A Multi-Centre Prospective Single Arm Intervention Trial Evaluating Focal Therapy using High Intensity Focused Ultrasound (Sonablate 500) for Localised Prostate Cancer

Study Protocol

Short Title: Focal Therapy for Prostate Cancer using HIFU

INDEX Study Group

Protocol code

Version 4

Date 14th April 2011
1. Study Group

Chief Investigator
Professor Mark Emberton

Co-Principal Investigator
Mr Hashim Uddin Ahmed

Co-investigators (UCLH/UCL)
Dr Clare Allen  
Dr Julie Barber  
Mr Paul Cathcart  
Miss Louise Dickinson  
Dr Alex Freeman  
Dr Charles Jameson  
Dr Alex Kirkham  
Mrs Caroline Moore

Study Co-ordination Centre
University College London Hospitals  
NHS Foundation Trust

Study Co-ordinator:
Miss Louise Dickinson

Address:
Department of Urology,  
Ground Floor, 250 Euston Road,  
London, NW1 2PG

E-mail: misslouisedickinson@gmail.com  
Tel: 0207 380 9194  
Fax: 0207 380 9303

Project Research Nurse
Jane Coe and Helena Stone  
Department of Urology,  
Ground Floor, 250 Euston Road,  
London, NW1 2PG

Project Manager
TBC

Participating Centres (TBC)
University College London Hospital NHS Foundation Trust  
Basingstoke and North Hampshire NHS Foundation Trust  
Imperial College Healthcare NHS Trust  
Jewish General Hospital, McGill University, Montreal, Quebec, Canada  
Oxford Radcliffe Hospitals NHS Trust  
Royal Marsden NHS Foundation Trust  
University Hospitals Bristol NHS Foundation Trust

Sponsor
University College London  
(Separate sponsorship for Canadian centre)
**Sponsor representative**
David Wilson  
Joint UCLH/UCL Biomedical Research Unit, 1st Floor Maple House, 149 Tottenham Court Road, London W1T 7NF.

Postal address:  
Joint UCLH/UCL Biomedical Research and Development (R&D) Unit, (1st Floor, Maple House), Ground Floor, Rosenheim Wing, 25 Grafton Way, London WC1E 6DB.

**Signatures**  
The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

**Chief investigator**  
Mark Emberton, Professor of Interventional Oncology and Consultant Urological Surgeon  
UCL/UCLH

SIGNATURE

DATE

**Sponsor**  
David Wilson, Research & Development, 1st Floor, Maple House, 149 Tottenham Court Road, London, W1T 7DN, UCL

SIGNATURE

DATE
**Trial Steering Committee and Data Monitoring Committee**

**Independent Chair**  
Dr John Fowler, Pelican Cancer Foundation

**Investigator members (TBC)**  
Professor Mark Emberton  
Mr Hashim U Ahmed  
Dr Julie Barber  
Dr Franck Bladou  
Mr Tom Leslie  
Miss Louise Dickinson  
Mr Richard Hindley  
Mr Chris Ogden  
Mr Raj Persad  
Mr Matthias Winkler

**Service User Representatives**  
Dr Michael Ford  
Dr Morton Schatzman

---

### 2. Details of healthcare professionals involved in the study from the host centre and academic collaborators (alphabetical order)

**University College London Hospitals NHS Foundation Trust/ University College London (Sponsor)**

- Mr Hashim Uddin Ahmed - MRC Research Fellow/ SpR in Urology
- Dr Clare Allen - Consultant Radiologist
- Dr Julie Barber – Lecturer in Statistics
- Mr Paul Cathcart – NIHR Clinical Lecturer/ SpR in Urology
- Miss Louise Dickinson – Clinical Research Fellow and NIHR Academic SpR
- Professor Mark Emberton - Reader and Consultant Urological Surgeon
- Dr Alex Freeman - Consultant Histopathologist
- Dr Charles Jameson – Consultant Histopathologist
- Dr Alex Kirkham - Consultant Radiologist
- Mrs Caroline Moore – Clinical Lecturer/ SpR in Urology

**Jewish General Hospital, McGill University, Montreal, Quebec, Canada**

Dr Franck Bladou – Chief Urologist, Department of Urology

**Department of Public Health, Erasmus MC, Rotterdam, Netherlands**

Professor Ewout Steyerberg - Professor of Medical Decision Making and Research Methodology

**Department of Urology, Memorial Sloan Kettering Cancer Centre, New York**

Professor John Mulhall – Professor of Urology and Director of Male Sexual Health
# Table of Contents

