish to withdraw from the study, the study team will determine which aspect(s) of the study the participant wishes to withdraw from; all other aspects of the study/follow-up will be continued.

The aspects of the study that the participant may request to withdraw from are as follows:

- No longer willing to receive study intervention
- No longer willing to complete study questionnaires
    - This refers to the health-related quality of life questionnaires and health care use questionnaires sent directly to participants by the study office
- No longer willing to take part in qualitative aspects of study
    - This refers to the interview for the QuinteT Recruitment Intervention/ the "Information Study"
- No longer willing to provide study tissue samples
    - This refers to any follow-up biopsies
- No longer willing to have study MRIs
- No longer willing to attend study visits
- No longer willing to be contacted by the research team to obtain CRF/outcome data
- No longer willing to have standard of care data from the medical record provided to the study
- No longer willing for standard of care data from Health data providers e.g. NHS digital, to be provided to the study

Where a participant wishes to withdraw from all aspects of study participation detailed above, this will be recorded on the Withdrawal CRF as full withdrawal.

Completion of the Withdrawal CRF will trigger a notification to the Study Office. Appropriate action will be taken by the study teams (centrally at the study office and by the local research team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any relevant communications which the participant had consented to receive regarding their participation are no longer sent.

Data collected up to the point of withdrawal will be used in the study analysis.

16.9 Communication with study participants by the central study team

Participants will be notified to completed study questionnaires by e-mail, or where they have selected to receive postal questionnaires these will be posted to the participant. Participants will receive an initial e-mail and up to two reminder messages. Participants that do not complete their study questionnaires may be telephoned by a member of the central study team to collect outcome data.

17 SAMPLES FOR LABORATORY ANALYSIS

17.1 Overview of study-specific samples

Table 4 provides a summary of all samples required by this study protocol

Sample Type and test(s) to be undertaken	Time point (post-treatment)	Analysis by local Trust lab or other
Blood sample for PSA test for eligibility*	Screening/Baseline	PSA tests will be arranged by sites in accordance with usual care practice and analysed by as per usual NHS practice.
Blood sample for PSA test	6 weeks 3 months 6 months 9 months 12 months 24 months** 36 months**	PSA tests will be arranged by sites in accordance with usual care practice and analysed as per usual NHS practice.
Prostate biopsy (PA arm only)	12 months 36 months** Clinical concern	Analysed by local laboratory

*blood test for PSA will be performed to confirm eligibility if no PSA test has been taken in the previous 120 days.

**#24-month and 36-month follow-up of all 800 participants is subject to receipt of additional funding for longer-term follow-up, and may not be collected for all participants. Where the test is standard of care this will be performed as usual outside of the study.

The above samples will be taken and processed by laboratories in accordance with local site practice. This includes labelling of samples with standard patient identifiers. Results will be reported back in the usual way according to local practice and accessed by the site research team. Such samples will be stored, held, reported and subsequently destroyed in accordance with standard local laboratory practice. Where required, data will be recorded within the CRF.

18 SAFETY REPORTING

18.1 Safety reporting period

Safety reporting for each participant will begin from the date of commencement of the randomised allocated treatment and will end when the participant has reached their final main follow-up time point (Participants will be followed-up in the study for as long as the study remains open – for those recruited early in the study this may be for 5 years post-randomisation).

18.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Investigator

Significant medical events are medical events that may jeopardise the participant and may require an intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Seriousness vs severity

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

18.3 Reporting of Serious Adverse Events (SAEs) from sites to the central study team

Only serious adverse events considered by the site investigator to be related (possibly, probably or definitely) to any of the study procedures and in the opinion of the Principal Investigator are considered unexpected for the study procedure will be collected in the study. Such events must be reported within 24 hours to the central study team using the SAE form within the REDCap study database. Refer to section 18.6 regarding expectedness assessment.

Treatment complications listed in section 18.4 should not be reported on a SAE form unless the complication is (in the opinion of the site investigator) considered more severe in nature than might be expected, or unexpected, for the particular intervention received. For participants undergoing IRE or HIFU treatment, the user manual for the devices should also be referred to when making an assessment of expectedness.

18.4 Treatment complications

The following treatment-related complications will be collected on the 'Treatment Complications' case report form and should not be reported separately on a SAE form unless the complication is (in the opinion of the site investigator) considered **more severe in nature than might be expected, or unexpected, for the particular intervention** received by the participant:

Events occurring intraoperatively, during the immediate post-operative period, or in the first 31 days post-procedure:

- Thromboembolic disease (DVT/PE)
- Respiratory complications
- Myocardial infarction
- Cerebrovascular accident
- Urine leak post-procedure requiring intervention
- Significant blood loss requiring intervention with either >3 units blood transfusion or packing of the pelvis and/or other surgical/radiological intervention
- Rectal perforation
- Bowel injury

Events occurring at any time during follow-up period likely related to a study intervention:

- Development of a recto-urethral fistula
- Development of a urethro-cutaneous fistula

- Development of post-procedure urethral stricture disease requiring subsequent surgical intervention
- Development of osteomyelitis
- Ureteric injury

18.5 Disease Progression

The following are outcomes for the trial and will be recorded on the case report form and should not be reported separately on a SAE form:

- Disease progression
- Death due to disease progression
- Cancer recurrence

18.6 Assessment of SAEs by the Principal Investigator (or delegate)

The Principal Investigator (or delegated individual) is responsible for assessing all reported serious adverse events for reason for seriousness, causality and expectedness.

