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IP14-FOCUS

Imperial Prostate 14 – FOcal therapy using Contrast-enhanced UltraSound

CLINICAL STUDY PROTOCOL
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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the IP14-FOCUS study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

AE	Adverse event
CEUS	Contrast-enhanced ultrasound
CRF	Case report form
CT	Computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events version 5.0
GG	Grade group
GP	General Practitioner
HES	Hospital Episode Statistics
HIFU	High-intensity focused ultrasound
HRA	Health Research Authority
IDEAL	Idea, Development, Exploration, Assessment and Long-term
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IP14-FOCUS	Imperial Prostate 14 – Focal therapy using Contrast-enhanced UltraSound
IRE	Irreversible electroporation
MCCL	Maximum cancer core length
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
NHSCR	National Health Service Care Register
NHS	National Health Service
ONS	Office for National Statistics
PET	Positron emission tomography
PI-RADS	Prostate Imaging Reporting and Data System
PIS	Participation information sheet
PPI	Patient and Public Involvement
PROM	Patient-reported outcome measure
PSA	Prostate-specific antigen
REC	Research Ethics Committee
RSI	Reference safety information
SAE	Serious adverse event
SmPC	Summary of product characteristics
TARGET	The Transatlantic Recommendations for Prostate Gland Evaluation with Magnetic Resonance Imaging After Focal Therapy

KEYWORDS

Contrast-enhanced ultrasound
Cryotherapy
High-intensity focused ultrasound
Irreversible electroporation
Prostate cancer
Focal therapy
Recurrent cancer

STUDY SUMMARY

Title	Imperial Prostate 14 – FOcal therapy using Contrast-enhanced UltraSound (IP14-FOCUS)
Aims	To evaluate the role of intra-operative contrast-enhanced ultrasound (CEUS) during focal therapy performed for localised prostate cancer
Primary objective	To estimate the proportion of patients with clinically-significant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively
Secondary objectives	To assess recruitment rate to the study and compliance to study interventions To estimate the proportion of patients with clinically-insignificant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively To assess how the use of intra-operative CEUS changes the delivery of focal therapy by urologists To assess the additional operative time needed to perform intra-operative CEUS and deliver further ablation To assess the learning curve of urologists to perform and interpret intra-operative CEUS To assess whether urologists can achieve high intervention fidelity for performing and interpreting intra-operative CEUS To assess the safety of using intra-operative CEUS with or without further ablation To assess the short-term functional effects of using intra-operative CEUS with or without further ablation To assess the diagnostic accuracy of MRI, interpreted using dedicated imaging-scoring systems, for detecting clinically-significant recurrent cancer after focal therapy
Design	Single-centre, single-arm prospective cohort development study (IDEAL phase 2a)
Sample size	Initially 59 patients, with potential to increase to 118 patients depending on initial recruitment rate assessed at 4 months
Eligibility criteria	Inclusion criteria: - Age 18 years or above (no upper limit) - Patients with localised prostate cancer defined as a T-stage of T1-T3a and PSA ≤20 ng/mL, either newly-diagnosed or on active surveillance - Patients suitable for and booked to undergo focal HIFU, cryotherapy, or IRE for localised prostate cancer, with or without use of androgen-deprivation therapy prior to focal

	therapy. 'Focal' here is defined as ablation delivered to a maximum of 75% of the prostate Exclusion criteria: - Unable to give consent - Patients undergoing surgery for symptoms of bladder outlet obstruction, for example transurethral resection of the prostate, at time of focal therapy - Any previous local therapy for prostate cancer, including radiotherapy (external-beam radiotherapy or brachytherapy), radical prostatectomy, and ablative treatments - Any surgery for benign prostatic obstruction within the previous 6 months - Any contraindication to receiving the sulphur hexafluoride ultrasound contrast agent including evolving or ongoing myocardial infarction, typical angina at rest, significant worsening of cardiac symptoms, recent coronary artery intervention, acute cardiac failure, class III/IV cardiac failure, severe cardiac arrhythmias, right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and adult respiratory distress syndrome - Unable to undergo MRI, including intravenous administration of gadolinium-based contrast
Main study procedures	Intra-operative: - CEUS performed before and after delivery of focal ablation - Further delivery of ablation after CEUS if deemed necessary by the treating urologist 12-months post-operatively: - Multiparametric MRI - Prostate biopsy
Primary objective outcome measures	Proportion of patients with clinically-significant prostate cancer within the treatment zone on biopsy at 12 months, defined as cancer that is grade group 2 or higher, in those patients having a biopsy
Secondary objective outcome measures	Recruitment rate: the percentage of approached patients who consent to participate per month Biopsy rate: the number of patients who agree and disagree to undergo prostate biopsy at 12 months, with reasons if disagreement Proportion of patients with clinically-insignificant prostate cancer within the treatment zone on biopsy at 12 months, defined as cancer that is grade group 1, in those patients having a biopsy Proportion determined by the treating urologist that the CEUS performed after focal therapy is negative, equivocal, or suspicious for residual tumour

	Proportion undergoing further ablation by the treating urologist after performing intra-operative CEUS The time in minutes required to set up and perform CEUS intra-operatively pre-focal therapy The time in minutes required to set up and perform CEUS intra-operatively post-focal therapy The time in minutes required to deliver further ablation, if performed Time required to perform intra-operative CEUS, measured on a per-urologist basis Agreement over CEUS image interpretation score between the treating urologist and an expert user, measured on a per-urologist basis Proportion of individual CEUS steps performed to completion, assessed by an expert user Proportion of individual CEUS steps performed to optimal quality, assessed by an expert user Proportion of CEUS images with suspicion score concordant with a score given by an expert user Proportion of patients experiencing adverse events Questionnaire scores pertaining to urinary, sexual, and bowel function and health-related quality-of-life, measured using validated questionnaires Concordance between MRI interpretation scores (index test) and targeted biopsies of the treatment zone (reference test) in detecting clinically-significant residual cancer, defined as grade group 2 cancer or higher (target condition), in those patients who undergo prostate biopsy
Duration	August 2025 to August 2028

1. INTRODUCTION

1.1 BACKGROUND

Treatment for localised prostate cancer

Prostate cancer is the most common male cancer, with over 50,000 men in the UK diagnosed every year [1]. This disease is increasingly prevalent, with annual incidence projected to more than double by 2040 [2]. Approximately 80% of newly-diagnosed patients will have localised disease that has not spread outside of the prostate [3]. For patients with localised disease an increasingly-popular treatment is focal therapy, using ablative modalities such as high-intensity focussed ultrasound (HIFU), cryotherapy, and irreversible electroporation (IRE). Ablation here is focused to the site of tumour and a safety margin, meaning that adequate tumour treatment is delivered whilst sparing damage to healthy prostatic tissue. Focal therapy has shown comparable medium-term outcomes to radical treatments but improved functional outcome subsequent to this tissue-sparing approach [4–6]. It is estimated that approximately half of patients with newly-diagnosed localised prostate cancer would be eligible for focal therapy and it is expected the numbers of patients undergoing focal therapy will continue to rise [7].

Recurrence after focal therapy

Given its non-extirpative nature, localised recurrences within the prostate after focal therapy is possible. This recurrent disease can be classified as either within the previous treatment zone or its margins (in-field recurrence) or outside of the previous treatment field (out-of-field recurrence). Previous UK data has demonstrated 18% of HIFU patients required a second treatment for localised recurrence [4].

A potential cause for in-field recurrence after focal therapy is the margin effect, whereby the focal treatment template applied does not completely include the tumour, leaving residual untreated tumour that then continues to grow. A second cause is inadequate tumour ablation due to sub-optimal energy delivery. This can be due to prostate swelling resulting in skip lesions or from tumour vascularity countering the ablative effect or from absorption of energy by extra-prostatic fat.

In keeping with oncological principles, focal therapy guidelines typically recommend 5-10mm treatment margins around the tumour as visualised on MRI [4,8–10]. However, there is evidence that MRI often underestimates tumour size, with 3 small radical prostatectomy studies concluding that such margins around MRI lesions would lead to incomplete tumour treatment in 7-26% of patients [11–14]. Although increasing the area of prostate treated could be a solution to these 2 causes of in-field recurrence, this increases the risk of damage to surrounding structures and is associated with inferior functional outcomes [15,16].

Some centres perform a contrast-enhanced MRI post-operatively up to 30 days after focal therapy to evaluate the treatment margins and identify any residual enhancing tissue that might represent under-treatment [17]. Whilst this early MRI does show areas of necrotic tissue and the treatment margins with good correlation to subsequent biopsy, this MRI rarely impacts immediate clinical management [18]. This is because even if there are concerns over under-treatment, further imaging and biopsy are typically required at 12 months to plan further treatment, once treatment-induced necrosis has fully resolved. Furthermore, the reactive prostate swelling seen in the early post-operative period can make delineation of the ablation zone and tumour difficult. Anecdotally, the number of centres that perform an early MRI post-focal

therapy is reducing over time. In addition, the recent TARGET consensus recommendations led by Imperial Prostate did not advocate performing this early MRI routinely [17]. These consensus recommendations instead advocated for performing the first MRI post-treatment at 12 months. Therefore, using early MRI is not considered an effective tool to reduce recurrence rates.

