Partial prostate Ablation versus Radical prosTatectomy

PART - A randomised controlled trial of *P*artial prostate *A*blation versus *R*adical pros*T*atectomy (PART) in intermediate risk, unilateral clinically localised prostate cancer

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1. SYNOPSIS

Study Title	A randomised controlled trial of *P*artial prostate *A*blation versus *R*adical pros*T*atectomy (PART) in intermediate risk, unilateral, clinically localised prostate cancer	
Internal ref. no. / short title	PART	
Study Design	A study comparing less-invasive partial ablation (PA) of the prostate with standard total ablative surgery in the form of radical prostatectomy (RP).	
Study Participants	Men with localised prostate cancer amenable to PA of the prostate or RP.	
Planned Sample Size	Stage 1: 100 patients Stage 2: 600-800 patients	
Planned Study Period	Stage 1: 18-months Stage 2: 5 years	
Enrolling Sites	Oxford University Hospitals NHS Trust University College London University of Sheffield North Bristol NHS Trust Additional recruiting sites (and PIC sites) will be invited to join the PART study as necessary	
STAGE 1:	**Objectives**	**Outcome measures**
Primary	Testing the feasibility of a randomised trial of PA using energy-delivery based technologies *versus* RP (surgical comparator) for intermediate risk unilateral prostate cancer.	- Randomisation of 100 participants within the proposed timelines - Uptake of consent & randomisation of ≥50% among invited, eligible patients.
Secondary	- Qualitative Recruitment Investigation (QRI) to understand recruitment challenges for this trial and inform optimal recruitment strategies for Stage 2 of the PART study. - To collect data on quality of life and resource usage and inform power calculations for Stage 2 of the PART study. - To explore methods and feasibility of data capture instruments to inform power	- Findings of the Qualitative Recruitment Investigation (QRI).

	calculations and health economic evaluation for Stage 2 of the PART study.	
STAGE 2:	**Objectives**	**Outcome measures**
Primary	- To compare treatment failure rates between the two treatment groups.	- Primary treatment failure as demonstrated by the need for whole gland ablation and/or secondary interventions.
Secondary	- To compare the short, medium and long-term risks and benefits of both treatment arms - The effect on Quality of Life and Health Resource Utilisation of both treatment arms - The role of imaging by mpMRI and biopsy protocols in determining suitability of patients for focal therapy	- Short, medium and long-term adverse events related to treatments - Disease progression including development of metastases - Disease-specific and all-cause mortality - Quality of life using conventional questionnaires (IIEF-15, IPSS, EQ-5D-5L, FACT-P, UCLA-EPIC) - The role of imaging by mpMRI and biopsy protocols in determining the suitability of patients for focal therapy using data collected in the CRF.

2. ABBREVIATIONS

AM	Active Monitoring
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
DC	Direct Current
EBRT	External Beam Radiotherapy
GCP	Good Clinical Practice
GP	General Practitioner
HIFU	High Intensity Focused Ultrasound
HRQL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ILP	Interstitial Laser Photocoagulation
IMRT	Intensity Modulated Radiotherapy
IRE	Irreversible Electroporation
MDT	Multidisciplinary Team
MIT	Minimally Invasive Technique
mpMRI	Multiparametric Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
OCTRU	Oxford Clinical Trials Research Unit
PA	Partial Ablation (focal therapy)
PI	Principal Investigator
PIL	Participant/Patient Information leaflet
PSA	Prostate-Specific Antigen
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QRI	Qualitative Recruitment Investigation
R&D	NHS Trust R&D Department

RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RF	Radiofrequency
RFA	Radio-Frequency Ablation
RITA	Radio-Frequency Interstitial Tissue Ablation
RP	Radical Prostatectomy
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TPM	Transperineal Prostate Mapping
TRUS	Transrectal Ultrasound
VTP	Vascular Targeted Photodynamic Therapy
WW	Watchful Waiting

3. BACKGROUND AND RATIONALE

3.1. Prostate Cancer in the UK

Prostate cancer has become the most common cancer in men, accounting for around 13% of male deaths from cancer in the UK and is the second most common cause of male cancer deaths, after lung cancer. In 2011, there were 41,736 new cases of prostate cancer diagnosed in the UK, and 10,793 died from the disease in 2011. The lifetime risk of being diagnosed with prostate cancer is 1 in 9 for men in the UK (Cancer Research 2011). The incidence is increasing with wider use of prostate-specific antigen (PSA) testing in asymptomatic men and with the UK's population ageing. Whilst prostate cancer can be lethal, the majority of men who are diagnosed through PSA-testing will not suffer clinically significant consequences from the disease during their life time, and evidence that treating such men with radical prostatectomy (RP) or radiotherapy improves survival sufficiently to outweigh the adverse impact on quality of life is weak. Consequently, there are concerns that increasing PSA-testing in the community is resulting in over-diagnosis, overtreatment, and an unnecessary burden to the NHS.

Despite its high incidence and social and economic impact, prostate cancer continues to be under-researched. The HTA NIHR ProtecT (Prostate testing for cancer and Treatment) study, conducted by the applicants, is testing the value of a single round of PSA testing in the community, and comparing the effectiveness of the three conventional treatment options of active monitoring (AM), RP and external beam radiotherapy (EBRT) in clinically localised disease at all risk levels. The study completed recruitment in 2009, having PSA-tested over 111,000 men in 9 UK centres and with over 60% (n=1600) of eligible men randomised between the 3 arms. The primary outcome analysis will be performed in 2015/16 when patients reach a median 10-year follow up. ProtecT will provide key information about the effectiveness of conventional treatment options, but has not been testing focal therapy, which forms the basis of this proposal and thus complements the ProtecT study.

A number of new minimally invasive techniques have been developed to treat prostate cancer, but as yet they have not been evaluated sufficiently to reliably inform their utilisation within the NHS. Techniques include HIFU, cryotherapy, VTP, radiofrequency interstitial tissue ablation (RITA), laser photocoagulation and irreversible electroporation. These technologies were the subject of an HTA commissioned systematic review undertaken by Professor Ramsay's team at the Health Services Research Unit, University of Aberdeen (HTA 10/136/01 http://www.hta.ac.uk/2808). We have been given access to this review prior to publication at the request of the NIHR. They conclude as follows:

"The increasing incidence of low and medium-risk localised prostate cancer indicates that demand for treatment interventions which are less aggressive in comparison with the established radical treatments will likely increase over the next decade in the UK. Such interventions include ablative therapy, which appears to be the ideal intervention because unlike active surveillance, it actively treats cancer, whilst being minimally invasive and potentially organ-sparing, unlike either radical prostatectomy or EBRT. This review was tasked to assess the evidence base regarding the clinical and cost effectiveness of ablative therapy for men with localised prostate cancer in the NHS.

The findings on focal ablative therapy were mostly derived from data on focal cryotherapy, which suggested that cancer-specific outcomes were at least comparable to full-gland cryotherapy, and there was a suggestion that urinary incontinence outcome may be better following focal cryotherapy compared with whole gland cryotherapy. In terms of the economic analysis, the findings suggest that of all the ablative interventions, HIFU is the most likely to be considered cost-effective when assessed against threshold values for a cost per QALY that society might be willing to pay.

However, marked uncertainties within the analyses and the lack of reliable estimates of its clinical effectiveness and harms mean that the cost-effective advantage needs to be interpreted cautiously. At best the data highlight that this modality might be a good target for further robust primary research.

The findings from the review indicate that there is insufficient evidence to form any clear recommendations on the use of ablative therapies which either influences or changes current clinical practice.

Implications for research

The main gaps in the evidence base are the lack of direct comparative studies of ablative therapies, the role of focal ablative therapies and the lack of longer-term data on cancer control, such as overall and cancer specific mortality. In general, the ongoing studies clearly illustrate that the evidence base for ablative therapies is following an upward trajectory, and, in particular, the evidence for focal ablative therapies is likely to increase in quantity. However, it is also clear that the quality of the evidence base will not be substantially improved given that the majority of the ongoing studies are case series. Research efforts in the use of ablative therapies in the management of prostate cancer should now be concentrated on the performance of more rigorous, high quality studies. Lessons from our systematic review lead us to the following areas in which further research would be important:

1. HIFU, and brachytherapy seem the most promising newer interventions but they lack high quality evaluation. Such evaluation should ideally be by multicentre RCT, with long-term follow-up and would include predefined assessment of cancer-specific, dysfunction and health-related quality of life measures. Such studies should incorporate economic evaluations and also inform economic modelling.

2. The role of focal therapies in the management of men with localised prostate cancer should be investigated. It may be desirable to incorporate the focal approach into the design described above. It is noted however that use of focal therapies is dependent on prior precise localisation of the cancer for which the technology remains developmental.

3. Active surveillance is an increasingly used strategy for men with localized prostate cancer that is deemed to be at low initial risk of spread. The results of on-going studies are required to assess its safety, acceptability to men with prostate cancer and cost-effectiveness.

4. Agreed definitions of outcomes in urology and agreed measures for recording them is urgently needed. Partnership between governing bodies and international initiatives such as COSMIN and COMET may be desirable."

The PART study will compare radical prostatectomy versus partial ablation of the prostate cancer in men with intermediate risk, unilateral prostate cancer. This is the first phase III study comparing these treatments.