18.6.1 Relatedness/causality assessment

The assessment of "relatedness" to the study intervention is the responsibility of the PI at site, or an agreed designee.

All AEs judged as having a reasonable suspected causal relationship to the study intervention/procedure(s) are considered to be adverse reactions/responses. The assessment of relatedness is made using the following:

Relationship to intervention	**Attribution (Causality)**	**Description**
Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

18.6.2 Expectedness

The Principal Investigator (or delegated individual) is responsible for assessing all serious adverse events for reason for causality. Only serious adverse events considered by the site investigator to be related (possibly, probably or definitely) to any of the study procedures should be reported to the CI or nominated person (NP) in the CTU. Such events must be reported within 24 hours to the central study team using the SAE form within the REDCap study database.

Assessment of expectedness will be made by the CI or NP. An unexpected event is not expected for the study intervention and is not listed in the treatment complications below. If in doubt, the CI will raise queries with the treating medical practitioner.

Related SAEs, which are in the opinion of the nominated person are considered unexpected for the study procedure will be submitted to the REC within 15 days of the CI/CTU becoming aware of the event, using the HRA report of serious adverse event form.

All intervention/study procedure-related SAEs will be recorded and reported to the REC as part of the annual reports.

18.7 Assessment of SAEs by the Chief Investigator

The CI shall be informed immediately of any SAEs via an automatic database alerting both to the SAE report. The CI shall assess the information in conjunction with any treating medical practitioners and confirm causality and expectedness. If in doubt, the CI will raise queries with the treating medical practitioner.

All intervention/study procedure-related SAEs will be recorded and reported to the REC as part of the annual reports. Unexpected SAEs related to the intervention/study procedures will be reported within the timeframes to the REC as stated below.

18.8 Reporting of unexpected SAEs to the Research Ethics Committee (REC)

All SAEs that are considered by the reporting Investigator or the Nominated Person to be related (i.e. resulted from administration of any of the research procedures) and unexpected (that is, the type of event is not expected for the study intervention) will be submitted to the REC within 15 days of the CI becoming aware of the event, using the HRA report of serious adverse event form.

18.9 Follow-up of Serious Adverse Events

A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available. Follow-up information must also be provided as requested by the study office.

19 STATISTICAL CONSIDERATIONS

19.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here, with details fully described in a statistical analysis plan (SAP) that will be drafted early in the study and finalised prior to the final analysis data lock, or any planned interim comparative analyses. The SAP will be written by the Study Statistician in accordance with the current OCTRU SOPs. The SAP will be reviewed and will receive input from the Trial Steering Committee (TSC) and independent Data and Safety Monitoring Committee (DSMC).

19.2 Sample Size/Power calculations

We aim to recruit a total of 800 patients over 5 years from multiple NHS centres with the appropriate skill mix and expertise. Available data indicate that approximately 15% to 25% of men with intermediate-risk PCa undergoing RP or RRT will demonstrate treatment failure (i.e. clinical or biochemical relapse) within 5 years, with most failures occurring in the first 3 years. At our final analysis, when we should have approximately 3 years median follow-up, we estimate that about 10%

of men undergoing radical treatment will demonstrate treatment failure. It is hypothesised that radical treatment may be superior to PA in terms of oncological efficacy, but that radical treatment is considerably inferior to PA in terms of functional outcomes. The anticipated worse HRQoL with radical treatment compared with PA, in particular functional outcomes such as urinary continence, erectile function, and bowel toxicity, leads us to consider that radical treatment would need to achieve a 10% lower primary treatment failure rate (e.g. 10% compared to 20%) for it to remain the preferable option in clinical practice. This study is therefore a superiority trial, with treatment failure, and HRQoL and functional outcomes, hypothesised to be superior for PA versus radical treatment. Allowing for a 10% total dropout rate across the entire study, 800 patients randomised on a 1:1 basis to radical treatment or PA would provide approximately 88% power at $p<0.025$ to detect a ≥10% lower treatment failure rate (10% versus 20%, a hazard ratio of 0.4722 = log(0.9)/log(0.8)) with radical treatment compared to PA treatment. The statistical power would not be much affected if the failure rate in the radical treatment group was somewhat lower, or somewhat higher, than 15%. For example, 800 patients (with 10% dropout) would provide approximately 79% power at $p<0.025$ to detect a difference of 15% versus 25% in failure rates (hazard ratio 0.5649 = log(0.85)/log(0.75)) and over 95% power to detect a 5% versus 15% failure rate (hazard ratio 0.3156 = log(0.95)/log(0.85)). With 800 patients randomised (and 10% lost to follow-up in total across the study), numerous sample size calculations using various parameters indicate that there will be ample statistical power to detect any meaningful differences in HRQoL scores, e.g. over 90% power at $p<0.01$ to detect a small to moderate (0.3sd) effect size. Put in perspective, this is a considerably smaller effect size than the 0.5sd effect size described by Norman *et al* (37) as the minimally important difference for HRQoL differences.