1. Study Group ................................................................................................................. 2
2. Details of all healthcare professionals involved in the study (alphabetical order) ....4
3. List of Abbreviations ........................................................................................................ 6
4. Study Protocol Summary .................................................................................................. 7
5. Summary .......................................................................................................................... 9
6. Prostate Cancer: Background .......................................................................................... 10
   6.1 Standard care
6.2 Focal therapy
6.3 Multifocal versus unifocal/unilateral disease
6.4 Disease detection and localization
6.5 High intensity Focused Ultrasound
6.6 Focal therapy trials
6.7 Outcomes in Focal Therapy Trials
6.8 The rationale for a multicentre prospective single arm intervention study
6.9 Cost effectiveness modelling
7. Specific Aims of the study ............................................................................................... 31
   7.1 Research question
   7.2 Objectives
   7.3 Outcome measures
8. Study Design ................................................................................................................... 36
   8.1 Verification stage
   8.2 Intervention stage
   8.3 Training and quality control
9. Study Group ..................................................................................................................... 47
   9.1 Eligibility
10. Trial Flow ....................................................................................................................... 49
11. Individual Study Visits ................................................................................................... 50
   11.1 Visit schedule
   11.2 Follow-up details
12. Evaluation of Safety and Tolerability ............................................................................ 56
   12.1 Adverse Event Monitoring
   12.2 Adverse Event Definitions
   12.3 Adverse Events Information Collection
   12.4 Serious Adverse Events (SAE) Reporting
13. Data collection ................................................................................................................ 58
14. Discontinuation of Study ............................................................................................... 59
   14.1 Study Discontinuation by the Sponsor
   14.2 Study Discontinuation by the Chief Investigator
   14.3 Discontinuation of Study for an Individual Centre
   14.4 Discontinuation of Study for an Individual Patient
15. Statistical considerations ............................................................................................... 60
   15.1 Sample size
   15.2 Statistical analysis
16. Reporting and dissemination of results ......................................................................... 64
17. Liabilities and Insurance ............................................................................................... 64
18. Ethics .............................................................................................................................. 65
19. References ...................................................................................................................... 66
### 3. List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNI</td>
<td>Bladder Neck Incision</td>
</tr>
<tr>
<td>CISC</td>
<td>Clean Intermittent Self Catheterisation</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest X Ray</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Dynamic Contrast Enhanced Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>DW-MRI</td>
<td>Diffusion Weighted Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ERSPC</td>
<td>European Randomised Study of Screening for Prostate Cancer</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>HIFU</td>
<td>High Intensity Focused Ultrasound</td>
</tr>
<tr>
<td>ICS</td>
<td>International Continence Score</td>
</tr>
<tr>
<td>IIEF</td>
<td>International Index of Erectile Function</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiotherapy</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prostate Symptom Score</td>
</tr>
<tr>
<td>LREC</td>
<td>Local Research Ethics Committee</td>
</tr>
<tr>
<td>mpMRI</td>
<td>Multi-parametric Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MRSI</td>
<td>Magnetic Resonance Spectroscopic Imaging</td>
</tr>
<tr>
<td>PCa</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>PIN</td>
<td>Prostate Intraepithelial Neoplasia</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate-Specific Antigen</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>TPM</td>
<td>Transperineal Template Mapping Prostate Biopsies</td>
</tr>
<tr>
<td>TRUS</td>
<td>Transrectal Ultrasound</td>
</tr>
<tr>
<td>TURP</td>
<td>Transurethral Resection of the Prostate</td>
</tr>
</tbody>
</table>
4. Study Protocol Summary

<table>
<thead>
<tr>
<th>Study title</th>
<th>A Multi-Centre Prospective Single Arm Intervention Trial Evaluating Focal Therapy using High Intensity Focused Ultrasound (Sonablate® 500) for Localised Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol code</td>
<td>To evaluate medium term cancer control, genitourinary, rectal and overall health-related quality of life outcomes, and to model potential cost effectiveness of focal therapy for localised prostate cancer using HIFU</td>
</tr>
<tr>
<td>Objective</td>
<td>Study type: Single arm (Phase II) therapeutic confirmatory Study population: Men with histologically proven localized low to intermediate prostate cancer (PSA &lt;/=15ng/ml, Gleason ≤4+3, T1-T2cN0M0 disease). Sample size: 140 patients Duration of follow up: 38 months follow-up post treatment Test Product: Sonablate 500 (Focus Surgery, Indianapolis, IN, USA)</td>
</tr>
<tr>
<td>Study type</td>
<td>Other participating centres (at commencement of trial): - Basingstoke and North Hampshire NHS Foundation Trust - Imperial College Healthcare NHS Trust - Jewish General Hospital, McGill University, Montreal, Canada - Oxford Radcliffe Hospitals NHS Trust - Royal Marsden NHS Foundation Trust - University Hospitals Bristol NHS Foundation Trust</td>
</tr>
<tr>
<td>Study population</td>
<td>Examination Dates: Screening visit Treatment (baseline) Follow up visits at 2 weeks, 6 weeks, 3, 6, 9, 12, 18, 24, 30, 36 and 38 months MRI and Trans-rectal biopsy at 12 months MRI and Template biopsy at 36 months</td>
</tr>
<tr>
<td>Sample size</td>
<td>Primary objectives: 1. To determine the proportion of men who are free of any prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU 2. To determine the proportion of men who are free of clinically significant prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU</td>
</tr>
<tr>
<td>Duration of follow up</td>
<td>Secondary objectives: 1. To determine the following after focal therapy using HIFU: - rate of erectile dysfunction - time to return of erectile function - rate of loss of ejaculation - rate of loss of orgasm - rate of pain during intercourse - number of men using phosphodiesterase-5 inhibitors to maintain erectile function - rate of urinary incontinence (pad free, leak free and pad-free alone) - time to return of continence (pad free, leak free and pad-free alone) - rate of lower urinary tract symptoms - rate of bowel toxicity - anxiety levels - general health related quality of life - to determine the histological outcomes in the treated and untreated area at 12 and 36 months</td>
</tr>
<tr>
<td>Test Product</td>
<td>Sponsor (UK centres): University College London</td>
</tr>
</tbody>
</table>
- proportion of men achieving trifecta status at 36 months
- rate of secondary prostate cancer intervention (prostatectomy, radiotherapy, androgen ablation, whole-gland HIFU or cryosurgery)
- risk factors for failure defined as a) presence of any cancer and b) clinically significant cancer at study end