The PART study will be conducted in two stages: a feasibility stage followed by the main recruitment stage. It is hoped the first phase of the PART study will show that it is feasible, and acceptable to the relevant patients, to carry out a larger RCT of partial ablation versus radical prostatectomy for intermediate risk, unilateral prostate cancer.

Our aim in **Stage 1** is to recruit 100 men to the PART study. These patients would be treated as if they were in the main, larger phase of the trial and have the same assessments and follow-up visits. If successful, it will be followed by the main recruitment phase of the PART study (**Stage 2**) where we aim to recruit a further ~600-800 men. The patients recruited into the first phase of the trial would automatically be rolled into the second phase of the study. Outcome data from both stages will be analysed on an intention to treat basis.

During Stage 1 of the PART Study, HIFU will be the sole technology used in the Partial Ablation arm. A Qualitative Recruitment Investigation (QRI) will also be carried out during this stage, in order to identify any potential barriers to recruitment. The QRI will help us develop and refine optimal recruitment strategies for the second stage of the PART Study.

Currently, funding is only available for Stage 1 of the study. Our aim is to apply for additional funding for Stage 2, once the feasibility of the PART study has been established.

3.2. Diagnosis of Prostate Cancer

The current diagnostic pathway in the NHS is much debated. It varies from centre to centre with a combination of transrectal prostate biospies, MRI (standard or multiparametric) and targeted biopsies.

Imaging

Prostate cancer is the last solid organ malignancy that does not rely consistently on imaging to detect disease and guide tissue sampling for histological confirmation. Conventional MRI is used in staging of localised disease and in the assessment of uni- or bilateral disease (T2), extra-capsular extension and seminal vesical involvement (T3), as well as the invasion of adjacent structures (T4). However, the literature shows a wide range in the accuracy of T-staging by MRI, from 50-92% (Heidenreich, Aus et al. 2008). mpMRI has demonstrated higher levels of accuracy in detection of clinically important disease.

Newer sequences such as diffusion-weighted, magnetic resonance spectroscopy imaging, and dynamic contrast-enhancement, have been used to improve the accuracy of MRI by capitalising on the different cellular density, metabolic activity and microvasculature of prostate cancer and benign tissue (Turkbey, Pinto et al. , Kim, Jang et al. 2009). Studies suggest that mpMRI, using a combination of sequences, has a high negative predictive value of 90-95% for lesions of greater than 0.2ml and 0.5ml in volume (Ahmed, Kirkham et al. 2009), the volume thresholds widely accepted as constituting indolent disease (Epstein, Oesterling et al. 1988).

There are two possible benefits that result from using mpMRI within the diagnostic pathway. The first is that many men might, as a result, safely avoid a biopsy. A negative mpMRI could reassure a man that he does not have clinically significant prostate cancer. By avoiding TRUS-guided biopsy he avoids the risk of detecting low risk prostate cancer, the diagnosis of which is more likely to confer harm rather than benefit. The second benefit will apply to men who do need a biopsy. mpMRI allows a targeted biopsy regime leading to improved detection and characterisation (grade and burden) of clinically significant cancer from fewer needle deployments. At present, mpMRI of the prostate is available in just a few expert centres (all centres within this trial). A definitive validating cohort study evaluating mpMRI as a triage test has received funding from HTA NIHR with two of the applicants as investigators – the PROMIS trial (Emberton and Ahmed). However, as is often the case, the uptake of mpMRI is increasing and many centres have already adopted its use.

Ideally, an mpMRI is performed pre-biospy as post biopsy interpretation can be significantly more difficult. Pre-biopsy mpMRI is offered in some centres, although as yet unsupported by NICE. However, in many centres MRI is only performed after a biopsy. This may take the form of a:

- conventional MRI for staging the disease;
- mpMRI for treatment planning for radical therapy. Confirmation of unilateral disease (focal therapy), precise disease location (RP, and focal therapy) and disease burden (brachytherapy and EBRT) are vital in many treatments;
- mpMRI in an active surveillance protocol;
- mpMRI where there is discordance between the clinical findings and the biopsy results e.g. a high PSA but negative biopsies, atypical cells that are not cancer (PIN or ASAP) or an abnormal DRE.

Microscopic capsular invasion by prostate cancer (pT3a) cannot be detected directly by imaging as the phenomenon is, by definition, microscopic. It is however inferred by radiologists from the length of capsular abutment (best seen on the T1 GAD sequence incorporating fat saturation) measured in millimetres in the axial plane, as this length is positively associated with microscopic invasion of the capsule. There is no pre agreed threshold above which this occurs and below which it does not as the association is likely to be linear. If the length of capsular abutment exceeds 5 millimetres in any plane the increased probability of pT3a disease would make it likely that any given patient would fail to conform to the intermediate risk status that confers eligibility to this study (PART).

Prostate Biopsy

In some centres, men will have a pre-biopsy mpMRI. mpMRI allows accurate disease localisation. Where a significant lesion is identified on mpMRI, targeted biopsies will be performed in the diagnostic set. If no significant lesion is identified, men will have a standard TRUS biopsy.

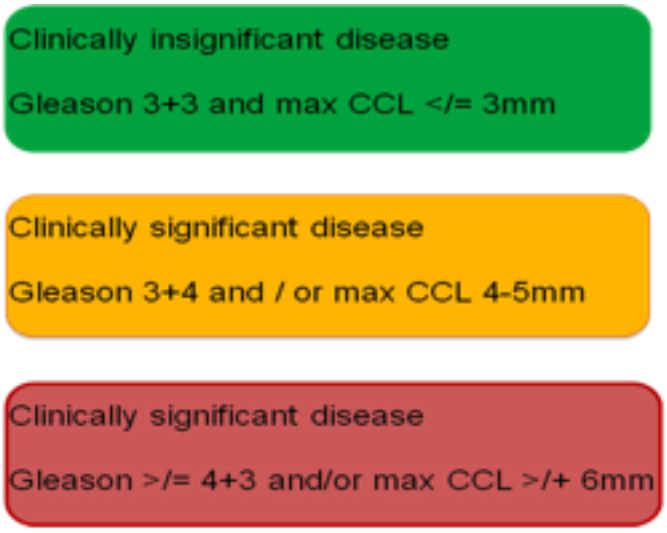
In other sites, for eligible patients, an mpMRI will be requested after the initial biopsies to further characterise the disease. Providing the mpMRI results are concordant with the TRUS biopsy findings then no further biopsies will be necessary. However, if there is discordance then a targeted biopsy will be recommended to assess the areas of the prostate that were previously felt to be cancer free. This is equally important in men considering focal therapy or radical surgery, as it is vital that a significant area of disease is not missed during the diagnostic pathway and as a result they are offered the wrong treatment, including in the case of radical surgery the decision for a nerve sparing procedure.

There is also a group of men who cannot have an mpMRI (e.g. a pacemaker, contrast allergy). These men will be investigated further with a targeted biopsy to determine the extent of their disease within the prostate.

What is significant disease?

We propose that any focus with more than one positive biopsy of greater than, or equal to, 4mm will be deemed above the threshold allowed for defining significant foci. This ensures that a cautious approach is adopted, one in which over-treatment of small lesions is built-in so as to ensure under-treatment of large lesions is less likely to occur.

These results allow us to derive two definitions of clinically significant cancer that approximate to the definitions used by Epstein in which green represents clinically insignificant disease, and yellow and red represent two thresholds for clinically significant disease. Importantly, these definitions can be applied prior to any therapy in contrast to Epstein's definitions that require whole mount processing of the prostate.



3.3. Treatment options for localised prostate cancer

In 2008, 63% of men diagnosed with prostate cancer in England were under 75 years old (ONS 2008), and around 7500 of these men would be suitable for potentially curative therapies. In terms of oncological effectiveness, the conventional treatments for localised prostate cancer appear to have similar outcomes in non-randomised studies, though with only short to medium term follow up. In general, the conventional treatments are RP and radiation therapy, either in the form of EBRT or brachytherapy. In addition, it is likely that for many screen-detected patients a policy of active monitoring/surveillance (AM) is suitable, (Klotz 2003), pending results of the ProtecT study in the UK. Newer treatments, based on minimally invasive approaches for delivery of ablative energy have emerged and are being used in a number of centres worldwide, without robust RCT evidence of their effectiveness.

Radical Prostatectomy

This procedure can be open, laparoscopic or robot-assisted. The fundamental principle is total surgical ablation to remove the entire prostate gland and seminal vesicles. In large reported series, RP conferred a 5-year disease free survival of between 69% and 84% (Catalona and Smith 1994, Trapasso, deKernion et al. 1994, Zincke, Oesterling et al. 1994, Han, Partin et al. 2001, Hull, Rabbani et al. 2002). A recent HTA NIHR commissioned systematic review of the relative clinical benefit and cost-effectiveness of laparoscopic and robotic RP suggests that robotic RP has lower per-operative morbidity and a reduced risk of positive surgical margins compared with the laparoscopic procedure (Ramsay, Pickard et al. 2012). Uncertainty about these differences remains, and rates of urinary incontinence, erectile dysfunction and cancer control are indistinguishable at present between the two procedures. The Scandinavian SPCG-4 RCT comparing surgery and watchful waiting (WW) in clinically detected prostate cancer showed an absolute risk reduction in preventing cancer mortality of 5% (from 14% to 9%) at 8 years (Bill-Axelson, Holmberg et al. 2005) with this absolute difference maintained to 14 years (Bill-Axelson, Holmberg et al. 2008, Bill-Axelson, Holmberg et al. 2011). However, the more recent PIVOT study (Prostate Intervention versus Observational Treatment) in the US compared RP with WW in over 700 men with localized PSA-detected prostate cancers (Wilt, Brawer et al. 2012), concluding that RP did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, with a median of 10 years of follow-up. Absolute differences were less than 3 percentage points. Just 13% of deaths were from prostate cancer though there were fewer such deaths with RP: 21/364 vs 31/367 (HR=0.63 (0.36-1.09); p=0.09).