19.3 Choice of primary outcome

A co-primary end-point, incorporating treatment failure and HRQoL, has been chosen as this best reflects the relative trade-offs between potential oncological efficacy and functional outcomes between the two different treatment approaches of radical whole gland therapy versus PA.

19.4 Description of Statistical Methods

The primary analysis will be performed according to the Intention-To-Treat principle. Treatment failure will be compared between radical treatment and PA treatment using survival analysis techniques. Statistical significance between treatment groups will be assessed using log rank methods, and Kaplan-Meier survival curves will be used for graphical representation. Patients without treatment failure will be censored at time of death or time of last follow-up. Additional supporting analyses will be undertaken using Cox proportional hazards regression models adjusting for stratification factors and time from randomisation to start of treatment. Patients without treatment failure will be censored at their last known treatment failure free time.

For PORPUS and the other disease-specific HRQoL outcomes, Mixed Models for Repeated Measures (MMRM) will be used to evaluate differences over time by treatment group. MMRM models will be adjusted for treatment, baseline score, stratification factors, visit and a treatment by visit interaction as fixed effect terms, with patient included as a random effect. Differences between treatment groups will be reported as mean difference with 95% confidence intervals. Absolute and percentage average changes in HRQoL outcomes from baseline assessment will be displayed graphically. HRQoL forms that are returned partially complete will be analysed according to the scoring instructions for each questionnaire. The MMRM analyses will minimise the impact of missing data so the use of multiple imputation or other methods for dealing with missing data is not planned. Survival analysis techniques, as described for the treatment failure primary outcome, will also be used to compare differences between radical treatment and PA treatment for time to disease progression (including metastases), time to disease-specific mortality, and time to all-cause mortality. Patients without

disease progression at time of analysis will be censored at time of death or time of last known alive date.

The primary analysis is planned in the final six-months of the seven-year study, at which point median follow-up (from randomisation) will be approximately 3 years. To allow for having two co-primary outcome measures, adjustment for multiplicity has been made using Bonferroni's adjustment and therefore a *p*-value of <0.025 will be considered statistically significant for each co-primary endpoint. 95% confidence intervals of comparative treatment effects will be reported.

19.5 Inclusion in analysis

All analyses will be on an intention-to-treat basis. This means that patients will be analysed as they are randomised irrespective of the treatment actually received. The intention-to-treat population will include all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomisation number.

19.6 Subgroup analysis

There are currently no proposed subgroup analyses planned.

19.7 Interim analyses and stopping rules

The main outcomes will be analysed as stated in the analysis plan once the study follow-up has been completed. No formal interim analyses of treatment effects are planned for any of the study outcomes.

As there are no formal comparative interim analyses included in the study, no stopping rules have been incorporated into the study design. An independent DSMC will review the accumulating data at regular intervals and may recommend pausing or stopping the study in the event of safety concerns, as specified in the DSMC Charter. The TSC will make any final decision to terminate the study if appropriate.

19.8 Internal pilot/Decision Points

An internal pilot phase to assess the feasibility of recruitment will be conducted. Stop-go criteria will be reviewed after 18 months of recruitment.

Stop-go criteria for the pilot phase are given in table 5 together with the definitions of how each will be measured.

Table 5: Stop-go criteria for internal pilot phase

Progression guidance	Number of participants recruited in 18 months
Continue with study – no action required	150+
Continue with study – action required: • Review recruitment strategies and modify/monitor closely • Report to TSC	100-149
Require review with potential to close study to recruitment	<100

The Trial Management Group (TMG) will closely monitor the progression criteria during the internal pilot, and together with the TSC and DSMC will perform a full review towards the end of the internal pilot. The TSC and funder would make the final decision to terminate the study.

The internal pilot phase will mirror the procedures and logistics undertaken in the main definitive study. It is intended that the study will progress seamlessly into the main phase, with internal pilot participants included in the final analysis.

19.9 Level of Statistical Significance

To allow for having two co-primary outcome measures, a *p*-value of <0.025 will be considered statistically significant. A *p*-value of less than 0.05 will be considered statistically significant for all secondary and tertiary endpoints. 95% confidence intervals will be reported for treatment effects.

19.10 Procedure for accounting for missing, unused and spurious data

The procedure for handling spurious or missing data will be described in the Statistical Analysis Plan, and the Data Monitoring and Sharing Plan. The study will attempt to collect data as completely as possible. It is recognised that in practice some patients may decline a study-related repeat prostate biopsy, particularly if their PSA and/or MRI imaging is stable. In that scenario, it will be recorded on the CRF that the patient declined a study repeat biopsy, and the patient will remain in the study and continue other aspects of clinical follow-up.