To analyse the following outcome parameters following focal therapy using HIFU:
- biochemical (PSA) kinetics including determining the optimal biochemical definition of failure
- describe composite outcomes of failure

2. To determine the costs of treatment and model potential cost effectiveness, by comparison to overall histological and functional outcomes at 36 months compared to other cohort trials involving the treatment of localized prostate cancer

3. To determine the clinical validity (sensitivity, specificity, negative and positive predictive values, inter-observer variability) of
   - multi-parametric MR-imaging to predict presence of clinically significant prostate cancer on template transperineal prostate mapping biopsies prior to focal therapy
   - MR-imaging changes to predict presence of residual/recurrent clinically significant prostate cancer on biopsy
   - HistoScanning™ to predict presence of clinically significant prostate cancer on template transperineal prostate mapping biopsies prior to focal therapy
   - HistoScanning™ to predict presence of residual/recurrent clinically significant prostate cancer on biopsy

4. To determine the following regarding MR-TRUS image registration
   - Number of patients in whom the planned treatment volume was increased as a result of image registration
   - Volume change between initial and registration-informed treatment plans
   - Time required to plan the treatment manually versus registration-based planning alone or a combination of the two methods (as proposed in this protocol).
   - Volume overlap between target volumes, as defined by the HIFU treatment plan, and the regions of necrosis visible in post-operative MR images
5. **Summary**

**Introduction**
Men with localised prostate cancer currently face a difficult decision between radical therapies and active surveillance. The former provides a greater certainty of cancer control but with a significant risk of side effects (50% impotence, 5-10% incontinence, 5-20% bowel dysfunction); the latter entails living with the diagnosis of untreated cancer and the risk of progression. Focal therapy is a strategy that could complement the current choices available to men by offering potential functional preservation whilst ablating clinically significant cancer and monitoring untreated benign tissue or clinically insignificant cancer.

**Aim and Objectives**
Prospective trials using hemi- ablation with high intensity focused ultrasound (HIFU) (Sonablate 500) have demonstrated feasibility, safety, and encouraging functional outcomes and early cancer control with 90% of men achieving trifecta status (no erectile dysfunction, leak-free pad-free continence, cancer control). However, these trials have involved small numbers of patients with men selected for good baseline function. A multi-centre prospective trial within a larger cohort of men that better represents the patient population with prostate cancer (external validity) is required.

**Design**
A prospective multi-centre phase II, single arm, cohort study (therapeutic confirmatory) offering focal therapy using HIFU (Sonablate 500) to 140 men with histologically proven localised low to intermediate risk prostate cancer (PSA ≤15ng/ml, ≤Gleason 4+3, ≤cT2cN0M0). Precise mapping and characterisation of the disease will be established using multi-parametric (mp)-MRI and transperineal template prostate mapping (TTPM) biopsies. Only the lobe with the dominant disease will be treated provided the contra- lateral side is free of clinically significant disease (Gleason ≥7 or ≥4mm maximum cancer core length on TTPM).

**Outcomes**
The primary outcome will be disease control. Disease control, as shown by histological outcomes, will be determined by TTPM biopsies at 36 months. Secondary functional outcomes will be assessed using validated patient questionnaires, including the evaluation of urinary, erectile, and bowel toxicity, and anxiety levels. In addition, we aim to determine the role of imaging and biochemical parameters in determining suitability for focal therapy and predicting histological outcomes of focal therapy, the rate of secondary prostate cancer therapy, and the potential cost-effectiveness of this new therapeutic pathway.
6. Prostate Cancer: Background

Prostate cancer is the most common malignancy among elderly men and is the second leading malignancy in the Western world\(^1\). The rising number of men diagnosed with prostate cancer is a result of increasing life expectancy along with the current practice of screening by PSA blood tests\(^2\).

6.1 Standard Care

Men with localised prostate cancer (PCa) have to choose between active surveillance or radical therapy.

There are two problems with the choices available. First, the options sit at the extremes of care. At one extreme lies no treatment – in the refined form of active surveillance. This is an option that is not generally accepted and has shown only limited acceptance and use in Europe and the USA\(^3,^4\). At the other extreme lies whole gland treatment, whether it is surgery (open, laparoscopic or robotic) or radiotherapy (external beam, high and low dose rate brachytherapy).

The difficult choices faced by men who have localised prostate cancer are further confounded by the findings from the recent publication of the third interim analysis from the European Screening study (ERSPC). This demonstrated a reduction in prostate cancer specific mortality from PSA screening and treatment\(^5\). The healthcare policy implications of screening need to be tempered. First, a randomised controlled study in the US has shown no difference between PSA screening and control\(^6\), although the control arm had a high degree of contamination since many men had already undergone a PSA test prior to enrolment. Second, there are considerable harms associated with a screening strategy. These include over-treatment and treatment-related harms.

The ERSPC showed that 1410 men need to be screened and 48 diagnosed and treated in order that one prostate cancer related death is avoided over a 9-year interval. Over-treatment becomes less of a problem if the treatment is cost-effective and associated with very low rates of harm, whilst eliminating potentially high-risk disease.