Radical Radiotherapy

The mainstay of radical radiotherapy remains EBRT. Intensity modulated radiotherapy (IMRT), an optimised form of EBRT, is gradually gaining ground in some centres (Heidenreich, Bolla et al. 2010). EBRT is a common treatment in the UK for men diagnosed with localised prostate cancer. It is usually preceded by a period of neo-adjuvant androgen suppression (3-6 months), and is given in daily fractions over 4–8 weeks as an outpatient. In large reported series, EBRT conferred a 5-year disease free survival of between 78 – 80% or 88 – 94% in combination with hormone therapy (Bolla, Collette et al. 2002, D'Amico, Manola et al. 2004, Speight and Roach 2005, Zietman, DeSilvio et al. 2005).

Brachytherapy

Brachytherapy can be given either as permanent radioactive seed implantation or as high-dose brachytherapy using a temporary source. For localised prostate cancer, the 5-year biochemical failure rates are similar for permanent seed implantation, high dose (>72 Gy) external radiation, combination seed/external irradiation, and RP (Kupelian, Potters et al. 2004).

Active Monitoring/Surveillance

Active monitoring/surveillance protocols involve regular clinical examination, PSA measurements and repeat biopsies. If these parameters suggest the risk of progression, men are offered radical treatment. A number of Phase II studies have shown that delayed intervention due to signs of progression occurs in approximately one-third of active surveillance groups within a 5-year follow-up from diagnosis (van As and Parker 2007, Klotz 2008). For those with intermediate disease, AM has been reported as conferring an 84% 5-year metastasis free survival rate (Chodak, Thisted et al. 1994). However, observational strategies can lead to significant anxiety (van den Bergh, Essink-Bot et al. 2009). It is anticipated that the ProtecT study will in due course provide robust information on the suitability and effectiveness of AM in screen-detected men compared with conventional radical treatment options.

Side Effects of Conventional Treatments

At present, as there is little difference between treatments in terms of cancer control in the short to medium term, much of the decision making process that governs treatment allocation is based on the differences in the side-effect profiles associated with the various interventions. Table 1 describe the side effect profiles for RP, EBRT and brachytherapy.

	30 day mortality (%)	**Major Bleeding (%)**	**Early Urinary Retention (%)**	**Stress Incontinence (%)**	**Bladder Outlet Obstruction (%)**	**Erectile dysfunction (%)**	**Proctitis (%)**	**Recto-urethral fistulae (%)**
RP	0-2.1	1-11.5	3	4-50	2-9	29-100	-	0.3-15.4
EBRT	0-1	0	4.5	5.3	27	55	8	0-0.6
Brachy	0	0	1.5-22	0-19	-	40	5-21	0.4-8.8

Table 1: Summary of complications following RP, EBRT and brachytherapy. Data source: European Association of Urology Guidelines (Heidenreich, Bolla et al. 2010).

Alternatives to conventional therapies

As radical treatments carry the potential for significant short, medium and long-term morbidity such as urinary leakage, erectile dysfunction and radiotherapy toxicity, there has been interest in developing alternative ablative therapies in an attempt to reduce treatment burden whilst retaining cancer control, and to avoid the psychological morbidity associated with surveillance. A number of such technologies have been described and each one is at a different stage in its evaluation and application to clinical practice. These new technologies have been introduced in a fairly haphazard manner and as such, the evidence for their use is varied. A further important consideration is the rapid evolution of the technologies over time, with constant new developments in order to improve energy delivery, targeting, safety and imaging.

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 may be performed under general or spinal 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.

Two systematic reviews of HIFU in the treatment of prostate cancer have been published recently (Lukka, Waldron et al. , Warmuth, Johansson et al.). Warmuth *et al.* (Warmuth, Johansson et al.) identified 20 uncontrolled prospective case series, totalling 3018 patients (2806 primary therapy & 211 salvage therapies). They concluded that for all HIFU procedures, the biochemical disease free rate at 1, 5 & 7 years was 78-84%, 45-84% and 69% respectively. The negative biopsy rate was 86% at 3 months and 80% at 15 months. Overall survival rates and prostate cancer–specific survival rates were 90% and 100% at 5 yr and 83% and 98% at 8 yr, respectively.

Adverse events included complications of the urinary tract (1–58%), erectile function (1–77%), the rectum (0–15%), and pain (1–6%). Lukka *et al.* (Lukka, Waldron et al.) found that there were no adequate randomised controlled trials or meta-analyses and concluded that the current evidence on HIFU use in prostate cancer patients is of low quality, rendering it difficult to draw conclusions about its efficacy.

Cryotherapy

Cryotherapy is the localised destruction of tissue by extremely cold temperatures followed by thawing, and may be performed under general or regional anaesthesia. A warming catheter is initially inserted into the urethra to prevent it being damaged by low temperatures. Cryoneedles or probes are inserted into the prostate via the perineum, using image guidance. Temperature monitor probes may also be placed percutaneously through the perineum. Argon gas is circulated through needles or probes, generating very low temperatures and causing the formation of ice around the prostate with profound tissue destruction. Newer cryotherapy techniques allow these needles to be removed or repositioned so that the frozen zone conforms to the exact size and shape of the target tissue.

In 2008, a Cochrane Library review on prostate cryotherapy as a primary treatment was published, recommending RCTs of cryotherapy versus established treatment modalities for early prostate cancer (Shelley, Wilt et al. 2007). All eight studies identified were case series and two were retrospective with a total of 1483 patients. At 5 years, overall survival was reported as 89 to 92% in two studies, and disease-specific survival as 94% in one study. The major complications observed in all studies included impotence (47- 100%), incontinence (1.3-19%), and urethral sloughing (3.9-85%), with less common complications of

fistula (0-2%), bladder-neck obstruction (2-55%), stricture (2.2-17%) and pain (0.4-3.1%). Most patients were discharged the following day (range 1-4 days). Since then, one Canadian RCT, comparing cryotherapy with EBRT as primary therapy for localised prostate cancer in over 200 men, was reported (Donnelly, Saliken et al.). With a median follow up period of 100 months, no significant difference in disease progression was observed between the two arms. However, due to recruitment difficulties, the study was closed before the target accrual was reached.

Vascular Targeted Photodynamic therapy

Vascular-targeted photodynamic therapy (VTP) uses light to activate an intra-venously administered photosensitizing drug to produce instantaneous vessel occlusion and subsequent tissue necrosis. The light is delivered by optical fibres placed transperineally under transrectal ultrasound guidance. VTP treatment is given under general anaesthesia and can be performed as a day case. Only small case series of VTP have been reported in both primary and salvage groups. The initial drug dose escalation studies, followed by a light dose escalation study, were performed in men who progressed following EBRT (Weersink, Forbes et al. 2005, Haider, Davidson et al. 2007, Trachtenberg, Bogaards et al. 2007, Trachtenberg, Weersink et al. 2008). They showed that around 60% of men receiving whole gland treatment at the maximal drug and light doses, had a complete response to treatment. Side effects included two recto-urethral fistulae, one of which required surgical intervention. Urinary side effects tended to last for up to six months. One of the applicants of this proposal reported early results in 40 men with no previous treatment for prostate cancer, with no significant side effects (Arumainayagam, Allen et al.).

Other Ablative Technologies

There are a number of other technologies that are under evaluation. None of them have sufficient evidence at this time to be used within this trial. Examples include Radiofrequency Ablation (RFA), which acts by converting RF waves to heat, resulting in thermal damage. Radiofrequency interstitial tumour ablation (RITA) has recently been proposed for treatment of prostate cancer (Djavan, Zlotta et al. 1997, Zlotta, Djavan et al. 1998, Shariat, Raptidis et al. 2005, Tucker, Huidobro et al. 2005).

Interstitial laser photocoagulation (ILP) was reported by Amin *et al.* (Amin, Lees et al. 1993) who described a percutaneous technique for local ablation. Irreversible electroporation (IRE) is a new non-thermal ablation modality that uses short pulses of DC to create irreversible pores in the cell membrane, thus causing cell death (Onik, Mikus et al. 2007, Rubinsky, Onik et al. 2008). This technology is in the early clinical phases of development.