Intra-operative contrast-enhanced ultrasound

An alternative solution to early MRI to address both causes of recurrence is intra-operative monitoring of the treated area to ensure complete and adequate treatment. Standard grayscale transrectal ultrasonography of the prostate is a key component of focal therapy, for example in confirming anatomy or ensuring correct needle placement. However, real-time feedback on ablative effect is currently not possible here as the standard ultrasound probe employed is unable to derive temperature nor necrotic effect. Instead, the use of contrast-enhanced ultrasound (CEUS) intra-operatively could have benefit.

CEUS is a modern ultrasonographic technique that specifically evaluates organ perfusion. This involves intravenous administration of an agent containing gas microbubbles (1-1000μm), usually a perfluorocarbon, which increases the echogenicity of blood. Tumours, which usually demonstrate increased vascularity, can then be visualised as an area of enhancement using a dedicated transrectal ultrasound probe. In a trial of 272 patients being investigated for prostate cancer, a prospective trial found that CEUS had an area-under-the-curve of 0.80 for detecting any cancer on prostate biopsy and 0.90 for detecting cancer with >50% core involvement and/or grade group ≥2 [19]. This was in comparison to an area-under-the-curve of 0.74 and 0.83, respectively, for standard B-mode ultrasound.

A few studies have evaluated the use of CEUS specifically during or after focal therapy. The largest study by Bacchetta et al. is a retrospective series of 32 patients undergoing focal HIFU at 2 centres, performed using the Focal One device [20]. One patient had bi-focal treatment, increasing the units of analysis to 33. CEUS was performed after HIFU within the same treatment session using sulphur hexafluoride microbubbles (SonoVue). 13/33 (39%) of lesions required further treatment within the same session based on CEUS. After the further treatment, CEUS was repeated. The CEUS images were retrospectively reported by a radiologist using a 3-point scoring system to assess the appearance of the MRI-visible lesion: 0 (no enhancement), 1 (mild enhancement), and 2 (marked enhancement). 21 lesions (64%) were scored 0, 11 (33%) were scored 1, and 1 (3%) was scored 2.

van der Bos et al. performed a prospective 2-centre, phase I-II ablate-and-resect study in 16 patients scheduled to have radical prostatectomy, who first underwent IRE 4 weeks prior [21]. CEUS using SonoVue was performed 4 weeks post-IRE, alongside a multiparametric MRI, on the day of the radical prostatectomy. In 15 patients, CEUS provided a clear, homogenous non-perfused image of the ablation zone. In comparison of treatment zone volumes measured on CEUS versus histopathology, the CEUS volume was 1.57x greater. The Pearson correlation index was 0.80, indicating strong correlation.

In a similar study design, van Riel et al. conducted a prospective 2-centre phase I-II ablate-and-resect study in 12 patients scheduled to have radical prostatectomy, who first underwent transperineal focal laser ablation 4 weeks prior [22]. CEUS was performed before, during, immediately after, and 4 weeks after ablation just prior to

radical prostatectomy. All CEUS images showed a homogenous ellipsoid approximating the shape of the treatment zone, with the treatment zone clearly demarcated. Compared to histopathology, the treatment zone volume on CEUS was underestimated by 0.68. Pearson correlation index was 0.94, suggesting strong correlation. There was no cancer observed within the treatment zone in any patient.

Jung et al conducted a retrospective study of 50 patients with grade group 1 cancer undergoing IRE [23]. CEUS was performed within 24 hours of treatment and compared to a multiparametric MRI performed at 6 months. Thirteen patients showed recurrence on the 6-month MRI. Compared to the 6-month MRI as the reference test for detection of residual tumour, CEUS had sensitivity of 76%, specificity 81%, positive predictive value 73%, and negative predictive value 83%. No histological verification was performed.

In a prospective single-centre study, Apfelbeck et al included 11 patients with grade group 1-2 disease and 1 patient with biochemical recurrence after previous radiotherapy undergoing whole-gland or hemi-gland HIFU using the Focal One device [24]. CEUS using SonoVue was performed the day before HIFU, intra-operatively after HIFU, and 1 day after HIFU. In all patients, the region of interest post-treatment did not show any vascularisation on immediate post-operative CEUS nor the day-1 CEUS. The authors noted that the prostate capsule still enhanced, as did the anterior aspects of the prostate, particularly in larger prostates. Two patients required retreatment within the same treatment session because of persistent enhancement anteriorly, outside of the target region of interest. Histological verification of imaging findings was not performed.

From the same centre, Apfelbeck et al conducted a retrospective study of 8 patients with grade group 1-2 disease, treated with whole-gland or hemi-gland HIFU using the Focal One device, to assess CEUS when performed in post-operative follow-up [25]. CEUS, performed using SonoVue, was performed at 3,6, 9, and 12 months post-HIFU. At 3 months, CEUS showed no enhancement of the treatment zone, but did show some vascularisation of the anterior prostate and capsule. At 6 months, only the capsule and a small rim of enhancement in the anterior section of the treated lobe showed enhancement. At 9 and 12 months, there was no enhancement in the treatment zone. Three patients underwent biopsy at 12 months, which showed grade group 1 cancer in 1 patient.

1.2 RATIONALE FOR CURRENT STUDY

Intra-operative CEUS to assess the extent of tissue ablation during focal therapy is potentially advantageous in being able to detect incomplete ablation and residual tumour intra-operatively and therefore facilitate additional selected ablation whilst the patient remains under general anaesthetic during the same operative session. Although this could reduce the risk of developing in-field recurrence, previous studies that report using intra-operative CEUS in their treatment protocol are limited by: (i) being small cohorts reflective of early experiences with focal therapy; (ii) not focusing on or reporting the specific therapeutic impact of CEUS; and (iii) and have only used 1 treatment modality, HIFU [20,26,27]. Our study aims to build on this initial work in CEUS by robustly assessing the implementation and therapeutic value of CEUS within a prospective and contemporary setting incorporating different ablation energies.

1.3 MRI DIAGNOSTIC ACCURACY SUB-STUDY

Although early contrast-enhanced MRI after focal therapy is not deemed to have an important role, a routine multiparametric MRI is typically performed at 12 months post-operatively. This is in keeping with the recent TARGET consensus recommendations led by Imperial Prostate [17]. This serves both to monitor for any suspicious lesions within the treated area and to assess untreated areas.

The interpretation of the treatment zone on MRI after focal therapy is known to be challenging owing to the ablative effect leading to necrosis then fibrosis alongside other phenomena like loss of zonal anatomy and asymmetric gland shrinkage. Little guidance exists for interpretation of MRI after focal therapy, unlike, for example, the primary diagnostic setting where the PI-RADS image scoring system is routinely used to aid and standardised image interpretation [28]. There are few data on the diagnostic accuracy of MRI after focal therapy measured robustly against a histological reference standard, and existing reports are limited by small sample size, inadequate biopsy protocols, or use of unclear or inappropriate MRI interpretation systems [17]. Recently the TARGET consensus meeting convened 24 expert users from 7 European and North American countries spanning urology, radiology, and pathology. Over a 2-round consensus process, a new image interpretation system was produced for use after focal therapy. This prioritises the dynamic contrast-enhanced sequence as the major sequence and gives specific image interpretation criteria. In comparison, in the PI-RADS system, the dynamic contrast-enhanced sequence is deemed to be a minor sequence.

Alternative image interpretation systems have also been proposed, for example the Prostate Imaging after Focal Ablation (PI-FAB) system [29]. This was created without any formal consensus methodology and instead reflects the anecdotal experience of a single expert centre. Like TARGET, the dynamic contrast-enhanced sequence is prioritised.