However, current treatments do not share these attributes. At present men can expect the following rates of toxicity: 30-90% erectile dysfunction, 5-20% incontinence and 5-20% rectal toxicity\(^7,^8\).

6.1.1 Radical Therapy

The Scandinavian randomised controlled trial comparing surgery and watchful waiting showed an absolute risk reduction in preventing cancer mortality within 8 years of 5% (from 14% to 9%) \(^9\). A recent update of this important RCT has shown that this absolute difference does not change with longer follow-up of 12 years \(^10\).

This difference is probably smaller in the PSA–screened population, as lower risk disease is detected earlier\(^11\).
The advantage to radical therapy may also become smaller if watchful waiting is substituted with active surveillance (with selective delayed intervention); the comparison of active surveillance with radical therapy is the subject of an ongoing prospective randomised trial (ProStart trial, NCT00499174). This trial has closed in the UK due to poor recruitment.

It is widely accepted that whole-gland radical therapy causes significant side-effects as a result of damaging structures surrounding the prostate (bladder neck, external sphincter, neurovascular bundles, rectum). This occurs because the whole gland and capsule are treated irrespective of the volume or location of cancer. Radiotherapy causes moderate ano-rectal and urinary side-effects in 5–20% of men. Surgery causes chronic urinary symptoms in one third of men. Both modalities cause impotence in 30–90% of men depending on which modality is used (radiotherapy causes impotence in over 50%) and the particular series looked at (high volume centres of excellence get better results).

The difference between newer forms of radical therapy, between say open surgery and laparoscopic/robotic, whilst declared to be significant, have not been borne out by retrospective studies and are in fact the subject of randomized controlled trials in themselves: (Lap vs. Open Prostatectomy NCT00695773; Robotic vs. Laparoscopic vs. Open NCT00578123; Laparoscopic vs. Open Europe Trial (LAPPRO) ISRCTN06393679; proposed UK Open vs. Robotic Radical Prostatectomy (OPERA).

Whilst recovery may be marginally quicker, rates of urinary incontinence, erectile dysfunction and cancer control are indistinguishable between the laparoscopic/robotic and open procedures. Whilst conformal and intensity modulated radiotherapy (IMRT) have lead to lower rates of toxicity, the incidence of such side-effects is still significantly high.

In order to achieve the reduction in toxicities and enhanced recovery in radiation therapy and surgery, respectively, additional cost has been incurred due to an increase in specification of the technology platforms used to deliver these two types of care. Robotics has largely replaced open surgery in the USA and IMRT and proton therapy are increasingly being offered as standard or ‘best’ care. If high quality prostate cancer care is to be offered to all that need it, irrespective of the ability to pay, then it will have to be both inexpensive and sustainable.

Choice is only ever of value if it can be exercised and if the differences between the options are both important and meaningful.

Nonetheless, it should be noted that the European Association of Urology Guidelines 2008 as well as the American Urology Association guidelines regard curative standard whole gland treatments as radical prostatectomy and radiation therapy (external or brachytherapy). Other forms of treatment are experimental and should be evaluated within carefully conducted clinical trials.

6.1.2 Active Surveillance

Active surveillance protocols usually involve monitoring the disease with clinical examination, prostate specific antigen (PSA) tests and biopsies at year 1 and then every
2-3 years or when PSA progression is detected. If these parameters demonstrate 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\(^{20, 21}\). However, there are a number of controversial aspects to active surveillance.

First, parameters indicating progression (clinical, biochemical and histological) have not been validated and indeed differ between groups in the USA/Canada and those in the UK.

Second, it is likely that a significant proportion of those men that ‘progress’ within 5 years do so not due to true cancer progression but due to the poor accuracy of diagnostic transrectal ultrasound guided biopsies in ascertaining baseline burden (cancer core length) and Gleason grade (undergrading occurs in one-third of men with Gleason 6)\(^{22, 23}\).

Third, there is some evidence that demonstrates men have increased levels of anxiety during this period\(^{24, 25, 26}\). Indeed, in some series about one-tenth of men decide to opt for radical therapy, despite having no objective measures of progression\(^{27}\). However, others have shown no increase in anxiety levels\(^{28, 29}\). These differences may be accounted for by the particular healthcare service in which these studies have carried out, with European centres demonstrating no change in anxiety levels.

Fourth, the latest series from Toronto has demonstrated that men who progress and have radical therapy have a higher than normal rate of biochemical failure\(^{30}\).

### 6.2 Focal Therapy

The attributes of a treatment that would appeal to patients faced with the therapeutic dilemma described above would have to share the well tolerated aspects of active surveillance and equal - or approach so closely as to be indiscernible - the oncological control afforded by surgery or radiotherapy.

**One way of reducing the unwanted side-effects from radical treatment of PCa may be to direct treatment to only areas of cancer - this is deemed focal therapy.**

Focal therapy is a new research area that has been subject to a number of key discussion papers by various groups and more recently, has been subject to discussions by the Food and Drug Agency in the USA\(^{31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42}\). Focal therapy conferences have been held in 2008, 2009, and 2010 in Duke, Amsterdam and Washington DC. In addition, all the major urology and oncology conferences have held plenary sessions on the topic (AUA 2009; AUA 2010; ASCO-GU 2009; EAU 2009, EAU 2010).