3.4. Why is the PART study needed now?

Partial Ablation (Focal Therapy) for prostate cancer

Over decades, the principle of surgical ablation and/or radical treatment for cancer has evolved from total and extensive treatment of the affected organs to a more targeted and focal approach with, apparently, equal if not superior effectiveness, as well as fewer adverse events and improved quality of life. The concept is now evolving in prostate cancer using the promising but largely untested emerging technologies described above. Rather than radical therapy treating the whole gland, the aim is to localise and treat the main focus of cancer. This may minimize morbidity by lowering the chance of damage to the neurovascular bundles responsible for erectile function, and the urinary continence mechanism. Focal therapy can be delivered using the ablative modalities as they can treat discrete areas of tissue, but their long-term oncological effectiveness has not been rigorously tested.

The current evidence for focal therapy for prostate cancer is from non-randomised Phase I and II trials in single centres and from case series with small numbers of patients. Phase I/II studies have demonstrated that as few as 5% of men suffer from genitourinary side-effects after focal therapy, with absence of clinically significant cancer in all treated patients (Ahmed, Freeman et al. , Muto, Yoshii et al. 2008, Ahmed, Sahu et al. 2009, Ahmed, Hindley et al. 2012). In men with intermediate risk disease, the primary role of focal therapy is to avoid total gland treatment, thus reducing side effects with comparable oncological effectiveness. A possible strategy which remains untested, is to use novel technologies to target and treat all clinically significant cancers in the gland focally, with careful follow-up and repeat treatments as necessary (particularly of emerging new lesions detected by biopsy). The strategy may obviate the need for any radical therapies. A key caveat with such a strategy is the risk of progression to metastases in intermediate risk disease and the need for accurate targeting and imaging modalities to direct minimally invasive interventions. Focal therapy relies on accurately assessing the status of the disease in the prostate using imaging and biopsies.

Cost-effectiveness evidence of treatment options

Previous reviews of health economics in the treatment for localised prostate cancer resulted in limited evidence on cost-effectiveness of radical treatment options and no evidence to date on the cost-effectiveness of the partially ablative techniques outlined above (Hummel, Paisley et al. 2003, National Collaborating Center for 2008, Hayes, Ollendorf et al. 2010, Hummel, Simpson et al. 2010). Professor Ramsay's team (HTA 10/136/01 http://www.hta.ac.uk/2808) have found that the main limitations of the cost-effectiveness models were the low quantity and poor quality of the data available on cancer-related outcomes and long-term adverse events of urinary incontinence, sexual and bowel dysfunction and changing technology over the review period, also based on indirect comparisons, limited UK specific and up-to-date resource use, cost and utility data and finally and most importantly the lack of any reliable evidence of effectiveness.

The treatment of localised prostate cancer remains a contentious clinical area. The PART study will inform the medical community about focal therapy versus surgery for intermediate risk localised prostate cancer. It will detail the absolute benefit of focal therapy, whilst comparing QoL and economic outcomes. Despite the poor quality of the few retrospective case series assessing the relative safety and efficacy of focal therapy, a change in practice has started towards focal therapy due to the reduction in side effects and apparent oncological safety. As retrospective case series are often selected and hence biased, we consider that an RCT is the only method to reliably compare these treatments.

Potential risks and benefits

The benefits of the main PART study will be great to the prostate cancer community and to new patients diagnosed with the disease (prostate cancer is the second most common cancer after lung cancer, estimated to account for 14% of all new male cancer cases worldwide in 2008 (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate)). It will provide patients, clinicians, healthcare commissioners and providers with reliable evidence on the clinical and cost-effectiveness of focal therapy to inform best practice.

There are potential risks and benefits of both randomised treatments. In the RP arm we anticipate a six-month post-operative mortality of 1-2% and a morbidity of 10-15%. To minimise this risk we are using high-volume surgical units and will only include those with good quality outcome data, prior to trial entry. Similarly focal therapy is not without risk and the centres in this trial have all been involved in early clinical

trials of the technologies. Section 12 outlines the quality assurance measures undertaken in PART relating to surgical and partial ablation delivery.

Potential trial participants will be informed of the study, together with its possible benefits and known risks following their discussion at the central cancer MDT. This will be 2 or more weeks prior to their randomised intervention. Potential participants will be provided with a standard patient information leaflet.

4. OBJECTIVES AND OUTCOME MEASURES

STAGE 1:

Objectives	**Outcome Measures**
Primary Objective Demonstrate the feasibility of recruitment to a randomised trial of PA using HIFU *versus* RP (surgical comparator) for intermediate risk unilateral prostate cancer.	- Randomisation of 100 participants within the proposed timelines. - Uptake of consent & randomisation of ≥50% among invited, eligible patients.
Secondary Objectives - Qualitative Recruitment Investigation (QRI) to understand recruitment challenges for this trial and to develop and refine optimal recruitment strategies for Stage 2 of the PART study. - To collect data on quality of life and resource usage to help decide which questionnaires to use for Stage 2 of the PART study - To explore feasibility of and refine data capture instruments to inform health economic evaluation for Stage 2 of the PART study.	- Findings of the Qualitative Recruitment Investigation (QRI)

STAGE 2:

Objectives	**Outcome Measures**
Primary Objective - To compare treatment failure rates between the two treatment groups.	- Primary treatment failure as demonstrated by the need for whole gland ablation and/or secondary interventions.

Secondary Objectives - To compare the short, medium and long-term effects of both treatment arms - The effect on Quality of Life and Health Resource Utilisation of both treatment arms - The role of imaging by mpMRI and biopsy protocols in determining suitability of patients for focal therapy	- Short, medium and long-term adverse events related to treatments - Disease progression including development of metastases - Disease-specific and all-cause mortality - Quality of life using conventional questionnaires (IIEF-15, IPSS, EQ-5D-5L, FACT-P, UCLA-EPIC) - The role of imaging by mpMRI and biopsy protocols in determining the suitability of patients for focal therapy using data collected in the CRF.

5. TRIAL DESIGN

5.1. Summary of Trial Design

The PART study is a prospective, multi-centre, parallel group (1:1) randomised controlled trial to assess the clinical effectiveness and cost-utility of partial ablation (using HIFU in Stage 1 of the PART study) or RP in patients with intermediate risk, unilateral clinically localised prostate cancer. Both Stage 1 and Stage 2 will be conducted according to the aforementioned trial design. The study flow chart is shown in Appendix A, the schedule of the visits in Appendix B.

The number of visits per participant will vary and be dependent on what treatment they are allocated to. All participants will have had an mpMRI, a biopsy and targeted biopsy (if necessary) before they can be randomized.

We will evaluate Quality of Life using validated questionnaires (IIEF-15, IPSS, EQ-5D-5L, FACT-P, UCLAEPIC) that will be taken at all follow up appointments:

1. *Sexual outcomes*
    a. The presence of severe erectile dysfunction, with or without the use of phosphodiesterase-5 inhibitors, at 12 and 36 months, as measured by the erectile function domain of the IIEF-15 questionnaire in those with absence of severe erectile dysfunction at baseline
    b. The presence of any new/ progression of erectile dysfunction at 12 and 36 months, measured as an at least 6 point drop in IIEF-15 questionnaire score within the erectile function domain.
    c. Time to return of erectile function (absence of severe ED on IIEF-15 questionnaire)
    d. Need for phosphodiesterase-5 inhibitors to maintain erectile function sufficient for penetration at 36 months
    e. The presence of ejaculatory function at 12 and 36 months as measured by the orgasmic function domain of the IIEF-15 questionnaire

f. The presence of orgasmic function at 12 and 36 months as measured by the orgasmic function domain of the IIEF-15 questionnaire
g. Presence of pain during intercourse requiring premature cessation of intercourse i.e. prior to climax, at 36 months

2. *Urinary incontinence*
   a. Presence of urinary incontinence (any pad usage plus any leakage of urine) as determined by the UCLA-EPIC urinary continence questionnaire, at 12 months and 36 months, in those men with no urinary incontinence at baseline
   b. Presence of urinary incontinence (requiring any pad usage) as determined by the UCLA-EPIC urinary continence questionnaire at 12 months and 36 months
   c. Time to return of urinary continence (as determined by UCLA-EPIC Urinary domain questionnaire)

3. *Other functional outcomes*
   a. Grading of lower urinary tract symptoms as determined by IPSS scores at 12 months and 36 months
   b. Presence of bowel toxicity as determined by the UCLA-EPIC Bowel questionnaire at 12 months and 36 months
   c. Anxiety levels as measured by the Memorial Anxiety Scale for Prostate Cancer
   d. General and prostate health related QoL as measured using EQ-5D-5L and FACT-P Version 4

Patients will also be asked to complete Health Economics questionnaires (in the form of self-reported diaries) in which we will ask them to identify and record items relating to utilisation of the health care resources mentioned and any other relevant health care resources. The self reported diaries will be piloted and adapted during Stage 1 of the PART study. Stage 1Stage 1Stage 1Stage 1Stage 2

Provided Stage 1 is successful, all patients recruited will be automatically rolled into Stage 2 of the PART study.

5.2. Qualitative Recruitment Investigation

Many randomised controlled trials are challenging in terms of recruitment because of difficulties in explaining and justifying to patients concepts inherent in the design (such as randomisation and uncertainty). There is a dearth of robust evidence about effective strategies to improve recruitment to RCTs (Treweek, Mitchell et al. 2010). However, qualitative research has been used to understand recruitment in specific RCTs (de Salis, Tomlin et al. 2008, Howard, de Salis et al. 2009, Wade, Donovan et al. 2009, Mills, Donovan et al. 2011, Paramasivan, Huddart et al. 2011) and has been shown to improve recruitment in some cases (Donovan, Mills et al. 2002, Donovan, Lane et al. 2009).