Given their novelty, very limited data exist outlining the diagnostic accuracy of these systems [30]. Robust prospective validation of these systems against a histological reference standard will be important for establishing their value and consequently justifying their use in routine practice. As a nested sub-study, we therefore plan to assess the diagnostic accuracy of MRI performed 12 months after focal therapy, assessed using dedicated image-interpretation systems, against a prostate biopsy reference standard.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

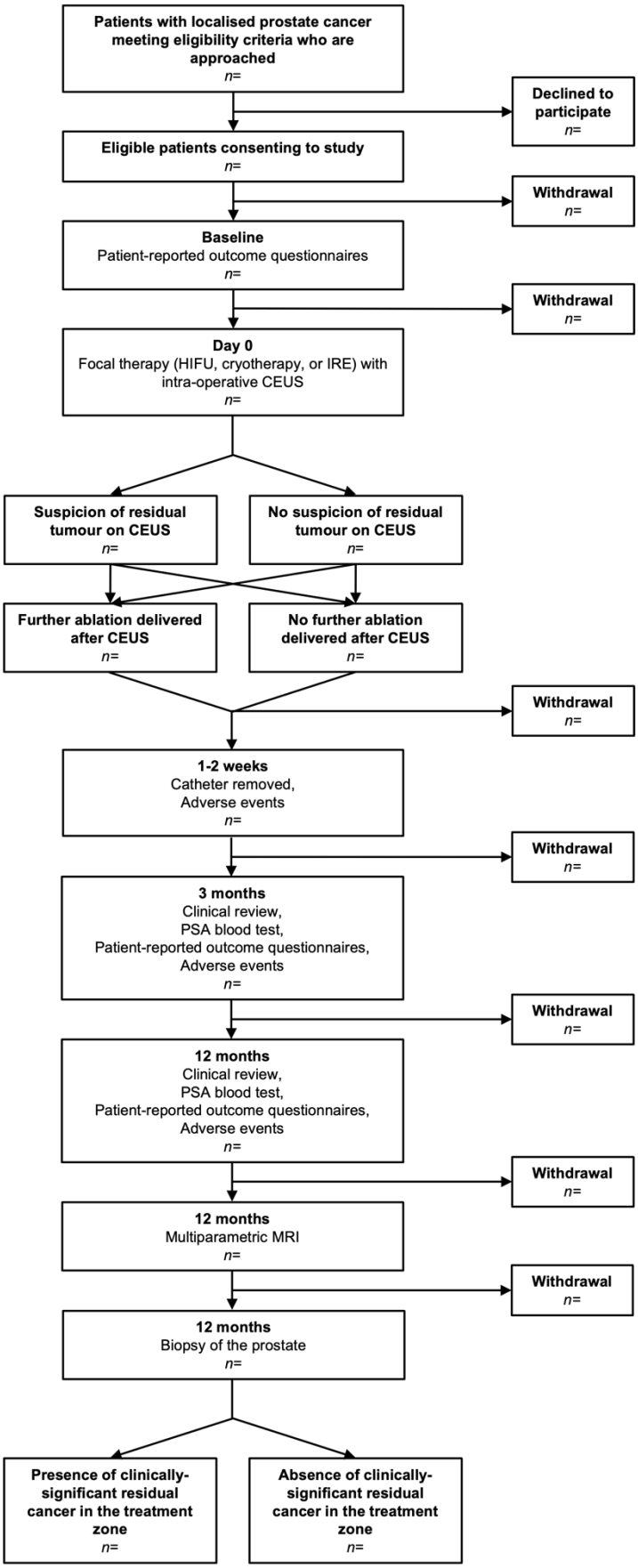
1. To estimate the proportion of patients with clinically-significant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively

2.2 SECONDARY OBJECTIVES

1. To assess recruitment rate to the study and compliance to study interventions
2. To estimate the proportion of patients with clinically-insignificant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively
3. To assess how the use of intra-operative CEUS changes the delivery of focal therapy by urologists
4. To assess the additional operative time needed to perform intra-operative CEUS and deliver further ablation
5. To assess the learning curve of urologists to perform and interpret intra-operative CEUS
6. To assess whether urologists can achieve high intervention fidelity for performing and interpreting intra-operative CEUS
7. To assess the safety of using intra-operative CEUS with or without further ablation
8. To assess the short-term functional effects of using intra-operative CEUS with or without further ablation
9. To assess the diagnostic accuracy of MRI, interpreted using dedicated imaging-scoring systems, for detecting clinically-significant recurrent cancer after focal therapy

3. TRIAL DESIGN

3.1 TRIAL OUTLINE



This will be a single-arm non-blinded prospective development cohort study investigating the use of intra-operative CEUS during focal therapy for localised prostate cancer. This represents an Idea, Development, Exploration, Assessment and Long-term (IDEAL) phase 2a study [31].

Patients with localised prostate cancer scheduled to undergo focal therapy and who otherwise meet the study's eligibility criteria will be identified from prostate cancer multidisciplinary team (MDT) meetings and outpatient clinic lists on a weekly basis, as well as patients already listed on the focal therapy operative waiting lists. After introduction and discussion of the study, provision of the participant information sheet (PIS), and then completion of the informed consent form, the patient will be entered into this trial.

At the start of the procedure, after the patient has been positioned, the urologist will perform CEUS to localise the lesion that requires treatment. Focal therapy will be conducted under general anaesthetic using either HIFU, cryotherapy, or IRE as decided pre-operatively by the treating urologist based on the patient's disease characteristics. At least 5 minutes after delivery of ablation to the tumour is complete, a second on-table CEUS will be performed by the treating urologist with the patient remaining under anaesthesia. If the treating urologist deems there to be residual tumour based on the CEUS images, further targeted ablation to the site of residual tumour will be permitted. After this point, the operation will finish. Once any further ablation has been performed, no further CEUS will be performed. There is no blinding in this study, either of patients, clinical staff, or study investigators.

Patients will proceed with standard care follow-up after focal therapy. They have their catheter removed at approximately 1-2 weeks post-operatively. They will then have their PSA value checked via blood tests at approximately 3 and then 12 months post-operatively. Given that a proportion of participants will have been referred to the study site from elsewhere in the country, to improve convenience the catheter removal and PSA blood tests can occur either at Charing Cross Hospital or a suitable site of the patient's choosing, for example their local GP. At 12 months, patients will also undergo routine multiparametric MRI followed by prostate biopsy, both including biopsies of the treatment zone and systematically from non-treated areas of the prostate in keeping with standard practice. Both the MRI and biopsy investigations will take place at Charing Cross Hospital. This will allow evaluation of how the use of intra-operative CEUS with or without delivery of further ablation corresponds with subsequent histological outcomes. If intra-operative CEUS is effective in identifying residual tumour and facilitating effective delivery of further ablation, this could lead to low rates of tumour recurrence within the treatment zone.

Adverse events will be recorded via patient interview at the following timepoints: intra- and immediately post-operatively (day 0), 1-2 weeks, 3 months, and 12 months. These will be graded per the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [32].

Patient-reported outcome measures (PROMs) and quality-of-life measures will be collected at baseline before focal therapy, then 3 months and 12 months after focal therapy. The validated questionnaires used will cover urinary function (Expanded Prostate Cancer Index Composite-26, International Prostate Symptom Score, and International Consultation on Incontinence-Urinary Incontinence Short Form questionnaires), sexual function (Expanded Prostate Cancer Index Composite-26,

International Index of Erectile Function), bowel function (Expanded Prostate Cancer Index Composite-26), and general health-related quality-of-life (EQ-5D-5L). These will determine what effect the use of intra-operative CEUS, with or without delivery of further ablation, has upon functional outcomes and quality-of-life. Questionnaires will be distributed to patients either in-person, via post, electronically via REDCap server or email, or over the telephone.

3.2 STUDY OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation
Primary Objective		
To estimate the proportion of patients with clinically-significant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively	Proportion of patients with clinically-significant prostate cancer within the treatment zone on biopsy at 12 months, defined as cancer that is grade group 2 or higher, in those patients who undergo prostate biopsy	12 months post-operatively
Secondary Objectives		
To assess recruitment to the study and compliance to study interventions	Recruitment rate: the percentage of approached patients who consent to participate per month Biopsy rate: the number of patients who agree and disagree to undergo prostate biopsy at 12 months, with reasons if disagreement	Recruitment rate: Baseline Biopsy rate: 12 months post-operatively
To estimate the proportion of patients with clinically-insignificant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively	Proportion of patients with clinically-insignificant prostate cancer within the treatment zone on biopsy at 12 months, defined as cancer that is grade group 1, in those patients having a biopsy	12 months post-operatively
To assess how the use of intra-operative CEUS changes the delivery of focal therapy by urologists	Proportion determined by the treating urologist that the CEUS performed after focal therapy is negative, equivocal, or suspicious for residual tumour Proportion undergoing further ablation by the treating urologist after performing intra-operative CEUS	Day 0 (intra-operatively)
To assess the additional operative time needed to perform intra-operative CEUS and deliver further ablation	The time in minutes required to set up and perform CEUS intra-operatively pre-focal therapy The time in minutes required to set up and perform CEUS intra-operatively post-focal therapy The time in minutes required to deliver further ablation, if performed	Day 0 (intra-operatively)
To assess the learning curve of urologists to perform and interpret intra-operative CEUS	Temporal changes in time required to set up and perform intra-operative CEUS, measured on a per-urologist basis Agreement over CEUS image interpretation score between the treating	Day 0 (intra-operatively)

	urologist and an expert user, measured on a per-urologist basis	
To assess whether urologists can achieve high intervention fidelity for performing and interpreting intra-operative CEUS	Proportion of individual CEUS steps performed to completion, assessed by an expert user Proportion of individual CEUS steps performed to optimal quality, assessed by an expert user Proportion of CEUS images with suspicion score concordant with a score given by an expert user	Day 0 (intra-operatively)
To assess the safety of using intra-operative CEUS with or without further ablation	Proportion of patients experiencing adverse events	Measured on day 0, then 1-2 weeks, 3 months, and 12 months post-operatively
To assess the short-term functional effects of using intra-operative CEUS with or without further ablation	Questionnaire scores pertaining to urinary, sexual, and bowel function and health-related quality-of-life, measured using validated questionnaires	Measured at baseline, then 3 months and 12 months post-operatively
To assess the diagnostic accuracy of MRI, interpreted using dedicated imaging-scoring systems, for detecting clinically-significant recurrent cancer after focal therapy	Concordance between MRI interpretation scores (index test) and targeted biopsies of the treatment zone (reference test) in detecting clinically-significant residual cancer, defined as grade group 2 cancer or higher (target condition), in those patients who undergo prostate biopsy	12 months post-operatively

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

As part of the standard care prostate cancer diagnostic pathway, all patients will have undergone a number of tests including but limited to: prostate-specific antigen (PSA), digital rectal examination, prostate MRI, and prostate biopsy. Some patients, typically those with high-risk disease classification, may have also undergone whole-body imaging including CT scan, bone scan, and PET/CT.