Such a proposed change in treatment of prostate cancer reflects the management of all other solid organ cancers, in which organ preservation is fundamental to functional preservation (breast, kidney, liver, lung). With focal therapy of prostate cancer, it is proposed that by avoiding the bladder neck, rectum, external sphincter and at least one
neurovascular bundle, side-effects could be reduced. For this to be feasible, localisation of cancer within the prostate must be more precise to ensure that malignant areas are not left untreated and areas of clinically significant cancer and a margin of normal tissue are within the treatment zone. In addition, ablative technologies that can treat parts of the prostate are also required. Focal therapy can be delivered using a number of ablative modalities that can treat discrete areas of tissue. These include high intensity focused ultrasound (HIFU), cryosurgery, photodynamic therapy, brachytherapy and radiofrequency ablation, and thermal lasers. All are at different stages of development in relation to their use as technologies capable of focal ablation. HIFU, cryosurgery and photodynamic therapy are at a stage of evaluation akin to phase II, non-comparative studies in drug development.

6.2.1 Focal therapy as an alternative to radical therapy or active surveillance

In order that as much information as possible is forthcoming from this evaluation it is desirable that the patient characteristics and the comparators are broad to reflect true clinical practice. There has been some debate recently on which group of men might serve as the ideal population when evaluating a novel intervention such as focal therapy. It has been argued that many men with low risk disease probably do not need treatment; if such men are comfortable pursuing a policy of active surveillance then this would appear to be the most appropriate therapy at the time of writing. This is especially the case as, increasingly, men are being characterised with greater precision through the use of MR and intensified biopsy strategies. The result is that the attribution of low risk status is much more secure than it has been historically.

In the USA, and in much of mainland Europe, there exists an imperative to treat all men who are diagnosed with prostate cancer. In these jurisdictions focal therapy tends to be seen as an alternative to active surveillance. Therefore, if active treatment is an inevitable consequence of diagnosis, the role of focal therapy might be to reduce both the harms and the costs associated with treating these men. Most commentators would agree that the oncological benefit that will result from this policy is marginal at best. In this context it is also likely that men with intermediate risk disease may be more likely to be offered radical whole gland therapy.

Defining who is and who is not a candidate for focal therapy is, in the absence of knowledge of the long-term outcomes of the intervention, possibly the most contentious and difficult issue in trial design. The arguments are polarized as follows. On the one hand, a novel intervention, that by definition has high levels of uncertainty associated with it, should only be offered to a group of men who have a low chance of disease progression and, as a result, a low chance of prostate cancer related death. This position is adopted in order to minimize the ‘loss to cure’ in the men that enroll into a non-randomised Phase I/II programme, or are randomized to the non-control arm of a randomized Phase II/III programme.

The alternative is to adopt the position that men with low risk characteristics are not destined to die of prostate cancer over a 15-20 year window and therefore any intervention has a very low chance of conferring benefit and therefore can do no more than incur cost and confer harm. This position would encourage the inclusion of patients that had characteristics that would increase their chances of disease progression if left untreated and might incorporate men with higher grade tumours, and at the same time
reduce the upper limit of tumour burden.

Our choice of a relatively broad spectrum of disease risk permits and encourages a range of views (that we feel reflects the equipoise of the investigators) on who should and who should not be offered focal therapy in the current UK climate.

6.2.2 Focal therapy as an alternative strategy to active surveillance in low risk disease

The arguments for focal therapy to be carried out only within men suitable for active surveillance are to:

1) reduce the potential psychological morbidity associated with men not having treatment for a cancer – offering these men ‘some form of treatment is better than none’
2) reduce the cancer progression and/or re-classification rate that currently occurs in about one-third of men who undergo active surveillance and require delayed intervention within 5 years.

Whilst up to 10% of men on active surveillance within 5 years choose to have intervention despite the absence of biochemical or histological progression, questionnaire surveys have shown conflicting findings about the level of anxiety present in such cohorts. Furthermore, despite the progression rate the mortality rate has been very low, so that it could be argued that most men can avoid treatment and those that have delayed intervention have a period of time free of treatment-related side-effects. However, the period of lower side-effects could be extended if focal therapy were to be carried out at diagnosis or indeed, at the time of disease progression (instead of radical therapy).

The arguments against men who are suitable for active surveillance undergoing focal therapy are that any treatment within this group is liable to be over-treatment. Any treatment, regardless of the encouraging functional outcomes that it may demonstrate, will carry greater morbidity than a management strategy in which two-thirds of men with low-risk disease can avoid treatment whilst the others can delay such morbidity. Nonetheless, active surveillance is not without harm – clinical examination and PSA tests every 2-3 months and biopsies every 1-2 years. Sepsis rates are increasing and repeat biopsies carry a greater risk of sepsis requiring hospital admission, and pose a significant and sustained healthcare burden for the individual and healthcare systems. In fact, the latest report from Toronto’s active surveillance cohort has demonstrated that of 450 on active surveillance, 117 were treated radically. In these 117 men, the PSA failure rate was 50%, a relatively high rate.