A qualitative recruitment investigation (QRI) will be integrated into Stage 1 of the PART study. The methods to be used were developed initially in the ProtecT study by the applicants (Donovan, Mills et al. 2002, Donovan, Lane et al. 2009), and have subsequently been used and refined in completed research with six other RCTs and are currently being further developed in collaborative research with five RCTs in feasibility phases. This research is being undertaken, led by Donovan, under the aegis of the MRC ConDuCT (Collaboration and Innovation in Difficult and complex RCTs) Bristol methodology hub.

The aim of the QRI is to understand the recruitment process and how it operates in clinical centres, so that sources of recruitment difficulties can be identified and suggestions made to change aspects of design, conduct, organisation or training that could then lead on to improvements in recruitment. The QRI will be undertaken in two stages:

Stage I: understanding recruitment

The aim of Stage I is to understand the recruitment process as it occurs. There are several distinct parts that can provide information about recruitment as it happens, where we can identify and investigate the sources of recruitment difficulties.

1. Patient pathway through eligibility and recruitment

A comprehensive process of logging of potential RCT participants through screening and eligibility phases will be undertaken to provide basic data about levels of eligibility and recruitment, and identify points at which patients opt in or out of the RCT.

2. In-depth interviews

In-depth, semi-structured interviews will be conducted and audio-recorded with:

(a) Members of the TMG, including the CI and those most closely involved in the design, management, leadership and coordination of the trial

(b) Clinical and recruitment staff across the four pilot clinical centres.

(c) Participants eligible for recruitment to the RCT, including those who accept or reject randomisation.

3. Audio-recording of recruitment appointments

Recruitment staff will be requested to audio-record appointments where they provide information to patients and attempt to recruit them to the RCT. The QRI researcher will listen to appointments, document relevant details and provide an account to be fed back to the RCT CI anonymously.

Stage II: Feedback to CI/TMG and plan of action

The QRI researcher will present summaries of anonymised findings to the RCT CI (and TMG, if agreed by CI), identifying the factors that appear to be hindering recruitment with supporting evidence. If the CI/TMG agree that particular factors are amenable to change, a plan of action will then be drawn up to try to improve recruitment. The plan for the RCT and the activities of the QRI researcher will be focussed on the issues emerging from the QRI. It is likely that some aspects will be generic, such as how to explain randomisation and deal with patient preferences and issues related to the differences between the treatments in the PART study. In previous studies, the action plan has included: re-drafting of study information, advice about presenting the study, and changing aspects of organisation in clinical centres. In previous studies, these have been addressed by new Patient Information Leaflets, changes to the protocol, or training for recruiters. Aspects of relevance to the PART trial will be elicited and implemented through the QRI.

Evaluation of the impact of the plan

Numbers of eligible patients, and the percentages of these that are approached about the RCT, are deemed eligible, consent to be randomised and immediately accept or reject the allocation will be assessed before the plan of action is implemented, and we will regularly check after implementation

whether rates are improving. Interviews with recruiters will ask about the acceptability of the QRI and any changes that occur.

5.3. Economic evaluation

The primary purpose of the health economic evaluation is to assess the resource utilization, cost impact and cost-effectiveness in terms of cost per quality adjusted life year (QALY) of treating prostate cancer patients using partial ablation therapy compared with RP. In Stage 1 of the PART study the aim is to explore the methods and feasibility of data capture instruments.

The cost analysis will adopt an NHS perspective. Data on health care resource use related to prostate cancer, 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, use of emergency departments, tests and equipment. Protocol-driven costs will be omitted. Where possible data on resource utilisation will be collected from electronic patient records or as documented in the trial CRF's, although it is likely that some resources will not be routinely documented in electronic format and data extraction from the medical notes will be supplemented by a resource utilisation questionnaire filled out by the patients. Patients will be asked to complete the diaries (for the period from 0-6 weeks, 6 weeks to 3 months, 3-6 months and 6-12 months and every 6 months thereafter) in which we will ask them to identify and record items relating to utilisation of the health care resources mentioned and any other relevant health care resources. These questionnaires will be designed and piloted and adapted during Stage 1 of the study.

Where possible, we will value our items on health care resource utilisation using appropriate unit costs obtained from published sources, including the most recent version of Unit Costs of Health and Social Care and NHS Reference Costs. We will estimate unit costs, which are not available from secondary sources using the approach used in the most recent version of Unit Costs of Health and Social Care.

Primary endpoint data will be collected within the trial. NICE recommends the use of preference-based health-related quality of life (HRQL) measures for the purpose of determining QALYs for economic evaluation. The use of QALY's aims to capture the impact of disease progression and non-fatal events on QoL in addition to any impact on survival.

The EQ-5D-5L will be used to measure patient health-related QoL at baseline, 6 weeks and every 3 months for the first year and every 6 months thereafter. 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 new algorithm based on the UK value set currently being conducted by the Euroqol Group, (if available at the time of analysis). If not available, the current crosswalk algorithm provided by the EuroQol group and algorithm estimated by Dolan *et al.* (derived from a survey of the UK population (n=3337)) will be used. Utility values in the tariff set range from no problems on any of the five dimensions in the EQ-5D descriptive system (value=1.0) to severe or extreme problems across all five dimensions (value=−0.594) (Dolan, Gudex et al. 1996, Dolan 1997). The utility scores will be combined with within-trial survival data to estimate the QALY's required for the cost-utility analysis.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Participants must have been diagnosed with intermediate risk, unilateral clinically localised prostate cancer and be fit for either radical surgery (RP) or partial ablation of the prostate.

6.2. Inclusion Criteria

- Men with unilateral clinically significant **intermediate risk** prostate cancer or dominant unilateral clinically significant intermediate risk & small contralateral low-risk disease:
    - Gleason grade score 7 (3+4 or 4+3)
    - High volume Gleason grade score 6 (> 4mm cancer core length)
    - PSA ≤ 20 ng/ml
    - Clinical ≤ T2b disease
- Life expectancy of ≥10 years
- Fit, eligible and normally destined for radical surgery
- No concomitant cancer
- No previous treatment of their prostate cancer
- An understanding of the English language sufficient to understand written and verbal information about the trial, its consent process and the study questionnaires

6.3. Exclusion Criteria

- Unfit for radical surgery
- Significant bilateral disease
- **Low risk** disease [Gleason score 6 or less, PSA 10ng/ml]
- **High risk** disease [Gleason score 8 or greater, PSA >20ng/ml]
- Clinical T3 disease
- Men who have received previous active therapy for prostate cancer
- Men with evidence of extra prostate disease
- Men with an inability to tolerate a transrectal ultrasound
- Men with latex allergy
- Men who have undergone a Transurethral Resection of the Prostate (TURP) for symptomatic lower urinary tract symptoms within 6 months.
- Metal implants/stents in the urethra
- Prostatic calcification and cysts which interfere with effective delivery of HIFU
- Men with renal impairment and a GFR <35ml/min
- Unable to give consent to participate in the trial as judged by the attending clinicians

7. STUDY PROCEDURES

The patient pathway is shown in Appendix C.

7.1. Screening and eligibility assessment

The dedicated research nurse or clinician will take a leading role in identifying appropriate patients. Potential participants will be identified at the MDT, where histopathological data will be discussed. Men with a histological diagnosis of intermediate risk prostate cancer following a biopsy and mpMRI, and evidence of unilateral disease will be assessed for the PART study.

Some patients may have to have a targeted biopsy to confirm unilateral disease.

7.2. Recruitment

Once confirmed as eligible for the study, patients will be approached at joint Oncology clinics in the centres and provided with written details of the study in the form of a Patient Information Leaflet (PIL). The PIL will detail the exact nature of the study, what it will involve for the patient; the implications and constraints of the protocol and the known side effects and any risks involved in taking part. If they fulfil all the entry criteria for the study, they will be invited to attend an information appointment to discuss the treatment options and the PART study in detail. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason 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 patient and their clinical team. Patients will have ample time to discuss the study with family, friends and their GP (it is typically around 6-weeks between MDT discussion, counselling and then randomisation).

Using qualitative research methods, as refined within the ProtecT study, nurse-led counselling to optimise recruitment will be developed. The reflective nature of the QRI element of the study also means that methods employed by the research nurses to counsel and recruit potential participants will be subject to change and improvement if new methods are identified by the QRI researcher. If a patient is not eligible for the PART study, they will be informed by their doctor, who will go through their treatment options with them.

7.3. Informed Consent and randomisation

Informed consent will be obtained by a trained trial Nurse, the Consultant Urologist responsible for the patient, or another appropriately qualified member of the research team. A copy of the signed Informed Consent will be given to the participant, a copy will be sent to the PART Offices and a copy will be kept in the patient's hospital notes. The original signed form will be retained at the study site, in the site file. During Stage 1 of the PART study, patients will also be given the Qualitative Recruitment Investigation (QRI) Patient Information Leaflet. Patients will be asked for their permission to have all of the appointments where their treatment options are discussed audio-recorded, until they have chosen whether to join the PART study.