Missing data will be minimised by careful data management, information provided to participants and training of study staff. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by intervention arm. All data collected on the database will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

19.11 Procedures for reporting any deviation(s) from the original statistical analysis plan

Any changes or deviations to the original SAP will be described and justified in the protocol, update SAP, final statistical report and/or publications, as appropriate to the timing of the changes.

20 HEALTH ECONOMICS

The primary purpose of this health economic evaluation is to assess the health care resource utilisation, cost impact and cost-effectiveness in terms of cost per QALY of treating PCa patients using PA compared with radical treatment.

20.1 Data Collection

The base-case cost-effectiveness analysis will adopt an NHS perspective. Data on health care resource use related to the primary intervention, further interventions, side-effects and treatment of recurrence will be collected from all trial patients, including all relevant hospital and primary care consultations, diagnostic workup, inpatient stays, medications, devices and aids, use of emergency departments, tests and equipment and time away from usual activities, including employment. Protocol-driven costs will be omitted. Data on health care resource utilisation will be collected via self-reported health care use questionnaires completed by the patients. Patients will be asked to complete the health care use questionnaire at baseline and at month 3, month 6, month 12 post-randomisation and annually thereafter. These self-reported health care use questionnaires were designed and piloted during the PART Feasibility Study and adapted thereafter for this definitive trial. In addition, patients will be flagged with national registries (HES, national death registries) to capture resource usage and monitor long-term survival (subject to funding for access to these data).

Where possible we will value our items on health care use questionnaire using appropriate unit costs obtained from published sources, including the most recent version of NHS Reference Costs. We will estimate unit costs that are not available from secondary sources using a standardised approach used for Unit Costs of Health and Social Care. This approach has been undertaken during the PART Feasibility Study.

Primary endpoint data will be collected within the trial. NICE recommends the use of preference-based HRQoL measures for the purpose of determining QALYs for economic evaluation. The use of QALYs aims to capture the impact of disease progression and non-fatal events on HRQoL in addition to any impact on survival. The EQ-5D-5L will be used to measure patient HRQoL at baseline, 6 weeks post-treatment, 3 months, 6 months, 12 months post-randomisation and annually thereafter. The EQ-5D-5L instrument and health care use questionnaire will be administered by the centre research nurses at baseline during the patient's clinical visit, thereafter they will be administered by the trial co-ordinating centre using an online format, with paper format where required. Patient's 5-dimension (mobility, self-care, usual activities, pain/discomfort, anxiety and depression) EQ-5D-5L health state classification at each trial time point will be converted into a utility score on a 0 to 1 scale, where 0 is equivalent to dead, and 1 to perfect health. This conversion will be made using the algorithm for the UK value set recommended by NICE at the time of analysis. The utility scores will be combined with within-trial survival data and extrapolation analyses (see below) to estimate the QALYs required for the cost-utility analysis. The EQ-5D was chosen to obtain the base-case utility weights due to the availability of a UK based valuation set and to enable comparability with other UK based economic evaluations across all diseases. However, there are concerns about the sensitivity of EQ-5D in capturing the full impact of side-effects of prostate cancer treatment that are of importance to patients. Hence, the impact of replacing the EQ-5D results with those from the disease-specific PORPUS-U utility measure will be explored in sensitivity analyses.

20.2 Analysis of health care resource use, cost and HRQoL data

20.2.1 Missing data

The resource use and HRQoL data obtained through EQ-5D will be investigated to ascertain the extent of missing data and whether this is due to random missingness and/or censoring. If this amounts to more than 10% of the data collected missing at random, multiple imputation using standard methods will be undertaken (38,39). The focus of studying the health care resource use is to investigate how PA therapies in PCa patients affect the health care costs. The aim of the economic analysis is to estimate how the cost of the intervention minus the difference in health care cost between the intervention and standard treatment (RP or RRT or LDR-B) group of patients balances against the health care benefits. An in-depth analysis of the health care resource use and their costs will be conducted. Firstly, the impact of the PA therapies on PCa-specific health care resource use/costs (including side effects, recurrence and progression-related costs) will be evaluated over the duration of the study and compared with those arising from radical treatment. Secondly, a regression framework that relates health care costs to baseline characteristics (age and gender), disease stage, progression, side effects, other co-morbidities and treatment type will be developed. The objective of this analysis is to provide estimates of health care costs for different treatment types, side effects and disease stages to inform the extrapolation model (see below). In order to inform the extrapolation model a similar regression framework approach will be used for the EQ-5D tariff data at the different data collection time-points.