As part of the standard care workup for patients due to undergo focal therapy, patients will undergo further tests including but not limited to: blood tests (including C-reactive protein, full blood count, creatinine & electrolytes, coagulation screen, group & save), urine culture, MRSA swabs. Patients will also receive a pre-operative assessment of fitness for anaesthesia.

In addition to the above standard care tests, this trial does not require any additional tests at the screening stage, or prior to focal therapy.

4.2 INCLUSION CRITERIA

- Age 18 years or above (no upper limit)
- Patients with localised prostate cancer defined as a T-stage of T1-T3a and PSA ≤20 ng/mL, either newly-diagnosed or on active surveillance
- Patients suitable for and booked to undergo focal HIFU, cryotherapy, or IRE for localised prostate cancer, with or without use of androgen-deprivation therapy prior to focal therapy. 'Focal' here is defined as ablation delivered to a maximum of 75% of the prostate

4.3 EXCLUSION CRITERIA

- Unable to give consent
- Patients undergoing surgery for symptoms of bladder outlet obstruction, for example transurethral resection of the prostate, at time of focal therapy
- Any previous local therapy for prostate cancer, including radiotherapy (external-beam radiotherapy or brachytherapy), radical prostatectomy, and ablative treatments
- Any surgery for benign prostatic obstruction within the previous 6 months
  Any contraindication to receiving the sulphur hexafluoride ultrasound contrast agent including evolving or ongoing myocardial infarction, typical angina at rest, significant worsening of cardiac symptoms, recent coronary artery intervention, acute cardiac failure, class III/IV cardiac failure, severe cardiac arrhythmias, right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and adult respiratory distress syndrome
- Unable to undergo MRI, including intravenous administration of gadolinium-based contrast

4.4 WITHDRAWAL CRITERIA

Patients can decide to opt out of this trial at any time. This is within their right to do so and this will not affect the quality of any subsequent care they receive. This will be made clear in the patient information leaflet. These cases will be reported to the

research team so no further data are entered into the trial database. Data captured prior to the point of withdrawing will still be used in the study, but no further data will be collected or used. The reason for withdrawal will be recorded in the trial database and recorded in the patient's medical record.

Specific reasons for patient withdrawal before the study end could include:

- Intra-operative CEUS not performed
- Receipt of further cancer treatment to the prostate, for example repeat focal therapy, radical prostatectomy, or radiotherapy
- Adverse event / serious adverse event
- If the investigator considers that a patient's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

Participants who receive further systemic cancer treatment, or who receive surgical treatment of benign prostatic hyperplasia (for example transurethral resection), will not be excluded.

5. ENROLMENT PROCEDURE

5.1 REGISTRATION PRACTICALITIES

Patients who have already been offered and chosen to undergo focal therapy will be approached for the study. These patients will be identified from prostate cancer MDT lists, outpatient clinic lists, and the focal therapy surgical waiting list by members of the patient's clinical team. These patients will be contacted by a member of the clinical team to introduce the study and provide the PIS. This will be via telephone or in-person during a prostate cancer outpatient clinic. It is anticipated that most occasions where the study is introduced will be during an outpatient clinic appointment to discuss focal therapy as a treatment option. A copy of the PIS will also be sent to them via email or post, or given to them in-person. An additional discussion with a member of the trial team will then be arranged either straightaway or at a later time to discuss participation in the trial in further detail, if required. There will be occasions where individuals are members of both the clinical and trial teams simultaneously.

If willing to participate after discussion with the clinical team, trial team and reading of the PIS, the patient can then sign the informed consent form electronically via a dedicated trial REDCap server or in-person. No minimum time between provision of the PIS and signing of the informed consent form is stipulated. However, if the patient would like additional time to consider the trial and/or discuss participation with people close to them, this will be encouraged. The patient will then be re-contacted at a later time by the trial team prior to their focal therapy date to discuss their participation further.

We are expecting to only include patients that are able to independently understand the information from the PIS. Routine use of an independent medical language interpreter would be acceptable. The interpreter will go through the PIS and consent form sentence by sentence with the patient as well as with the research team member present to answer any questions. We will ensure that, if an interpreter is required, this is arranged prior to the consent/screening. The screening/consent will then occur, after the patient has reviewed the PIS, with the independent interpreter again with a full discussion about the study with the research team member. If the patient still wishes to participate then consent will be taken.

As part of this study, patients will have their CEUS images recorded as video files. At the time of consent, patients will also be asked if they consent for their CEUS video files to be stored within a secure data repository recommended by the Sponsor to be shared and used in future research, either academic or commercial.

A pre-screening log will collect the number of eligible patients who were given the PIS and will provide information regarding the number of drop-outs/withdrawals, the reasons behind why the patients decided not to enrol onto the study, and the proportion of patients accepting entry into the study.

A screening log will be kept to collect and track details of all the patients with completed informed consent and any reasons for screen failures and patient withdrawals.

Patients will also be asked to give optional consent for identifiable data to be linked with national databases (for example, ONS and HES databases). The identifiable fields (NHS number) required for linkage will be encrypted using a one-way encryption algorithm. We will ask patients if they are happy to give consent for their health status

to be followed up over time. This will be done by linking the patient's name and NHS number with records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register, or any applicable NHS information system. Pending receipt of further funding from academic or charity partners, and approval of a study amendment from the HRA to extend the study's end date, this will allow us to track what happens after the study finishes and observe if anyone gets further investigations and treatments.

We will also ask patients whether or not they give permission to be contacted by a member of the central / local study research team within 10 years of signing their consent form, after the study has ended to assess their willingness to complete a questionnaire about their health status (including details of any other tests and treatment they have had since the study) and quality of life. Pending receipt of further funding from academic or charity partners, and approval of a study amendment from the HRA, if the patient decides to take part a member of the study research will check the hospital/GP records to ensure patient status before sending this request to the patient's home address or via email.

6. PROCEDURES

6.1 FOCAL THERAPY

HIFU, cryotherapy, and IRE will be used in this study. At the study centre they are offered as part of the 'à la carte' treatment strategy, wherein the choice of treatment modality is decided primarily by an individual's prostate and tumour anatomy in order to ensure that tumour is best treated. Until the point of performing CEUS, it is expected that focal therapy will be performed exactly as per standard clinical practice. All surgeons who perform focal therapy at the study site are eligible to take part in this study.

6.2 CONTRAST-ENHANCED ULTRASOUND

Contrast agent

The intravenous contrast agent to be used in this study is sulphur hexafluoride microbubbles (SonoVue; Bracco, Italy). This is supplied at 8 microlitres/mL powder and solvent for dispersion for injection. On reconstitution as directed, 1mL of the resulting dispersion will containing 8 microlitres of sulphur hexafluoride microbubbles. A 2.4mL bolus will be administered via a peripheral intravenous cannula followed by a 10mL saline flush. This is the recommended dose for vascular imaging as listed in the SmPC [33].

The sulphur hexafluoride microbubbles increase the echogeneicity of blood, which is then visualisable with an ultrasound probe. This leads to marked increase in the signal intensity of 3-8 minutes for Doppler imaging of the microvasculature. Per the SmPC, a second bolus of the same dose can be given shortly after the first if required [33].

Use of CEUS in the operating theatre

In the operating theatre, with the patient under anaesthesia and appropriately positioned, the treating urologist will first perform CEUS to familiarise themselves with the appearance of the prostate and position of the tumour and proposed treatment area. Next, the urologist will perform focal therapy with HIFU, cryotherapy, or IRE, per standard care. Once concluded, the urologist will then perform CEUS again.