If patients agree to this, they will be asked to sign a QRI consent form. Staff involved in recruiting patients into PART will also be requested to sign a consent form.

Eligible patients will be randomised using the web based secure randomisation system provided by the Oxford Clinical Trials Research Unit (OCTRU). In the feasibility study, we aim to recruit 100 patients over a period of 18 months. In Stage 2 of the PART study we aim to recruit a further 600-800 patients.

7.4. Baseline Assessments (at screening visit)

- Review of medical history and Physical Examination, including digital rectal examination and routine blood tests
- Completion of validated patient questionnaires (refer to Appendix B)
- PSA blood test

7.5. Intervention

Once participants accept their allocation, treatment should, if possible, be delivered within 8 weeks from randomisation. Those participants randomised to RP will be listed for surgery optimally within two weeks of randomisation, and no longer than two months following randomisation. For those participants randomised to PA, following the biopsy there is a mandatory four-six week rest period to allow swelling and inflammation to settle in the prostate. This rest period should be sufficient to maintain patients within national cancer treatment targets. This will be co-ordinated by local investigators and study research nurses.

7.6. Subsequent Visits

In patients randomised to RP:

1. Routine removal of catheter at **10-14 days**
2. Follow up in the clinic at approximately **six weeks** post-surgery as per routine NHS care. Patients will have had a PSA test prior to their follow-up appointment, the result of which should be available. Quality of life questionnaires will be presented to the patient (see Appendix B).

Followed up in the clinic approximately every **three months** post-surgery in the first year and then approximately every **6 months** as per routine NHS care for 3 years (See Appendix B). Patients will have had a PSA test prior to their follow-up appointment, the result of which should be available. Quality of life questionnaires will be presented to the patient (see Appendix B) If at any point disease progression is suspected (rising PSA ≥0.2) the patient will be restaged.

In patients randomised to PA:

1. Routine removal of catheter at **7 days**
2. **For sites new to performing HIFU, a study specific mpMRI should be performed on the first 5 patients at 2 weeks. These will be centrally reviewed within the Partial Ablation working group.**
3. Followed up routinely at approximately **six weeks** post-surgery as per routine NHS care. Patients will have had a PSA test prior to their follow-up appointment, the result of which should be available. Quality of life questionnaires will be presented to the patient (See Apendix B).
4. Followed up in the clinic approximately every **three months** post-surgery for the first year and then approximately every **6 months** as per routine NHS care for 3 years. Patients will have had a PSA test prior to their follow-up appointment, the result of which should be available. Quality of life questionnaires will be presented to the patient (See Apendix B).
5. Standard care includes an mpMRI at **twelve months**
6. Standard care includes transrectal biopsies at **twelve months**
7. Standard care includes an mpMRI at **three years**
8. Standard care includes transrectal biopsies at **three years**

7.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. All participants will continue to be followed up as per routine NHS standard of care.

7.8. Treatment failure

Radical prostatectomy

In patients receiving RP, primary treatment failure will be defined as a rising serum PSA level reaching ≥0.2ng/ml following initial reduction to <0.1ng/ml after surgery; or a failure of serum PSA to reach the level of <0.1ng/ml after surgery; or clinical progression to local recurrence/systemic disease.

Partial ablation

In patients receiving PA, primary treatment failure will be determined by a combination of repeat prostate biopsies, serum PSA levels and clinical appearance of symptoms/signs suggesting disease progression. Prostate biopsies following PA will determine one of five defined scenarios:

1. negative biopsies, in which case the patient will continue to be followed-up as described;
2. positive biopsy in the originally treated area, in which case the patient will be allowed one additional HIFU treatment before the treatment is classed as having failed;;
3. positive biopsy in the untreated area demonstrating a new focus of intermediate risk disease, in which case the patient will be offered additional partial ablation in this area.
4. positive biopsies in any 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 as described;
5. positive biopsy following 2 consecutive treatments in any area of the prostate, in which case the treatment will be deemed as having failed.

If follow-up biopsies demonstrate high-risk disease at any point, this will be considered as primary treatment failure and patients will be offered whole gland treatment according to standard of care.

In the presence of primary treatment failure as described above, the patient will be re-staged using pelvic cross-sectional imaging. Patients will be fully informed of their disease status, grade, clinical stage and the treatment options, such as salvage external beam radiotherapy. Regardless of decisions about additional interventions, patients will continue to be followed up and analysed within the trial in accordance with 'intention-to-treat', with full documentation of subsequent treatments.

7.9. Definition of End of Study

The end of the trial will be when the last participant has been contacted to arrange their final follow-up visit, whether or not the visit takes place.

The trial will be stopped prematurely:

- If mandated by the Ethics Committee;
- following recommendations from the Trial Steering Committee (TSC);
- If review of safety data suggests 1 arm has significant disadvantages to the extent that patient safety is endangered, compared to known standard outcomes for each treatment arm.

The Research Ethics Committee (REC) will be notified in writing if the trial has been concluded or terminated early.

8. INTERVENTIONS

Patients will be randomised to either Partial Ablation (PA) using HIFU or Radical Prostatectomy (RP).

8.1. Treatment with Radical Prostatectomy

Patients randomised to RP will receive this in the form of open, laparoscopic or robot-assisted procedure, according to local centre expertise and clinical judgement. Patients undergoing RP will be listed for surgery optimally within 2 weeks, and no longer than 2 months, unless requested otherwise by the patient.

8.2. Treatment with HIFU focal ablation procedure

HIFU is a relatively new treatment option for patients with prostate cancer and there is some variation in HIFU delivery across sites. In the PART study, patients randomised to the partial ablation arm will have a mandatory 4-6-week rest period following biopsies to allow swelling and inflammation to settle in the prostate, to lower the risk of side effects such as rectal damage. Patients will then be admitted on the day of the procedure or the evening before as appropriate. A phosphate enema will be administered on the morning of surgery to ensure an empty rectum. The type of anaesthesia (regional/ general) will be discussed with the patient and depend on the anaesthetic opinion. The type of anaesthesia chosen will aim to eliminate any patient movement during HIFU treatment to avoid any adverse complications. 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 120-160mg of intravenous Gentamicin will be given as antibiotic prophylaxis. A suprapubic catheter will be inserted under cystoscopic guidance before the proposed HIFU treatment. The skin surrounding the supra-pubic entry site should be infiltrated with 10-20cc Bupivucaine 0.5%. The catheter will be placed on gentle traction during the procedure in order to avoid haematuria by strapping to the thigh with adhesive bandage. Should haematuria be evident at the end of the procedure a urethral catheter can be placed to irrigate the bladder whilst in recovery.

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 as per the manufacturer's instructions. The probe is covered with a latex protector and primed with degassed water. The HIFU probe is then lubricated with degassed lubricant gel. About 10 to 20mls of this same gel is placed within the rectum. At this point a gentle dilatation of the anus is sometimes required. This is done using one or two digits. Once this is done the probe is introduced into the rectum with as little trauma as possible. Views of the prostate are then obtained to ensure that the images are of high quality and that the proposed therapy is technically feasible. Please refer to the additional Trial Specific Instructions (TSI) relating to the HIFU treatment/re-treatment strategy and training of HIFU clinicians.

9. SAFETY REPORTING

9.1. Definition of Serious Adverse Events

A serious adverse event 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.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

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.

9.2. Reporting Procedures for Serious Adverse Events

Trial centres will use a standardised safety reporting form to inform the Trial Manager of serious adverse events within twenty-four hours of becoming aware of them (initial report). SAEs which may be linked to trial procedures and are unexpected will be recorded as Suspected Unexpected Serious Adverse Reactions (SUSARs) until the end of the study.
Other adverse events which may be linked to trial procedures, but not deemed to be serious, will be recorded as Adverse Reactions (ARs). The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form. All SAEs, SUSARs and ARs will be reviewed by the Chief Investigator, to determine whether the SAE is *related* and *unexpected* as defined by the NRES guidance.

The trial co-ordinating centre is responsible for reporting SAEs, where appropriate, to the Sponsor and ethics committee within required timelines. An SAE occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form. OCTRU safety reporting procedures will be followed at all times.

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

Stage 1:
Stage 1 of the PART study aims to randomise 100 men from 4 centres starting in January 2015, and to achieve an uptake of consent and randomisation of 50% of eligible patients who are invited to take part.

Stage 2:
If Stage 1 is successful, we will apply to the HTA for additional funding with the aim of recruiting a further 600-800 additional patients over 5 years (Stage 2) in participating centres (minimum 10) with appropriate skill mix. We will review the statistical power calculations in the light of information from the first 100 patients – in particular, the true incidence of unilateral disease qualifying for PA, the comparative quality of life scores, and primary treatment failure rates. A pragmatic decision will then be made on the final recruitment target. We anticipate that QoL will be better with ablative therapy than radical surgery, particularly functional outcomes such as urinary continence and erectile function, such that an increase of 10% in the primary treatment failure rate (i.e. 25% increased to 35%) might well be considered acceptable to underpin a change in clinical practice. Even allowing for a 10% drop-out rate, 800 randomised 1:1 between PA and RP would provide 80% power at $2p<0.05$ to detect a 10% worse treatment failure rate with ablative therapy than radical surgery. If primary treatment failure rates were substantially more than 10% higher with PA than RP then this would be detected with high statistical power enabling a good point estimate of the difference and meaningful subgroup investigations to identify any patient or tumour characteristics that were predictive of treatment failure.