20.2.2 Within-trial cost-effectiveness analysis

The economic evaluation will compare the implementation of PA therapy with standard radical treatment for PCa patients. We plan to conduct a within-trial economic analysis, and if the trial demonstrates clinical effectiveness, "within-trial" results will be used to extrapolate beyond the trial endpoint and model the likely lifetime cost-effectiveness of PA. A "within-trial" cost-consequence analysis will be reported, describing all the important results relating to the health care resource use, costs and consequences (side-effects, disease progression and recurrences) of PA therapy compared with radical treatment for PCa patients. A subsequent "within-trial" cost-utility analysis will determine cost per QALY gained. Adjustment for any baseline differences in resource use or utilities will be undertaken if required. The use of QALYs aims to capture the impact of disease progression and non-fatal events on HRQoL in addition to any impact on survival. This is particularly pertinent to this trial to evaluate the trade-off between an improved HRQoL due to reduced side effects with the increased possibility of recurrence. Results will be expressed in terms of incremental cost-effectiveness ratios (ICERs). Sensitivity analysis will test the robustness of the results. This will explore uncertainties in the trial-based data itself, the methods employed to analyse the data and the generalisability of the results to other settings, to determine the impact of changes on results. Sensitivity analysis will also explore the impact on the ICER of using the PORPUS-U results in place of EQ-5D and the inclusion of societal costs.

20.2.3 Lifetime cost-effectiveness analysis

If trial results demonstrate clinical effectiveness, an extrapolation analysis beyond the 3 years median follow-up will be undertaken. The methods used will depend on the "within trial" data, and it will enable the long-term cost-effectiveness of PA versus radical treatment in terms of cost per QALY gained to be determined. This will be based on the individual patient data (using the results from the regression analysis outlined above) from the study and external data (where required). It will be carried out from an NHS and Personal Social Services perspective, to consider health care costs and longer-term social care costs and the impact on life expectancy and quality-adjusted life expectancy. The analysis will be run over the remaining patient lifetime.

21 DATA MANAGEMENT

The data management aspects of the study are summarised here, with details fully described in the study-specific Data Management Plan. See section Participant Confidentiality for information on management of personal data.

21.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. For this study, source data will include the following:

- Hospital records including biopsy and radiology reports (from which data will be summarised into the CRF)
- mpMRI images
- Patient-reported outcome measures that are submitted directly to the study office.

21.2 Location of source data

The location of source data in the study is listed with the tables within the section OBJECTIVES AND OUTCOME MEASURES.

21.3 Case report forms (CRFs)

The Investigator and study site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Source data to be recorded directly on the CRFs

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no prior written or electronic record of data).

21.4 Non-CRF data

mpMRI images will not be held in the CRF. Data from the radiology report will be transcribed onto the CRF.

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor and host institution to permit study-related monitoring, audits and inspections. The data submitted by study participants directly via the study database (i.e. electronic patient reported outcomes) will also be made available to the participating site.

21.5 Data Recording and Record Keeping

The case report forms will be designed by members of the study management team which will include the CI, study statisticians and study manager.

Data will, wherever possible, be collected in electronic format with direct entry onto the study database by site staff or participants. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent forms. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford. The data will be entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to members of the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis. Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the participants within the study patient information leaflet. The identifiable data will be kept separately from the outcome data obtained from/about the patients. Patients will be identified by a study ID only.

Where participants are referred to a different participating study site to receive their randomised treatment, a member of the research team at the site where the participant received treatment will complete a paper worksheet to collect the data required for entry onto the electronic CRF. This will be returned to the recruiting centre for entry onto the study database, via secure e-mail between NHS e-mail accounts.

Direct access to source data/documents will be required for study-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required.

The data management and sharing plan will list explicitly when sensitive personal information will be destroyed.

Data captured during phone calls to participants or from paper-based study questionnaires returned to the study office will be entered into the study database by suitably trained central office staff and original paper copies retained as source data. Full details will be recorded in the Data Management Plan. The participants will be identified by a unique study specific number in any data extract. Identifiable data will only be accessible by members of the study team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g. follow-up reminders for online form completion or telephone follow-up).

21.6 QRI data

Upon initial consent, participants will be given a unique identifying number (PART QRI ID). All data will be labelled by the reference number (with no personal information). This will be linked to personal information in a key breaker document which will be encrypted, password protected and stored securely on the University of Bristol servers.

Audio files, recorded using encrypted audio-recorders (supplied by the University of Bristol), will be transferred securely to and retained by the University of Bristol. To ensure safe and secure transfer of digital data, a Trust-approved secure encrypted electronic data transfer system will be used (data on the recording device will be deleted after successful transfer), or the qualitative researcher will use an encrypted device (memory stick, SD Card or encrypted audio-recorder) to transfer the audio recordings from the recruiting site to University of Bristol. Separate communication (via secure email) will confirm the password to the encrypted device. The encrypted device will be posted back to the qualitative researcher via secure delivery. All digital data will be stored securely on the University of Bristol servers, adhering to University of Bristol's data storage policies.

Transcription will be completed by the QRI research team in-house at University of Bristol. Transcripts will be de-identified so that participants cannot be recognised. Only members of the research team will have access to the audio recordings and transcripts. The transcripts and the audio recordings will be stored in separate locations on the University of Bristol servers. Although the transcripts can be fully de-identified, there may be aspects of the audio-recordings that contain personal/identifiable information (such as participants' voices in the recordings). Only authorised members of staff involved in the research will be able to access the data. We may use this data as part of publications, teaching and presentations at academic meetings. All quotes will be completely anonymised. If a section of audio is played (i.e. for training), voices will be modified voices and any personal information will be removed. Information about how the data are stored and used is provided in the information leaflet, and participants will confirm they understand that their data will be used in this manner.