CEUS will be performed using a transrectal Hitachi CC41R Endocavity Bi-Plane probe and Fujifilm Arietta 750 device and Medcom BiopSee system. For CEUS performed after focal therapy, the treating urologist will need to wait at least 5 minutes after the end of ablation and always until the hyperechoic (Uchida) changes have subsided (after HIFU and IRE), the ice ball has melted (after cryotherapy).

CEUS performed both pre- and post-treatment will be performed with the same technique. The prostate will first be scanned slowly along its anatomical axis in B-mode. The area of prostate that contained the tumour and was treated will then be brought into view on the axial plane. The intravenous contrast is then injected. The treating urologist will keep the same view until the prostate is fully perfused with contrast and at least 45 seconds after injection has passed. The rest of the prostate will then be examined using the bubble-burst feature.

If the treating urologist deems there to be residual tumour present on the CEUS images, they will be permitted to deliver further ablation selectively to the site of the residual tumour identified on CEUS.

All ultrasonography performed as described in this section will be recorded as a continuous video recording.

Ultrasonography images will be interpreted by the treating urologist intra-operatively. They will also be reported at a later timepoint by an external expert user through review of the video recordings obtained intra-operatively. All videos will be given a score from a 3-point scoring system developed previously for visual interpretation of the treatment zone contrast-enhanced transrectal ultrasonography after HIFU [34]:

- Score 1/3: no enhancement
- Score 2/3: mild and/or patchy enhancement, but no marked enhancement
- Score 3/3: marked enhancement

It is expected that patients with images graded as score 3/3, and a proportion of patients with score 2/3, will require delivery of further ablation intra-operatively owing to sufficient suspicion of residual tumour. However, the decision to deliver further ablation will be made ultimately by the operating surgeon.

Surgeon training

Training will be provided for performing intra-operative CEUS by an external expert user of this technique prior to the trial starting. This will include both undertaking the procedural steps of this technique, detailed below, and interpretation of the images using the aforementioned 3-point scale. These procedural steps will also form the basis of assessing the learning curve for this procedure, forming a secondary objective of this trial.

Training will be provided in the form of an online seminar and will involve case examples. These examples and others will be provided separately to urologists in this trial to act as a reference guide. It is anticipated that urologists in this study will already have good procedural technique for performing CEUS, given that transrectal ultrasound of the prostate is a core urological procedure and its use forms a core component throughout focal HIFU, cryotherapy, and IRE. Furthermore, the surgeons involved in this trial have prior experience with using transrectal ultrasonography through previous trials in prostate cancer diagnostics at our centre [35,36].

Step	Completion (complete, incomplete, not performed)	Quality (optimal, adequate, inefficient, poor)	Comments
Pre-focal therapy CEUS			
B-mode: recording of axial plane images			
B-mode: recording of sagittal plane images			
CEUS: recording of axial plane images focused on treatment zone			
CEUS: recording of bubble burst images focused on remaining prostate			
Post-focal therapy CEUS			
B-mode: recording of axial plane images			
B-mode: recording of sagittal plane images			
CEUS: recording of axial plane images focused on treatment zone			
CEUS: recording of bubble burst images focused on remaining prostate			

6.3 MULTIPARAMETRIC MRI

At approximately 12 months after focal therapy, a routine multiparametric MRI at Imperial College Healthcare NHS Trust. Using a 1.5 or 3.0 Tesla scanner. This will be performed to assess for residual cancer within the treatment zone and well as to assess for the presence of cancer within the non-treated area of the prostate. The MRI sequences used will include T2-weighted, diffusion-weighted (both apparent diffusion coefficient and high b value), and dynamic Gadolinium contrast-enhanced sequences. This MRI will be conducted in accordance with PI-RADS v2.1 specifications [28].

An experienced prostate radiologist will evaluate the MRI once complete. They will not be blinded from any clinical, biochemical, histological, or radiological information related to the given patient. The appearance of the treatment zone will be assessed and given a suspicion score using image-interpretation scoring systems, which will include the TARGET and PI-FAB systems, in addition to any other notable scoring system that emerges during the conduct of the trial [17,29]. The appearance of the non-treated prostate will be assessed and given scores out of 5 using the PI-RADS v2.1 scoring system and a 5-point Likert scoring system in line with current practice [28]. Scores of 4-5 in 5-point scoring systems, or 3 in a 3-point system, will indicate that there is suspicion of cancer in that domain. A score of 3 in 5-point scoring systems, or 2 in a 3-point system, will indicate equivocality. Scores of 1-2 in a 5-point system, or 1 in 3-point system, indicate low suspicion. For the purpose of this study, a score of 4-5 (for 5-point scoring systems) or 3 (for 3-point scoring systems) will be used to denote a ‘positive’ MRI. These thresholds will be used to produce 2x2 contingency tables to derive diagnostic test performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value).

6.4 PROSTATE BIOPSY

After multiparametric MRI has been performed, patients will undergo a dedicated transperineal prostate biopsy of the treatment zone per standard of care. This will span the extent of the treatment zone and will also concentrate on any lesions inside the treatment zone identified on the 12-month multiparametric MRI. Biopsy operators will not be blinded to any patient information.

Systematic (random) biopsies of non-treated prostate will also routinely be taken in keeping with standard of care practice. If the 12-month multiparametric MRI has identified any new lesions outside of the treatment zone then these will also be sampled as additional targeted cores during this biopsy in addition to systematic biopsy cores, as would occur in standard clinical practice.

Biopsies will take place under local anaesthetic. If patients cannot tolerate this, or express a preference for sedation or general anaesthetic procedure, this will be arranged.

6.5 OTHER PROCEDURES

Patients in this trial will be permitted to receive other treatments in keeping with standard care, for example neoadjuvant or adjuvant androgen-deprivation therapy, although receipt of these is not anticipated.

7. ADVERSE EVENTS

7.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject

AEs will be classified as mild, moderate or severe:

- Mild: awareness of event but easily tolerated
- Moderate: discomfort enough to cause some interference with usual activity
- Severe: inability to carry out usual activity

The CTCAE v5.0 is a system for grading the adverse events associated with medical procedures and gives specific examples organ and system-based adverse events [32]. This will also be used to grade AEs:

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care activities of daily living
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death

CTCAE v5.0 grade 3-5 events will be deemed as severe adverse events.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that at any dose:

- Results in death.
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

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

Below is a list of expected adverse events that may require hospitalisation and serious adverse events that will not require reporting as SAEs but will be collected:

- Urinary retention and any hospitalisation required for this
- Urinary tract infection and any hospitalisation required for this
- Epididymo-orchitis and any hospitalisation required for this
- Dysuria
- Debris in urine and any hospitalisation required for this
- Haematuria and any hospitalisation required for this

- Erectile dysfunction and any other sexual sequelae side-effects including dry orgasm, lack of orgasm, and poor libido
- Urinary incontinence
- Rectal discomfort, bleeding, diarrhoea
- Recto-urethral fistula and any operations required for this
- Lethargy, tiredness, poor appetite
- Urethral stricture and any operations required for this
- Transurethral resection of the prostate and any operations required for this
- Operations required for treatment of symptoms of bladder outlet obstruction
- SonoVue-, Gadolinium-, or buscopan-related allergic reactions of any severity
- Claustrophobia leading to abandoning of MRI scan
- Vasovagal fainting episode before, during, or after MRI scan or biopsy

7.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

Non serious AEs

All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to prostate cancer, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the North West - Haydock Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-Investigational Medicinal Product studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs: RGIT@imperial.ac.uk

Please send SAE forms to:
Chief Investigator: Mr Taimur Shah
Email: focus@imperial.ac.uk
Telephone: 02075895111 (Monday to Friday 09:00-17:00)

8. ASSESSMENT AND FOLLOW-UP

8.1 SCHEDULE OF EVENTS

At the point of trial screening, patients will already have been diagnosed with prostate cancer and chosen to undergo focal therapy following MDT discussion. Therefore, patients will already have baseline data for their PSA value, stage, tumour grade, and tumour length. Aside from collection of PROMs (questionnaires), this trial will not require patients to undergo any further specific tests at baseline.

At baseline, potential participants will be reviewed by the research team to ensure they meet the eligibility criteria. Informed consent will be taken. They will be asked to complete their PROMs.

Patients will next attend on the day of their focal therapy procedure to undergo focal therapy with intra-operative CEUS.

Per routine clinical practice, the patient will then have their catheter removed as an outpatient approximately 1-2 weeks after focal therapy ('catheter removal'). They will then have PSA blood tests and outpatient reviews by the clinical team ('medical history') at 3 and 12 months. Also per routine clinical practice, patients will undergo a multiparametric MRI then prostate biopsy at approximately 12 months to evaluate for any recurrent disease.

For this trial specifically, patients will be asked to complete PROMs ('questionnaires'). at baseline, 3 months, and 12 months. Data on adverse events will also be collected on day 0 (intra- and immediately post-operatively), 1-2 weeks, 3 months, and 12 months.