10.2. The Number of Participants

Stage 1 of the PART study aims to randomise 100 men with a histological diagnosis of unilateral intermediate risk prostate cancer following a biopsy and mpMRI,between partial ablation of the prostate or RP. If Stage 1 is successful, we aim to randomise a further 700 patients in Stage 2 of the study, though this sample size may be amended in the light of Stage 1.

10.3. Analysis of Outcome Measures

Time to primary treatment failure will be analysed by standard logrank methods. Dichotomous variables (such as presence absence of erectile dysfunction) and ordinal variables (such as toxicity grades) will be analysed using Mantel-Haenszel tests. Continuous outcome measures such as quality of life scores will be analysed using independent t-tests or repeated measures regression techniques.

<u>Analysis of healthcare resource use, cost and EQ-5D data - Stage 1</u>
The purpose of the economic analysis in Stage 1 of the PART study is to evaluate the response rate and completion rates of the resource use questionnaires and EQ-5D-5L instrument and to assess the feasibility and usefulness of the self-reported patient resource use diary compared with electronic patient-data capture. A preliminary analysis of the resource-use data and cost-consequence analysis will be used to update the sample size calculations required for Stage 2 of the PART study.

<u>Analysis of healthcare resource use, cost and EQ-5D data - Stage 2</u>

Missing data:
The resource-use/cost and EQ-5D data 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 (Rubin and Schenker 1991, Briggs, Clark et al. 2003). The focus of studying the healthcare resource use is to investigate how partially ablative therapies in prostate cancer patients affect the health care costs. With the aim of the economic analysis to estimate how the costs of the intervention minus the difference in health care costs between the intervention and standard treatment (radical prostatectomy) group of patients balances against the health care benefits. An in depth analysis of the healthcare resource use and their costs will be conducted. First the impact of the partially ablative therapies on prostate-cancer specific healthcare 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 surgery. Secondly, a regression

framework that relates healthcare costs to baseline characteristics (age, disease stage), progression, side-effects, other co-morbidities and treatment type will be developed. The objective being to provide estimates of healthcare costs for different treatment types, side-effects and disease stages to inform the extrapolation model (see below). A similar regression framework approach will be used for the EQ-5D tariff data at the different data collection time-points, again to inform the extrapolation model.

Within-trial cost-effectiveness analysis:

The economic evaluation will compare the implementation of partially ablative therapy with standard radical surgery for prostate cancer patients. We plan to conduct a within-trial economic analysis, then if the trial demonstrates clinical effectiveness, these within trial results will be used to extrapolate beyond the trial endpoint and model the likely life-time cost-effectiveness. A within-trial cost-consequence analysis will initially be reported, describing all the important results relating to the health care resource use, costs and consequences (side-effects, disease progression, recurrences) of partially ablative therapy compared with radical prostatectomy for prostate cancer patients. Subsequently, a within-trial cost-utility analysis will determine cost per quality-adjusted life year (QALY) gained. The use of QALY's aims to capture the impact of disease progression and non-fatal events on health-related quality of life in addition to any impact on survival. This is particularly pertinent to this trial where we are trying to evaluate the trade-off between an improved quality of life due to reduced side-effects with the increased possibility of recurrence. Discounting at a rate of 3.5% will be applied. 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. Non-parametric bootstrapping and probabilistic sensitivity analysis will explore uncertainty in the confidence placed on the results of the economic analysis and cost effectiveness acceptability curves will be presented.

Lifetime cost-effectiveness analysis:

If trial results demonstrate clinical effectiveness, extrapolation beyond the trial period of 78 months will be undertaken. The methods used will depend on the within trial data, but will either use parametric methods as set out by the NICE Decision Support Unit (Latimer 2011) or use a lifetime decision-model, in order to determine the long-term cost-effectiveness of the intervention in terms of cost per QALY gained. 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 take into account health care costs and longer term social care costs and the impact on life expectancy, quality adjusted life expectancy. The model will be run over remaining patient lifetime, with costs and benefits discounted at a rate of 3.5%. The lifetime cost-effectiveness analysis will be driven by the decision analytic model and the way treatment effects are propagated in the model. Extensive deterministic sensitivity analysis will be undertaken to assess the impact of changing the values of key parameters and will be used to explore the importance of modelling assumptions. Probabilistic sensitivity analyses will be conducted to deal with uncertainty in model parameters and cost-acceptability curves presented.

11. DATA MANAGEMENT

A Data Management Plan (DMP) will be in place for the trial, according to OCTRU's DMP template.

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2. Data Recording and Record Keeping

The patient data will be entered onto a validated installation of OpenClinica (www.openclinica.com), the data is held in a Postgres database and can only be accessed by authorised users via the OpenClinica application. The OpenClinica application resides on a webserver hosted and managed by Oxford University's Medical Services Division IT Services department (http://www.imsu.ox.ac.uk/). The server is on the university's backbone network and is backed up nightly to a secure off-site location. Consent will be obtained from the patients to be able to share information and prior to sharing, data will be anonymised. In addition, any indirect identifiers that may lead to deductive disclosures will be removed to reduce the risk of identification. After closure of the trial and data analyses, the data will be made publicly available at the time of publication. The data types obtained will be preserved for 10 years from the end of the study. Paper resources will be archived.

12. QUALITY ASSURANCE PROCEDURES

PART will be conducted in accordance with the standard operating procedures of the UCKRC registered unit overseeing the study. A risk assessment will be undertaken of the trial and a proportionate monitoring plan will be put in place to decide on the extent and nature of any on-site monitoring. Central monitoring of incoming data and operational aspects of the trial will be done by the CTU according to a written plan.

To ensure quality standards of care across all participating sites in PART, all clinicians performing procedures in the study will be asked to complete a **case audit** which will be independently reviewed. The following working groups have also been established:

Partial Ablation Working Group
As HIFU is a relatively new technology, proctoring is important. A separate consensus document will be implemented, outlining the necessary steps to ensure that treatment is delivered to a high standard across all sites in PART.

Surgery Working Group
This Group will be responsible for auditing outcomes and exchanging experiences of operating on patients who have received HIFU. They will also act as an oversight group within the study.

Radiology Working Group
The current radiological pathway has changed significantly over the last few years. mpMRI is now being widely used in sites, however the reporting and multi-parametric aspect of these MRI scans may differ from site to site. As such, this group will be responsible for ensuring a consensus document is written to ensure radiological reporting continuity in PART. From time to time, a selection of mpMRI scans may be centrally reviewed within the Working Group.

Pathology
Routine histopathological evaluation will be performed by local pathology departments. The pathology reports and slides will be centrally reported for additional paramaters not routinely reported.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

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

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with International Conference of Harmonisation Principles Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information leaflet and any proposed advertising material will be submitted to the Research Ethics Committee (REC) for approval.

The Chief Investigator will submit and, where necessary, obtain approval from the REC for all amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study, or on request, a progress report to the REC Committee, the funder and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

We will record the patients' names and NHS numbers for the long-term follow-up using NHS IC data. Only dedicated trial staff will have access to those data. Patients will be informed and asked to consent to this prior to joining the study. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

14. FINANCE AND INSURANCE

14.1. Funding

The study is funded by HTA NIHR, project ref: 12/35/54

14.2. Insurance

The University has indemnity insurance 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 which is provided.
NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by HTA NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Results of the pilot and later main study if undertaken will be disseminated in the form of national and international presentations at learned societies, and published in abstract and full manuscripts in peer-reviewed journals. In particular results of the Qualitative Research Investigation will be shared with our patient representatives and co-applicants, to inform the main study if appropriate. This study should produce a definitive document for publication by the HTA programme. Sub-analyses of interest will be published in the appropriate peer reviewed journals.

16. Conflict of Interest:

M Emberton is consultant to: GSK, Sanofi Aventis, Jensen, STEBA Biotech, AMD, USHIFU. He provides research support to: GSK, Sanofi Aventis, STEBA Biotech, AMD, USHIFU and he is Medical Director to Mediwatch PLC. M Emberton is a shareholder in Nuada Medical Group.
HY Ahmed has been paid by UKHIFU/USHIFU for proctoring to other centres and they have paid travel and personal reimbursement for lectures in Europe and the US. USHIFU currently fund a multicentre trial with the grant held at UCLH. Angiodynamics (distributors of Electroporation device, Nanoknife) have given a loan machine and probes to conduct a prospective development study at UCLH. He has no shares/equities/medical consulting relationships with any of the above or other companies.
None of the other investigators have any conflicts of interest.