At the end of the study, audio recordings will be pseudonymised by the University of Bristol and securely returned to University of Oxford and deleted from University of Bristol servers.

22 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The trial management group will be responsible for ensuring adherence to the study protocols at the study sites. Quality assurance (QA) checks will be undertaken by OCTRU to ensure integrity of randomisation, study entry procedures and data collection. The OCTRU has a QA team who will monitor this study by conducting audits (at least once in the lifetime of the study, more if deemed necessary) of the Trial Master File and compliance with requirements in OCTRU SOPs. The University of Bristol may also conduct audits for the QRI component of the study. The study will undergo a formal check of the documentation as part of OCTRU giving the green light to open the study. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the trials unit staff. Written reports will be produced for any oversight committees as applicable, informing them if any corrective action is required. Additionally, the study may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

A study-specific data management and sharing plan and monitoring plan will be in place prior to the start of the study.

22.1 Audit and regulatory inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this study must inform the Study Office without delay.

22.2 Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the study opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the study or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

22.3 Study monitoring

Regular monitoring will be performed by the University of Oxford study office according to a study-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report form data will be validated using appropriate

set criteria, range and verification checks. The study site must resolve all data queries in a timely manner (usually within 14 days unless otherwise specified). All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution.

Study sites will also be monitored remotely and/or by site visit, as necessary, to ensure their proper conduct of the study. Study Office staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Any monitoring reports/data discrepancies will be sent to the site in a timely fashion. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a minimum, or sooner if the monitoring report requests.

22.4 Study committees

22.4.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established for the study and operate in accordance with a study-specific TMG charter. The TMG will manage the trial, including the clinical and practical aspects and will meet approximately monthly during the recruitment phase of the study to assess progress. Other specialities/ individuals will be invited as required for specific items/issues.

22.4.2 Data and Safety Monitoring Committee (DSMC)

An independent Data & Safety Monitoring Committee (DSMC) will be established for this study made up of independent experts external to the study who will assess the progress, conduct and critical outcomes of the study. The DSMC will adopt a DAMOCLES based charter, which defines its terms of reference and operation in relation to the oversight of the study. The DSMC will meet regularly throughout the study at time-points agreed by the Chair of the Committee and the CI. At a minimum this will be on an annual basis. The DSMC will review study progress, accruing interim data and all safety aspects of the study and make recommendations as to whether any changes to the study should be undertaken, including stopping early for safety reasons. Full details of responsibilities are included in the DSMC Charter. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

22.4.3 Trial Steering Committee (TSC)

The TSC, which includes independent members, provides overall supervision of the study on behalf of the funder. The TSC will act in accordance with a TSC charter which will outline its roles and responsibilities. Full details including names will be included in the TSC charter. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the study towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the study

The TSC will consider, and act, as appropriate, upon the recommendations of the DSMC.

23 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

23.1 Identification of recruitment sites

Recruitment sites will be selected based on suitability to conduct the study. Potential sites will be invited to complete a site feasibility questionnaire (SFQ) which will be used by the Trial Management Group/Coordinating Centre to assess suitability of the site for the study; the suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

23.2 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study, but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete delegation log provided by the central study team prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

23.3 Study site set up and activation

The Principal Investigator leading the investigational study site is responsible for providing all required core documentation. Mandatory Site Training which is organised by the study office (usually carried out as a tele- or video- conference call or personal visit) must be completed before the site can be activated. Training in the study processes will be administered at site initiation visits delivered online by the Central Study team. The Study Office will check to confirm that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the study database and are able to begin recruiting patients.

23.4 Training

Training in the study processes will be administered at site initiation visits (delivered face to face or online) by the Central Study team.

23.5 Study documentation

The study office will provide an electronic Investigator File to each investigational site containing the documents needed to initiate and conduct the study. The study office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the study, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the study.

23.6 Arrangements for sites outside the UK

It is not anticipated that this study will open in non-UK sites.

24 ETHICAL AND REGULATORY CONSIDERATIONS

24.1 Declaration of Helsinki

The Investigator will ensure that the study is conducted in accordance with the principles of the Declaration of Helsinki.

24.2 Guidelines for Good Clinical Practice

The Investigator will ensure that the study is conducted in accordance with relevant regulations and with the principles of Good Clinical Practice.

24.3 Ethical conduct of the study and ethical approvals

The protocol, patient information sheet, informed consent form and any other information that will be presented to potential study participants (e.g. advertisements or information that supports or supplements the informed consent process) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC), HRA and host institution.

24.4 NHS Research Governance

Once HRA & HCRW approval is in place for the study, sites will confirm capability and capacity to participate in the study.

24.5 Protocol amendments

All amendments will be generated and managed according to the study office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study participants (see below).

It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the study. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

24.6 Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the protocol are not allowed. Changes to the approved protocol need prior approval unless for urgent safety reasons.