Following from the 12-month timepoint after biopsy, patients will resume follow-up per routine clinical practice. This usually involves ongoing regular PSA tests and outpatient clinical reviews every 6-12 months. Any change to routine management on the basis of the 12-month MRI or biopsy will be made as per standard clinical practice.

All timepoints post-operatively are intended to be approximate. Due to scheduling logistics, it is expected that the actual date of post-operative activities will take place within a 6 week window before or after each timepoint.

	Visit					
Activity	**Screening**	**Baseline**	**Day 0**	**1-2 weeks**	**3 months**	**12 months**
Inclusion & exclusion criteria	X	X				
Medical history		X			X	X
Informed consent		X				
Intra-operative CEUS			X			
Focal therapy			X			
Second intra-operative CEUS			X			
Further focal therapy if needed			X			
Catheter removal				X		
PSA blood test					X	X
Multiparametric MRI						X
Prostate biopsy						X
Questionnaires		X			X	X
Adverse events			X	X	X	X

8.2 INCIDENTAL FINDINGS

Any incidental findings should be identified at the study visits and reviewed by the site teams and if necessary will be reported to the clinical care team and subject's GP.

8.3 LOSS TO FOLLOW-UP

If patients are lost to follow-up, they will be contacted via their supplied telephone number and address. If patients remain uncontactable, they will be deemed to have been lost to follow-up and their clinical team and GP informed.

8.4 TRIAL CLOSURE

The trial will end once the final visit, that is the 12-month prostate biopsy, has occurred for all patients, with the number of patients recruited as per the target sample size.

9. STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

The primary outcome is the detection of clinically-significant prostate cancer on targeted biopsy of the treatment zone at 12 months, defined as cancer that is grade group 2 or higher. Our hypothesis is that the use of intra-operative CEUS, and subsequent delivery of further ablation if there is a suspicion of residual tumour, will lead to a low proportion of patients with clinically-significant prostate cancer diagnosed on biopsy at 12 months post-operatively. Although this is a single-arm study with no comparison to standard practice included, we hypothesise this proportion would be lower than what would be expected if intra-operative CEUS were not used.

To determine an expected proportion of clinically-significant prostate cancer, the reference lists of 2 recent focal therapy systematic reviews were reviewed to identify focal HIFU, cryotherapy, and IRE studies published within the last decade where all patients were mandated to have a targeted biopsy of the treatment zone at 6-12 months [17,37]. Only studies that reported data on at least 50 biopsied patients were included.

Study	Modality	*n*	Biopsy timepoint	Clinically-significant cancer definition	In-field clinically-significant cancer detected	Biopsy refusal
Chuang et al. 2020 [38]	Cryo	61	6m	GG ≥2	11/61 (18.0%)	0/61 (0.0%)
Wysock et al. 2021 [39]	Cryo	83	6m	GG ≥2	1/70 (1.4%)	13/83 (15.7%)
Fernandez-Pascual et al. 2022 [40]	Cryo	75	>6m	GG ≥2	10/50 (20.0%)	25/83 (33.3%)
Baskin et al. 2022 [41]	Cryo	95	12m	GG ≥2	7/75 (9.3%)	20/95 (21.1%)
Aker et al. 2023 [42]	Cryo	143	6m	GG ≥2	32/136 (23.5%)	7/143 (4.9%)
Abreu et al. 2020 [43]	HIFU	100	6-12m	GG ≥2	8/58 (13.8%)	42/100 (42.0%)
Annoot et al. 2019 [44]	HIFU	55	12m	GG ≥2 or MCCL ≥6mm or ≥3 positive sextants	12/55 (21.8%)	0/55 (0.0%)
Rischmann et al. 2017 [45]	HIFU	101	6-12m	GG ≥2 or MCCL ≥4mm or ≥3 positive cores	5/101 (5.0%)	0/101 (0.0%)
Ahmed et al. 2015 [46]	HIFU	56	6m	GG ≥2 or MCCL ≥4mm	8/52 (15.4%)	4/56 (7.1%)
Bass et al. 2019 [47]	HIFU	150	12m	GG ≥2	19/87 (21.8%)	63/150 (42.0%)
Mortezavi et al. 2019 [48]	HIFU	75	6m	GG ≥2	14/68 (20.6%)	7/75 (9.3%)
Shoji et al. 2020 [49]	HIFU	90	6m	GG ≥2 or MCCL ≥4mm	0/90 (0.0%)	0/90 (0.0%)
Dellabella et al. 2021 [50]	HIFU	189	12m	GG ≥2 or MCCL ≥4mm	22/177 (12.4%)	12/189 (6.3%)
Ehdaie et al. 2022 [10]	HIFU	101	6m	GG ≥2	5/101 (5.0%)	0/101 (0.0%)
Hong et al. 2022 [51]	HIFU	164	12m	GG ≥2	10/103 (9.7%)	61/164 (37.2%)
Rómpre-Brodeur et al. 2021 [52]	HIFU	77	6m	GG ≥2	18/77 (23.4%)	0/77 (0.0%)
Garcia-Barreras et al. 2018 [53]	HIFU or Cryo	236	12m	GG ≥2 or MCCL ≥4mm	41/236 (17.4%)	0/236 (0.0%)
Scheltema et al. 2023 [54]	IRE	229	12m	GG ≥2	14/190 (7.4%)	39/229 (17.0%)
Wang et al. 2022 [55]	IRE	109	6m	GG ≥2 or MCCL ≥4mm or upgrading	1/100 (1.0%)	9/109 (8.3%)

The definition of clinically-significant prostate cancer here varied, though all studies as a minimum utilised the grade group 2 or higher definition that will be used in our study. The proportions of patients with clinically-significant in-field prostate cancer diagnosed on follow-up biopsy was also variable and ranged from 0.0 to 23.5%, with a median of 13.8% amongst these studies.

We hypothesise that the use of intra-operative CEUS with further ablation if needed may improve cancer control, and would lead to a low proportion of clinically-significant prostate cancer diagnosed on prostate biopsy at 12 months. We hypothesise that the proportion of patients experiencing the primary outcome in our study will be 7.5% at most and potentially as low as 1-2%. For a given sample size, precision will increase as the proportion of participants experiencing the primary outcome decreases. Therefore, we will calculate target sample size based estimating a confidence interval width around the higher estimate of 7.5%.

To measure the higher estimate of 7.5% with a 15% confidence interval width (±7.5% points), 50 patients would be needed. For greater precision, to derive this 7.5% estimate with a 10% confidence interval width (±5%) would require 100 patients.

Another key factor in calculating the target sample size here is the risk of patients declining a prostate biopsy at 12 months. This is a known limitation of many focal therapy studies, especially where the patient has reassuring PSA kinetics post-operatively or a non-suspicious MRI at 12 months. For the tabulated studies, biopsy refusal rates ranged from 0.0 to 42.0%, with a median of 7.1%. Given this, and given previous trials in focal therapy our group has run, we conservatively estimate up to 10% of patients will refuse a biopsy at 12 months. Combined with up to 5% of recruited patients withdrawing from the trial for other reasons, we will adjust sample size calculations to account for a potential patient drop-out of up to 15%.

Therefore, accounting for 15% patient drop out, 59 patients would be needed for a 15% confidence interval width around a 7.5% expected outcome proportion. Accounting for 15% patient drop out, 118 patients would be needed for a 10% confidence interval width around a 7.5% expected outcome proportion.

We will initially aim to recruit 59 patients with contingency to increase the target sample size if recruitment is progressing well. After 4 months of recruitment, if at least 40 patients have been recruited, then the target sample size will be increased to 118 patients. We anticipate good recruitment to this study given the broad eligibility criteria, inclusion of all available ablative energies, and minimal change to standard care practice.

9.2 ANALYSIS OF OUTCOME DATA

The following table displays the trial's outcome measures, timepoints of evaluation, and plan for statistical analysis. Data will be presented for all patients and for patients stratified by post-focal therapy CEUS positivity and whether further ablation was delivered. However, no formal statistical comparisons between these stratifications is planned.

All reported hypothesis testing will be 2-tailed. Statistical significance will be set at $p<0.05$. Missing data for non-outcome variables will be imputed via multiple imputation

where required, for example in logistic regression analyses. No outcome data will be imputed; patients with missing outcome data will be excluded from specific analyses.

Further details will be reported in a separate statistical analysis plan.