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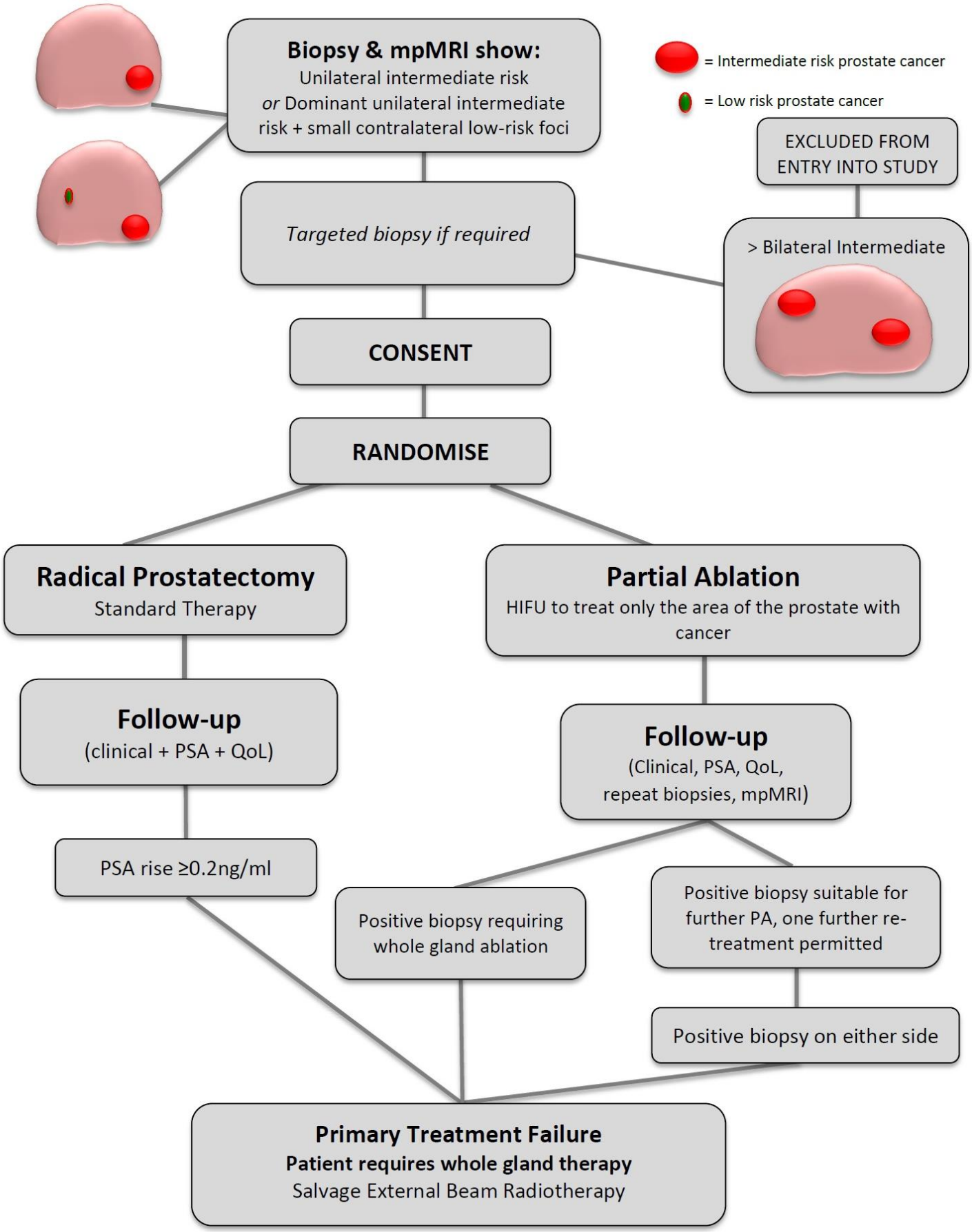
18. APPENDIX A: STUDY FLOW CHART



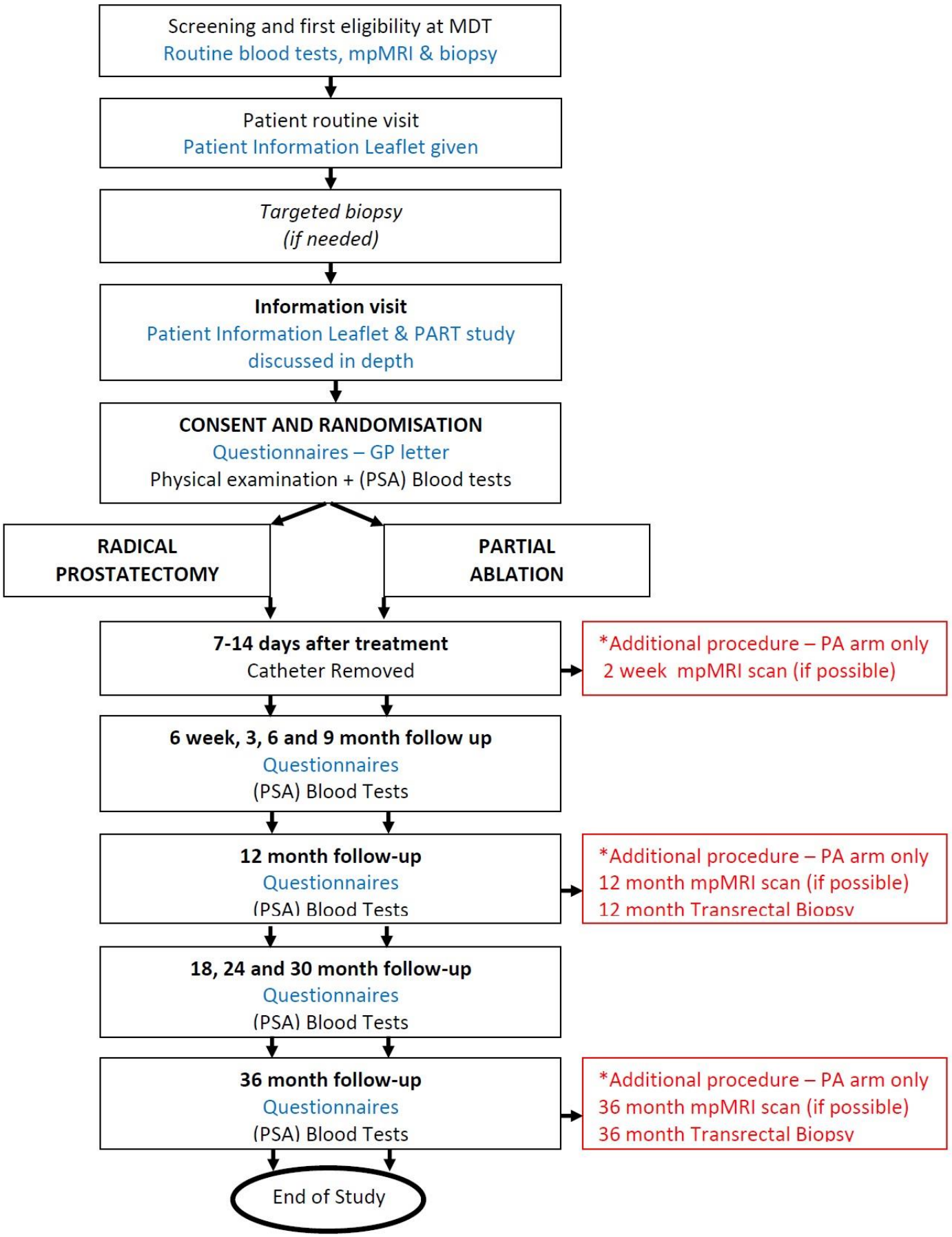
19. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

VISITS	1	2	4 (procedure)	5	6	7	8	9	10	11	12	13	14
DAY/MONTH			**Day 0**	**Day 7-14**	**6W**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**	**30M**	**36M**
Give patient PART Patient Information Leaflet (PIL)	X												
Give patient Qualitative Recruitment Investigation PIL & Consent Form	X												
Add patient to screening log	X												
Targeted biopsy (if needed)	X												
PART PIL & Consent Form re-given (if necessary)		X											
Informed Consent		X											
Inclusion criteria		X											
Exclusion criteria		X											
Patient History		X											
Examination		X											
Routine blood tests		X											
PSA blood test		X			X	X	X	X	X	X	X	X	X
Randomisation		X											
Screening log updated		X											
Partial Ablation (ARM 1) or Radical Prostatectomy (ARM 2)			X										
Catheter removal				X									
MRI (HIFU ONLY)				X*					X				X
Biopsy (HIFU ONLY)									X				X
Adverse event reporting			X	X	X	X	X	X	X	X	X	X	X
IIEF-15 Questionnaire		X			X	X	X	X	X	X	X	X	X
IPSS Questionnaire		X			X	X	X	X	X	X	X	X	X
UCLA-EPIC Questionnaire		X			X	X	X	X	X	X	X	X	X
EQ-5D-5L		X			X	X	X	X	X	X	X	X	X
FACT-P Version 4		X			X	X	X	X	X	X	X	X	X
The Modified 18-term Memorial Anxiety Scale Questionnaire		X			X	X	X	X	X	X	X	X	X
Resource Utilisation Questionnaire (patient diary)			X		X	X	X	X	X	X	X	X	

X - Additional visit for MRI and biopsy - for PA arm only

*2 week MRI only required for the first 5 HIFU patients in sites new to performing HIFU.

20. APPENDIX C: PATIENT PATHWAY



21. APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	08Dec2014	Steffi le Conte	Changes as per REC's request.
2	3.0	02Nov2015	Steffi le Conte	1. Further detail regarding the diagnostic pathway of prostate cancer patients (section 3.2). 2. Additional exclusion criteria 'clinical T3 disease' (section 6.2). 3. HIFU treatment failure definition clarification (section 7.8).