A study related deviation is a departure from the ethically approved study protocol or other study document or process or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Deviations from the protocol will be captured within the study database. Deviations will be handled and reviewed in a timely manner in accordance with a study-specific Data Management and Sharing Plan and a Monitoring Plan.

The investigator must promptly report any important deviation from Good Clinical Practice or protocol to the study office. Examples of important deviations are those that might impact on patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP (see serious breach 24.9 below).

24.7 Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect study participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The study may continue with the urgent safety measures in place. **The Investigator must inform the study office IMMEDIATELY if the study site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the study office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The Study office will follow written procedures to implement the changes accordingly.

24.8 Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the treatment of participants already in the study for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the study in a timely manner.

The study office will report the temporary halt via an expedited substantial amendment procedure. The study may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the study this will be reported as an early termination.

24.9 Serious Breaches

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation.

24.10 Study Reports

This protocol will comply with all current applicable Research Ethics Committee, Funder and Sponsor reporting requirements.

24.11 Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database (ISRCTN), which will be kept up to date during the study, and results will be uploaded to the registry within 12 months of the end of the study declaration. A Final Report will be submitted to the REC containing a lay summary of the study results which will be published on the HRA website.

The results of the study will be published and disseminated in accordance with the PUBLICATION AND DISSEMINATION section.

24.12 Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which will require data to be de-identified as soon as it is practical to do so. Personal data on all documents will be regarded as confidential. The processing of the personal data of participants will be minimised by making use of a unique participant study number on all study documents and any electronic databases). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participant's personal data. See section DATA MANAGEMENT for more details.

Study questionnaires sent directly to study participants will be sent via e-mail with a unique URL link to the participant's study questionnaire; this will be unique to the participant's record, visit and case report form.

Site staff at participating sites will ensure that contact details for study participants are up to date when participants attend for study visits.

The patient's name and NHS/CHI number (where available and consent has been given for this) will be collected once to allow flagging with NHS Digital.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally. Data Breaches will be highlighted to the relevant site staff and reported as required by the GDPR and Data Protection Act 2018. This will also be deemed a protocol deviation.

24.13 End of study

The end of study is the point at which all follow-up data has been collected and all queries resolved.

The sponsor and the CI reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

25 PUBLIC AND PATIENT INVOLVMENT (PPI)

The PART study team have established a good relationship with the Oxfordshire Prostate Cancer Support Group (OPCSG), who were actively involved for the duration of the PART feasibility study. OPCSG continue to support this definitive study. The PART study team will present the proposed research, as well as regular updates to OPCSG. The PART Study team has engaged with PPI to obtain feedback on all patient-facing materials before submitting for approvals to ensure they are appropriate. PART will have a PPI representative on the Trial Steering Committee (TSC), who will have ongoing input into the research. A member of OPCSG is a PPI co-applicant on the study grant and will also be a member of the TSC. The study have used the INVOLVE patient cost calculator to budget for involving and supporting PPI representatives for the duration of the study to cover any out of pocket expenses, training, and conference/meeting attendance to help with dissemination of results. Necessary costs for re imbursement of time, expenses and any other appropriate costs have been budgeted for to allow regular input, review of study information, and attendance at meetings. PPI members will be invited to attend any relevant PPI meetings to help promote public and patient

awareness of the study. In particular, there will be an important role for them to collaborate with the rest of the research team to help publicise the results of the main study. PART study participants will be informed of the findings via the study website and social media.

26 EXPENSES/PAYMENTS TO PARTICIPANTS

It is anticipated that over the duration of the conduct of the main PART study most patients allocated to receive one of the PA treatments will be able to receive this treatment at their centre, alongside all standard of care radical treatment options. However, in the Internal Pilot Phase of PART patients randomised to PA will likely receive that PA treatment in one of a few PART treatment centres offering that PA modality, in a cooperative approach, as expertise develops across the study network. If the allocated PA treatment is not available locally, the patient will be referred to an appropriate nearby centre delivering this therapy in a model of centre cooperation. In these cases where patients may have to be treated at an alternative study centre, patient travel expenses will be reimbursed (on production of receipts, or mileage allowance provided as appropriate).

27 SPONSORSHIP, FINANCE AND INSURANCE

27.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship.

27.2 Funding and support in kind

The table below provides detail of all funding and support in kind for the study.

Funder(s)	Financial and non-financial support given
National institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme	Provision of funding for study conduct
Angiodynamics	Angiodynamics is providing the following in-kind support: • Comprehensive training in performing irreversible electroporation using the Nanoknife including proctoring • Provision of Nanoknife generators to administer IRE for any site that is within the PART trial • Provision of Nanoknife Electrode consumables to apply IRE to cover the treatment of up to 400 men with PCa randomised to PA • Clinical support for all centres until the centre decides they are sufficient to run machine themselves
EDAP TMS	EDAP TMS is providing the following in-kind support: • Comprehensive training in performing HIFU using Focal ONE including proctoring

	• Provision of Focal ONE generators to administer HIFU for any site that is within the PART trial • Provision of Focal ONE consumables to apply HIFU to cover the treatment of up to 400 men with PCa randomised to PA • Clinical support for all centres until the centre decides they are sufficient to run machine themselves

27.3 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

28 CONTRACTUAL ARRANGEMENTS

Appropriate contractual arrangements will be put in place with all third parties.