6.2.3 Focal therapy as an alternative strategy to radical treatments in men with intermediate risk disease

It can be argued that the emergence of focal therapy as a strategy to reduce the side-effects of conventional whole-gland therapies requires us to evaluate its potential within men who, as a result of harbouring intermediate risk disease, would undergo radical therapy. Despite the higher risk disease status, evidence points towards the benefits of radical therapies with respect to cancer control and prevention of death is seen in very few men within 10 years, with this benefit probably seen after 10 years, and rare in men over the age of 65. A strategy that treats all clinically significant cancer and carefully
monitors untreated tissue for *de novo* cancers and/or progression of clinically insignificant disease, may obviate the need for any further radical therapies in future or delay it for a number of years during which the man is free of treatment-related side-effects.

The theoretical problem posed by focal therapy is that selective treatment of a target volume of tissue deemed to contain a cancer may incur a miss due to poor targeting, poor staging, or both. The result would be that a cancer with metastatic potential may be given a time window to progress that would not have been available had radical whole gland therapy been employed.

Whilst possible, we have good cause to believe that this risk is low. The reasons are as follows:

a) An estimated lead time bias of approximately 5 years, perhaps more, conferred by screening versus non-screening in the recently published US screening study failed to demonstrate any difference in survival\(^6\).

b) In the very high risk disease seen in the Swedish study, progression rates are going to be greater than in the screened population. The difference in survival between men treated by radical prostatectomy versus those men who had delayed systemic therapy was small (5% absolute risk reduction)\(^51\). It therefore follows that the likely difference in survival between radical whole gland therapy and a targeted therapy to the dominant cancer is going to be considerably smaller than this.

c) The longer lead time seen in the European Screening study\(^5\) that resulted from the lower rates of ‘contamination’ from non-screened to screened groups did show a difference in survival. However, once again this difference was small, indicating that few men progress if left undiagnosed and untreated for a fairly prolonged period of time. Even if the Swedish arm of the European screening trial, which showed a number needed to treat of 12 over a longer period of time [15 years]\(^52\), were to be replicated across the whole European Screening study, this still represents a significant over-treatment burden. The risk to the man treated with focal therapy must be less than it was to the man randomized to non-screening.

d) The upfront diagnostic strategy and the treatment verification test after focal therapy that has been incorporated into this protocol has been planned with safety in mind. Template transperineal prostate mapping biopsies at entry reduce any staging error to a minimum. Exit biopsies will have a 95% probability of detecting any man with residual disease that may require either re-treatment or consideration of salvage therapy.

### 6.3 Multifocal versus unifocal/unilateral disease

#### 6.3.1 Unilateral/Unifocal Prostate Cancer

A number of studies have shown that prostate cancer in the PSA screened era is increasingly unilateral or unifocal. Indeed, unilateral disease has been shown to exist in 20-40% of men, whilst unifocal disease in contemporary series may be present in 10-44% of men with newly diagnosed localised prostate cancer \(^{53, 54, 55, 56, 57, 58, 59}\).
However, the data on multifocality arises from verification studies performed on men who have undergone radical prostatectomy. Such information is liable to be influenced by a significant degree of work-up bias. Men who are recommended to undergo (and agree to undergo) radical prostatectomy are subject to numerous selection events. They are likely to over-represent the proportion of men who have multifocal disease compared to those men with screen detected disease who opt for other management strategies (surveillance, radiotherapy/brachytherapy, minimally invasive treatments). Although this is more likely in European countries, and particularly in the UK in which active surveillance is well established, it is difficult to verify.

6.3.2 Multifocal Cancer

A strong argument against focal therapy is the fact that the majority of men with localised prostate cancer have multifocal disease. Indeed, at diagnosis most men have between 2 and 3 separate cancer foci. Amongst these foci there usually exists a dominant lesion that accounts for about 80% of the total tumour volume (mean tumour volume varies between 0.5 and 2.3cc)\(^6^0, ^6^1, ^6^2, ^6^3\). The implication of this observation is that the ‘other’ non-dominant lesions account for 0.1 to 0.4cc of tumour on average. By far the majority of these small cancer foci will be of low grade and will conform therefore to most of the definitions of ‘indolence’\(^6^4, ^6^5\).

Lesions above 0.5cc are the ones that tend to harbour Gleason scores of 7 or greater and are responsible for extra-capsular extension if present.

Epstein et al\(^6^6\) have classified foci into insignificant tumours, and minimal, moderate and advanced tumours using a radical prostatectomy series but drawing on the literature demonstrating pathological characteristics of tumours found in radical prostatectomy, autopsy studies and cystoprostatectomy.

Table 1. Categorization of Clinical Stage T1c Tumours \(^6^2\)

<table>
<thead>
<tr>
<th>Insignificant Tumour</th>
<th>Minimal Tumour</th>
<th>Moderate Tumour</th>
<th>Advanced Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV &lt; 0.2cm(^3) and Confined</td>
<td>0.2 &lt; TV &lt; 0.5cm(^3) and Confined</td>
<td>Confined, TV ≥ 0.5cm(^3) or FCP, Gleason score &lt; 7 or ECP, Gleason score &lt; 7 and margins (-)</td>
<td>FCP or ECP, Gleason score ≥ 7 or ECP, margins (+) or SV (+) or LN (+)</td>
</tr>
<tr>
<td>and Confinéd and SV (-) and LN (-) and No Gleason pattern 4 or 5</td>
<td>and Confined and SV (-) and LN (-) and No Gleason pattern 4 or 5</td>
<td>and margins (-)</td>
<td>or SV (+) or LN (+)</td>
</tr>
</tbody>
</table>