Objectives	Outcome Measures	Timepoint(s) of evaluation	Statistical analysis plan
Primary Objective			
To estimate the proportion of patients with clinically-significant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively	Proportion of patients with clinically-significant prostate cancer within the treatment zone on biopsy at 12 months, defined as cancer that is grade group 2 or higher, in those patients who undergo prostate biopsy	12 months post-operatively	Reported as the proportion of patients with clinically-significant prostate cancer within the treatment zone on biopsy at 12 months, with 95% confidence interval Granular biopsy data will be summarised including distribution of grade group, MCCL, total biopsy cores, and positive biopsy cores. These will also be classified by whether further ablation was performed or not Multivariable logistic regression will be used to assess what patient and surgeon factors were associated with this outcome, giving odds ratios with 95% confidence intervals
Secondary Objectives			
To assess recruitment to the study and compliance to study interventions	Recruitment rate: The percentage of approached patients who consent to participate per month Biopsy rate: he number of patients who agree and disagree to undergo prostate biopsy at 12 months, with reasons if disagreement	Recruitment rate: Baseline Biopsy rate: 12 months post-operatively	Recruitment rate: the proportion of approached patients who consent to participate, including a 95% confidence interval and reasons for non-consent Biopsy rate: The proportion of recruited patients who consent and do not consent to prostate biopsy, including a 95% confidence interval and reasons for declining biopsy
To estimate the proportion of patients with clinically-insignificant in-field recurrent cancer at 12 months after focal therapy when using CEUS to guide focal therapy ablative planning intra-operatively	Proportion of patients with clinically-insignificant prostate cancer within the treatment zone on biopsy at 12 months, defined as cancer that is grade group 1, in those patients having a biopsy	12 months post-operatively	Reported as the proportion of patients with clinically-insignificant prostate cancer within the treatment zone on biopsy at 12 months, with 95% confidence interval
To assess how the use of intra-operative CEUS changes the delivery of focal therapy by urologists	Proportion determined by the treating urologist that the CEUS performed after focal therapy is negative, equivocal, or suspicious for residual tumour Proportion undergoing further ablation by the treating urologist after performing intra-operative CEUS	Day 0 (intra-operatively)	Reported as the proportion of patients who are deemed to have a positive CEUS, equivocal CEUS, or negative CEUS after focal therapy, with 95% confidence interval Reported as the proportion of patients who receive further ablation after intra-operative CEUS, with 95% confidence interval Multivariable logistic regression will be used to assess what patient and surgeon factors were associated with these outcomes, giving odds ratios with 95% confidence intervals
To assess the additional operative time needed to perform intra-operative CEUS and deliver further ablation	The time in minutes required to set up and perform CEUS intra-operatively pre-focal therapy The time in minutes required to set up and perform CEUS intra-operatively post-focal therapy	Day 0 (intra-operatively)	Reported as medians with inter-quartile range

	The time in minutes required to deliver further ablation, if performed		
To assess the learning curve of urologists to perform and interpret intra-operative CEUS	Temporal changes in time required to set up and perform intra-operative CEUS, measured on a per-urologist basis Agreement over CEUS image interpretation score between the treating urologist and an expert user, measured on a per-urologist basis	Day 0 (intra-operatively)	Cumulative summation test for learning curve analyses will be performed to determine the per-urologist learning curve for performing and interpreting intra-operative CEUS [59]. These analyses will focus on time to perform CEUS and on concordance in image interpretation score between the treating urologist and expert user
To assess whether urologists can achieve high intervention fidelity for performing and interpreting intra-operative CEUS	Proportion of individual CEUS steps performed to completion, assessed by an expert user Proportion of individual CEUS steps performed to optimal quality, assessed by an expert user Proportion of CEUS images with suspicion score concordant with a score given by an expert user	Day 0 (intra-operatively)	For each individual step of the CEUS technique, the proportion deemed to have each level of completion (complete, incomplete, not performed) and quality (optimal, adequate, inadequate) will be reported. The proportion of patients for whom 100% completion of all steps, and the proportion for whom optimal quality of all steps, were achieved will also be reported Cohen's kappa will be used to measure the level of agreement in recorded image-interpretation scores between the surgeon and the expert user
To assess the safety of using intra-operative CEUS with or without further ablation	Proportion of patients experiencing adverse events	Measured on day 0, then 1-2 weeks, 3 months, and 12 months post-operatively	Proportion of patients experiencing complications, with descriptions and timepoints, over the length of the trial characterised and graded using the CTCAE v5.0 system
To assess the short-term functional effects of using intra-operative CEUS with or without further ablation	Questionnaire scores pertaining to urinary, sexual, and bowel function and health-related quality-of-life, measured using validated questionnaires	Measured at baseline, then 3 and 12 months post-operatively	Mean scores in each questionnaire and EPIC domain at each timepoint, with 95% confidence intervals. These will be plotted for each timepoint using jitter and violin plots. Scores will be compared using the Wilcoxon signed rank test
To assess the diagnostic accuracy of MRI, interpreted using dedicated imaging-scoring systems, for detecting clinically-significant recurrent cancer after focal therapy	Concordance between MRI interpretation scores (index test) and targeted biopsies of the treatment zone (reference test) in detecting clinically-significant residual cancer, defined as grade group 2 cancer or higher (target condition), in those patients who undergo prostate biopsy	12 months post-operatively	For each scoring system assessed, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for detection of clinically-significant prostate cancer. Sensitivity and specificity will be compared using the McNemar test. Positive predictive value and negative predictive value will be compared using a generalised estimating equation logistic regression model Comparison of cancers detected by and not detected by MRI, described using grade group (percentage for each grade group), MCCL (median and IQR), number of positive cores (median and IQR). Characteristics of MRI-detected and MRI-undetected tumours will be compared using a chi square test for trend (grade group) and Kruskal-Wallis test (MCCL and number of positive cores). For MCCL and number of positive cores, mean or median differences between groups will be reported with a 95% confidence interval

Subgroup analyses

The patient cohort will be divided into 3 subgroups based on what focal therapy modality was used, either HIFU, cryotherapy, or IRE. Analyses will be repeated within each subgroup and separately reported. No formal statistical comparisons will be made between these subgroups.

The patient cohort will also be divided into patients who those with a positive CEUS and those without, and those who underwent further ablation after CEUS and those

who did not. Relevant analyses will be repeated within each subgroup and separately reported. No formal statistical comparisons will be made between these subgroups.

Secondary analyses

First, the definition of in-field clinically-significant prostate cancer on prostate biopsy at 12 months will be changed from grade group 2 or higher to:

- Any cancer
- Grade group 2 or higher, or grade group 1 with MCCL 4mm or higher
- Grade group 3 or higher, or grade group 1 with MCCL 6mm or higher
- Cancer of equivalent or higher grade to initial diagnosis

Second, the threshold for 12-month MRI to be deemed positive will be changed:

- For 5-point scoring systems (for example TARGET), changing from a score of 4-5 to indicate positivity to a score of 3-5
- For 3-point scoring systems (for example PI-FAB), changing from a score of 3 to indicate positivity to a score of 2-3

10. MONITORING

The study will be monitored continuously by the trial management group to assess the study's progress, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data. Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

Recruitment numbers will be ascertained after 4 months of recruitment. If at least 40 patients have been recruited by this point, then the target sample size will be expanded to 118 patients.

11. REGULATORY ISSUES

11.1 DECLARATION OF HELSINKI

The investigator will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki

11.2 GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the guidelines laid down by the ICH GCP E6 guidelines.

11.3 ETHICAL APPROVAL

The Study Coordination Centre has obtained approval from the North West - Haydock Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.4 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, the PIS offered. Patients will be given as much time as they require to consider their participation in the trial, and if needed a further discussion with the trial team, either via telephone or in-person, will be scheduled. Ultimately, signed participant consent will be obtained if the patient wishes to participate and give their informed consent. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if they feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

It is the investigator's responsibility to inform the subject's general practitioner (where applicable) by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Patient Information Sheet and Informed Consent Form. A copy of the letter should be filed in the subject's medical records

11.5 CONFIDENTIALITY

Access to medical records by those outside the direct healthcare team

Medical records and other personal data might be examined by appropriately trained study staff that are employed by or have an honorary contract with each NHS trust participating in the study. Medical records and other personal data generated during the study may be examined by representatives of the sponsor, by people working on behalf of the Sponsor, and by representatives of Regulatory Authorities, where it is

relevant to this research. Those outside of the direct care team cannot have access to identifiable information without consent already being in place

Electronic transfer by magnetic or optical media, email or computer networks
Potential participants will be able to use the NHS email address on the PIS (imperial.focus.trial@nhs.net). Access to this email will be highly restricted to select members of the IP14-FOCUS Study group. Emails to and from the assigned study Imperial College Healthcare NHS trust email address will be kept for 10 years after study closure.

Participants will also be permitted to complete the informed consent form and any PROM measure questionnaires electronically via a secure, individualised REDCap link. This will automatically link their response to their corresponding entry in the trial-specific REDCap database, maintained and on an Imperial College London network protected by a firewall. Access to the database is restricted to the research team by login and password for user. All REDCap users will be trained and certified in the usage of the database. REDCap will automatically pseudonymise any data on export.

Storage of personal data on NHS computers
Personal identifiable data will be held by site as part of their medical record, either on each sites patient administrative system, electronic medical records system accessible only to those granted it by that trust by substantive or honorary contract.