This study is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the study as appropriate.

29 PUBLICATION AND DISSEMINATION

The sponsor will retain ownership of all data arising from the study.

Publication and dissemination of study results and associated study publications (e.g. the study protocol, statistical analysis plan (SAP), health economics analysis plan (HEAP) and secondary analyses) will be in accordance with the OCTRU Standard Operating Procedure and irrespective of study findings.

The study protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The study results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT) including any applicable extensions to this. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention.

29.1 Study results

All data will be presented such that no individual participants can be identified. Dissemination of results will include the following methods:

Conference: The results of this study will be disseminated to the clinical community via presentations at national and international meetings. Traditional conference dissemination will focus on presentations to include the key professional stakeholders. It is expected that findings from this study will be presented at national and international conferences.

Publications: Results will be published in peer-reviewed journals. Where possible, plain English summaries will be published alongside the full paper, along with links to other digital media on the study website to explain the study result in an accessible format – i.e. an explainer video and infographic.

- **Public Dissemination:** To ensure a broad campaign we will target a range of social media outlets (this may include an explainer video and infographic). We will seek to engage the NHS Dissemination centre and seek to publish 'digital story' as part of the 'NIHR Signal'.

All participants will be asked at the time of recruitment if they would like to receive a copy of the study results. This document will be written collaboratively with clinicians and patient representatives and distributed accordingly. Newsletters, Facebook, Twitter etc. will be used to ensure the results of PART are communicated to the wider community once they are available.

The wider public will be alerted via links with relevant organisations/charities, and the Research Media Offices. Engagement with the NIHR Dissemination Centre will also be sought, to ensure global awareness of study findings. Moreover, the University of Oxford and Oxford University Hospitals NHS Trust have professional communication officers. It is anticipated that together these individuals, and NIHR equivalents, we will agree upon effective communication strategies including co-ordinated press releases, interviews etc.

29.2 Authorship

Authorship of any publications arising from the study will be determined in accordance with the ICMJE guidelines and any contributors acknowledged accordingly.

All publications arising from this study must acknowledge the funder, OCTRU, the Surgical Intervention Trials Unit (SITU) and the Sponsor.

29.3 Use of social media

Social media (e.g. Twitter) may be utilised to promote the study, and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment ay a site etc). Also, it is anticipated that patient bodies may either create their own tweets or retweet regarding the study and its achievements.

30 DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTIAL PROPERTY (IP)

Ownership of IP generated by employees of the University of Oxford vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

31 ARCHIVING

During the study and after study closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical study and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed.

Retention and storage of laboratory records for clinical study samples must also follow these guidelines.

It is the University of Oxford's policy to store data for a minimum of 3 years following publication. Investigators may not archive or destroy study essential documents or samples without written instruction from the study office.

Study data and associated metadata will be retained electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the mandatory archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

31.1 CTU Trial Master File

All paper and electronic data including the Trial Master File and study database will be archived in accordance with the OCTRU standard operating procedures and retained for at least 3 years after completion of the study.

31.2 Investigator Site File and participant medical records.

Archiving and eventual destruction of the Investigator Site File (ISF) is the responsibility of the Principal Investigator/site. The medical files of study participants must be retained for at least 3 years and in accordance with the maximum period of time permitted by the participating site. As part of the close-out procedure for each participating site, the Study Office will notify each participating site when the ISF may be destroyed. No documents will be destroyed prior to this.

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33 VERSION HISTORY

Previous versions of this protocol and a summary of the changes made are provided in the table below:

Protocol version no.	Protocol date	Summary of key changes from previous version
V1.0	25Nov2022	N/A - 1st version of the protocol
V2.0	13Nov2023	- Lay Summary updated with current NICE guidelines & information. - Resource Use questionnaire removed from 6-week post-treatment timepoint. - Timing of PSA tests in inclusion/ exclusion criteria changed from "within the last 90 days" to "within the last 120 days". - Timing of MRI in inclusion / exclusion criteria now specified to be "within the previous 6 months". - mpMRI and Biopsy removed from 6-month follow-up timepoint for Partial Ablation randomised participants. - SAE Expectedness updated. - Section 19.2 (Sample Size/Power calculations) updated to clarify sample size and clarify that the PART study is a superiority trial. - Section 20 (Health Economics) updated. - SD card added as storage device option for QRI data.
V3.0	15 May 2024	- Clarification around Radiotherapy (RRT) and Brachytherapy (LDR-B) delivery; that they should follow local NHS Trust protocols, which do differ. The previous wording in the protocol was unclear and will now allow sites to follow their local standard-of-care for these treatment options. - Clarification around patient identification via MDT.

APPENDIX 1 – STUDY FLOW CHART