TV = Tumour Volume; FCP = Focal Capsular Penetration; ECP = Established Capsular Penetration; Plus sign, positive; Minus sign, negative; SV = Seminal Vesicles, LN = lymph nodes

Additional evidence pointing to the role of volume of cancer driving disease progression have emerged from retrospective cohorts evaluating rates of biochemical failure after
surgery and radiotherapy\textsuperscript{67, 68, 69}. Other studies have shown total tumour volume predicts failure on univariate analysis but not on multivariate analysis likely due to the strong influence of Gleason score\textsuperscript{70, 71}. Evaluating the predictive power of the index lesion seems to demonstrate a relationship\textsuperscript{72, 73}. This may explain some of the discrepancy evident in the literature.

Evidence from molecular genetic studies, which point to a single clone being responsible for metastases demonstrate that there is usually only one clinically significant clone in the prostate and therefore presumably one clinically significant lesion. This study could not demonstrate whether the metastatic clone resided in the index lesion\textsuperscript{74}. It may seem reasonable to propose that ablation of the dominant lesion(s) by volume and grade will give rise to disease control provided the remaining lesions can be well characterized in the pretreatment evaluation\textsuperscript{75}. In fact, it could be argued that definitive knowledge of whether index lesions drive disease progression could only be answered within a clinical trial that involves careful selection and follow-up to ensure that progression of untreated areas of cancer is detected early.

\section*{6.4 Disease detection and localisation}

\subsection*{6.4.1 Template Transperineal Prostate Mapping Biopsies in Localising Prostate Cancer}

It has been argued that template transperineal biopsies can serve this purpose to the highest available performance characteristics with sensitivity for 0.2cc and 0.5cc lesions above 90\%\textsuperscript{76, 77}. We propose using a more accurate technique for disease characterization and localization, so that these errors are reduced significantly. This technique has been shown to be approximately 95\% accurate in locating all significant tumor foci. Recently, the Colorado group demonstrated that prostate mapping biopsies detect all tumour subsequently found on whole-mount radical prostatectomy specimens\textsuperscript{78, 79, 80}. Further, it has been accepted as the standard to which trials in focal therapy should evaluate patients' eligibility\textsuperscript{81, 82}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Method used for transperineal template prostate mapping biopsies.}
\end{figure}
The graphs below represent template simulations on reconstructed radical prostatectomy specimens with each individual lesion also reconstructed. Although this represents the ideal setting for template biopsies, this work allows us to define what minimum amount of cancer within positive biopsy cores accurately represents a significant and insignificant lesion as defined by work drawn from the Stamey and Epstein groups.

A. Template Biopsy Simulations at Lesion Level

The ability of a threshold Cancer Core Length to Detect Lesions of >/=0.2cc.
The point at which test performs optimally (Max. Youden index): Sen: 0.958, Spc: 0.861,ppv: 0.672, npv: 0.986. (Max. Youden: 0.818). Cut-off for cancer core length involvement is 4mm. In other words, if >/=4mm is used as the threshold we can be confident that 92% of all lesions >/=0.2cc will be detected (92% sensitivity). In addition, the level of specificity (also at 92%) demonstrates that 8% of lesions </=0.2cc will be falsely designated as a lesion >/=0.2cc.
B. Template Biopsy Simulations at Lesion level

The ability of a threshold Cancer Core Length to Detect Lesions of volume >=0.5cc.

The point at which the test performs optimally (Max. Youden index): Sen: 0.906, Spc: 0.927, ppv: 0.687, npv: 0.982. (Max. Youden: 0.833). Cut-off for cancer core length involvement is 6mm.

If we use the threshold of 4mm used for detection of >=0.2cc lesions, then if a biopsy is >=4mm then we can be confident that 98% of all lesions >=0.5cc in volume will be detected. However, for this greater sensitivity we accept a greater degree of false-positive. In other words, using a 4mm threshold means that we only correctly designate 83% of lesions <=0.5cc as such.

In the focal therapy multicentre trial, 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.

6.4.2 Template Transperineal Prostate Mapping Biopsies in Determining Optimal Standard Care and Suitability for Focal Therapy

Our data also shows that if men with low to intermediate unilateral disease on TRUS are subjected to prostate mapping, the following change in management can occur with the potential for 90% of these men to be treated in a focal manner, as demonstrated by the following table.

Table 2: Template Biopsies and Change in Prostate Cancer Management

<table>
<thead>
<tr>
<th>Recommended Standard Management on TRUS Biopsy</th>
<th>Recommended Standard Management on TPM</th>
<th>Focal Therapy strategy based on TPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical Therapy</td>
<td>Radical Therapy</td>
<td>Hemiablation (unilateral any burden, Gleason ≤4+3)</td>
</tr>
<tr>
<td>Active Surveillance</td>
<td>Active Surveillance</td>
<td>Focal ablation of all foci (unilateral or bilateral, ≤60% gland ablation, Gleason ≤4+3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index lesion ablation (dominant lesion(s) ablated with max 3mm Gleason 3+3 in untreated areas)</td>
</tr>
<tr>
<td>46</td>
<td>89</td>
<td>43</td>
</tr>
<tr>
<td>89</td>
<td>43</td>
<td>80</td>
</tr>
<tr>
<td>43</td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td>80</td>
<td>14</td>
<td>23</td>
</tr>
</tbody>
</table>
Depending on the intervention that is used, we have estimated that approximately 50-75% of men who currently undergo prostatectomy could have a form of focal therapy (based on an evaluation of their whole-mount specimens). Our template data demonstrates that 80-90% of men with low to intermediate risk cancer on TRUS biopsy could be suitable for focal therapy, if this is defined as hemiablation with absence of clinically significant prostate cancer in untreated areas. The data currently available suggest that the benefits of focal therapy are likely to be realized if at least 40-50% of the total prostate tissue is untreated and at least one neurovascular bundle is preserved.