Storage of personal data on manual files
The enrolment log and informed consent forms will be kept at the the NHS site's Investigator Site File, held within secure offices only accessible by authorised trained personnel. Pseudonymised paper questionnaires will be securely held at Imperial College London. The files will be locked and secured in filing cabinets held in a locked room only accessible by IP14-FOCUS research team members. The trial master file will be kept in a secured, locked Imperial College Office space accessed only by appropriately trained study staff, people working on behalf of the Sponsor, and by representatives of Regulatory Authorities, where it is relevant to this research. Storage and handling of confidential trial data and documents will be in accordance with GDPR and the Data Protection Act 2018 (UK).

Storage of personal data on university computers
A secure REDCap database containing trial related data will be maintained. The database is stored on an Imperial College London network protected by a firewall. Access to the database is restricted to the research team by login and password for user. All REDCap users will be trained and certified in the usage of the database. Although REDCap will be used to deliver and record informed consent forms and questionnaires to patients, any data exported from REDCap will be strictly pseudononymised. Other data, such as CEUS video files, will be stored securely as pseudononymised files on university computers via software approved by the sponsor.

MRI image files from scans, and CEUS video files performed during focal therapy, will be exported in a pseudonymised format from NHS computers onto an encrypted hard drive then immediately uploaded to secure Imperial College London servers. Once this has occurred, the data on the hard drive will be deleted.

To facilitate linkage to national databases, participants will be asked for optional consent for identifiable fields (NHS number) to be linked and assigned to their

pseudonymised HES patient identification (HESID). The identifiable fields (such as NHS number) required for linkage will be encrypted using an approved one-way encryption algorithm. This will be kept separately from the main study database and access will be highly restricted. This is an optional consent point and is explained the PIS and informed consent form.

Sharing of personal data with other organisations and export of personal data outside the EEA

Data collected in this trial will be shared in a strictly pseudononymised manner with the study's statistician based at the University of Leeds. These files will be transferred electronically via secure systems employed by Imperial College London. No patient-identifiable information will be shared.

Recordings of the CEUS procedure will be labelled with the subject ID only, and will not include any patient-identifiable information. These files will be transferred electronically via secure systems employed by Imperial College London to the expert user for analysis of the quality and completion of CEUS. No patient-identifiable information will be shared with the expert user. The expert user is based at the University of Southern California, United States of America. The investigators will ensure that it is transferred in accordance with data protection legislation. If, at the time of transfer, the United States of America is not subject to a European Commission adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient research partner that incorporates UK approved standard contractual clauses or utilise another transfer mechanism that safeguards how participant data is processed.

There may be other requirements to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates European Commission-approved standard contractual clauses that safeguard how personal data is processed.

Use of personal addresses, postcodes, faxes, emails or telephone numbers

For trial follow-up purposes, researchers are required to contact each participant directly for collation of patient questionnaires. This is permitted either in-person during an existing clinic appointment, by telephone, by post, electronically via REDCap, or electronically via email. We will ask patients from the study site to permit the central research team at Imperial College London to hold their full name and contact details so that PROM questionnaires can be delivered to them on a regular basis. Confidentiality is maintained using the trial ID (pseudononymised) which will be on the questionnaire and no other identifiable information will be available. To allow for this, the team will require the names, addresses, telephone numbers, and email address where applicable of each participant. These details will be securely walled off on Imperial College London university computers with access only granted to the study research team. These details will also be used to contact either patient or their GP for regular updates on their health status where require.

If participants give optional consent to be contacted by the research team within 10 years about willingness to complete a health status and quality of life questionnaire,

then contact information will also be stored by Imperial College London for this purpose.

11.6 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS resolution for NHS Trusts in England, which apply to this study.

11.7 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trust taking part in this study.

11.8 FUNDING

The National Institute for Health and Care Research (NIHR) are funding this study through an NIHR Doctoral Fellowship award (NIHR304727).

11.9 AUDITS AND INSPECTIONS

The study may be subject to inspection and audit by Imperial College London under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

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12. DATA MANAGEMENT

12.1 SOURCE DATA

All written or electronic patient health records held by the hospital or GP or other medical facility. Source data also include the completed questionnaires collected as part of this study.

12.2 LANGUAGE

CRFs will be written in in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood and be in the language appropriate for the study site.

12.3 DATABASE

The REDCap online database application on a server hosted by Imperial College London will be used for electronic data capture of case report form data for patients participating in the study. REDCap is a regulatory compliant database that has been used in clinical trials for over 15 years and is sponsor-approved for non-Investigational Medicinal Product studies. Study staff at the participating site will enter baseline and follow-up data into the online database. REDCap can also be used to facilitate electronic consent and electronic completion of PROM questionnaires by patients. The database is password-protected and users will have passwords to access, enter, and use the data for the full study duration. All members of the research team will receive training appropriate to their role and duties and will respect and comply with patient confidentiality. Any data exported from REDCap will strictly contain only pseudononymous identifiers.

12.4 DATA COLLECTION

CRFs will be based on relevant data collection tools tested in previous studies that we have undertaken and will undergo review by the study team, relevant clinical staff, and the statistician prior to use. Patient-level data collection will include baseline clinical factors, diagnostic data (e.g. PSA, MRI, and biopsy results), treatment details (including CEUS use), post-treatment follow-up data, adverse events, and questionnaire data. Details of procedures for the CRF completion will be provided in a study manual.

12.5 ARCHIVING

All trial documentation, including that held at the trial site, will be archived for a minimum of 10 years following the end of the study.

13. TRIAL MANAGEMENT

A Trial Management Group (TMG) has been appointed including the Chief Investigator, co-investigators, trial statistician, and a patient and public representative. Please see page 2 of this document for its members. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms.

14. PATIENT AND PUBLIC INVOLVEMENT

Two patient focus groups were held between December 2023 and January 2024 to discuss focal therapy for localised prostate cancer, incorporating a total of 9 prostate cancer patient representatives recruited through Prostate Cancer UK and the Mid Sussex Prostate Cancer Support Group. These patients had undergone different treatment strategies including focal therapy, in addition to active surveillance, radical prostatectomy, and radiotherapy. A major area of discussion was the theme of prostate cancer recurrence after treatment like focal therapy and how this should be detected and treated. It was highlighted in both focus groups that prostate cancer recurrence is a major source of anxiety for patients. In the second of these focus groups, an outline of this trial was presented and strongly supported by attendees as a potential way of reducing recurrence without placing much additional burden on the patient.

From these focus groups, a PPI representative has joined the TMG, who has previously undergo 2 focal therapy procedures followed by salvage radiotherapy. They are therefore highly-knowledgeable regarding the focal therapy pathway as well as what it is like to develop recurrent disease and require further treatment. They will advise on the conduct, delivery, and dissemination of the study. They will meet with members of the Trial Management Group in the first 3 months then every 6 months thereafter. They will advise on all patient-facing documents, for example the patient information sheets and consent form, as well as recruitment strategy. They will also be fully involved in the results dissemination strategy, which will include a summary of results provided to participants, lay summaries of the main findings placed on our media outlines (X, Bluesky, Linkedin, study-specific, and group websites), lay accessible summaries of peer-reviewed manuscripts and reports, and other media, for example short summary videos for patients and clinicians housed on institutional websites and YouTube channels.

The PPI representative will be offered formal training using structured courses, available through the Imperial Patient Experience Research Centre and the National Institute for Health and Care Research. Study staff will also be asked to attend training on PPI through the Imperial Patient Experience Research Centre and the National Institute for Health and Care Research.

All costs for reimbursement of time and expenses are included in the study budget, as recommended by INVOLVE, to allow for representatives to input regularly, review study information, and attend meetings.

15. PUBLICATION POLICY

Participants who have indicated they wish to receive a summary of the findings of the results on their consent form will be sent this via post or email. Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only. It is understood by the investigator that the Sponsor will use information developed in this clinical study and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical study, the investigator understands that they has an obligation to provide complete test results and all data developed during this study to the Sponsor. Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor. Therefore, all information obtained as a result of the study will be regarded as confidential, at least until appropriate analysis and review by the investigators are completed. Permission from the Executive/Writing Committee is necessary prior to disclosing any information relative to this study outside of the Trial Management Committee. Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the Trial Management Group. A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of the study. A similar report will also be presented to the funder. Analysed work from this trial will be submitted for presentation at national and international conferences, and submitted for publication in peer-reviewed journals. Named authors will include the trial's Chief Investigator, Co-Investigators, Study Statistician, and key collaborators. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group. Public access to the full protocol, participant-level dataset, and statistical code will be available upon reasonable request to the Chief Investigator.

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17. REVISION HISTORY

Version	Date	Summary of changes
1.0	23/01/2025	First version prior to Sponsor review
1.1	07/05/2025	Clarification of information based on Sponsor review comments