Table 3: Template Biopsy Series (other centres)

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Re-biopsy Protocol</th>
<th>Upgrading &gt;=Gleason Score 7</th>
<th>Unilateral to bilateral</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onik</td>
<td>180</td>
<td>5mm mapping Individual cores</td>
<td>23%</td>
<td>61%</td>
<td>19% no cancer (35/36 had Max CCLI &lt;5mm)</td>
</tr>
<tr>
<td>Barzell</td>
<td>80</td>
<td>5mm sampling 28 zones</td>
<td>16%</td>
<td>54%</td>
<td>36 unsuitable for focal: 100% detected by TG; 14% by TRUS. 66 had TGB and TRUS at same time: 92% deemed suitable for focal; 45% by TGB</td>
</tr>
<tr>
<td>Merrick</td>
<td>294</td>
<td>5mm sampling 24 regions</td>
<td>N/A</td>
<td>N/A</td>
<td>1 neg biopsy: 55% 2 neg biopsy: 42% 3 neg biopsy: 34%</td>
</tr>
<tr>
<td>Pinkstaff</td>
<td>210</td>
<td>5mm sampling Individual pots</td>
<td>N/A</td>
<td>N/A</td>
<td>37% cancer</td>
</tr>
</tbody>
</table>

6.4.3 Multi-parametric Magnetic Resonance Imaging

Studies suggest that multi-parametric MRI (mpMRI), which uses a combination of different functional sequences, has a high negative predictive value of 90-95% for lesions of greater than 0.2cc and 0.5cc in volume. In addition, mpMRI will allow the morphological characteristics of the tumours to be visualised so that margins are better incorporated within the treatment plan. Imaging for prostate cancer with the use of mpMRI has progressed from its initial use to stage the disease to its present day capability to identify tumour burden and precise location of tumour foci within the gland. Traditional MRI uses T1 and T2-weighted
sequences, but newer sequences such as diffusion-weighted (DW), magnetic resonance spectroscopy imaging (MRSI), and dynamic contrast-enhancement (DCE) using intravenous gadolinium, have been used to improve the accuracy of this imaging modality.  

A study by Kim et al 93 comparing DCE-MRI and T2-weighted sequences to locate tumour reported the sensitivity, specificity and accuracy for prostate cancer detection being 55%, 88% and 70% for T2-weighted imaging, and 73%, 77% and 75%, respectively, when DCE-MRI was added. They concluded that tumour contour detection was achieved in 67% of cases by T2-weighted imaging alone and in 90% by T2-weighted and DCE-MRI. Similar results were reported by Villers et al 94 who showed good accuracy for lesions 0.5cc or larger – the threshold for significant cancer lesions. It is therefore appropriate to use DCE-MRI to identify, localise, and aid in targeting the delivery of focal HIFU therapy to, the index lesion.

One inconsistency in studies using mpMRI is in the use of scoring systems to report on the probability of prostate cancer being present. Most studies apply a Likert-type scale, most frequently ranging between scores 1 and 5, to report on the imaging findings (e.g. 1=no cancer seen, 5=cancer definitely present) 95, 96, 97. However, these scales are non-standardised and have not been validated. Furthermore, the prostate can be divided into sectors, or ‘Regions of Interest’ (ROI), whereby the prostate can be assessed for the presence of cancer for each individual region. This not only allows division of the prostate into different anatomical zones according to natural borders (such as between the peripheral and transition zones, which differ in how easily cancers can be diagnosed by imaging 98), but also allows for direct comparison of imaging outcomes using radical prostatectomy specimens as the reference standard. The number of Regions of Interest used range from one (whole prostate) 99, through six 100, 101, fourteen 102, and up to twenty 103.

A European consensus meeting, initiated by the chief investigator (Emberton), and organised by the study co-ordinator (Dickinson) was held in December 2009 at The Royal College of Surgeons, London. Sixteen experts within radiology, urology and oncology attended, representing Bristol (Persad), Brussels (Tombal), Leeds (Carey), Lille (Puech, Villers), Nijmegen (Heijmink, Futterer, Barenstz), Mount Vernon (Hoskins, Padhani), Royal Marsden Hospital (Sohaib), and University College Hospital (Allen, Kirkham, Punwani, Ahmed, Emberton), and coordinated through the Royal College of Surgeons Clinical Effectiveness Unit (Dickinson, van der Meulen). Agreement was reached on the conduct of mpMRI for the detection and localisation of prostate cancer, and on the use of a scoring system for this purpose. A minimal and optimal number of Regions of Interest was also recommended as a result of this meeting, which were sixteen and twenty-seven ROIs, respectively. These recommendations will be implemented and integrated within this protocol to ensure reproducibility and standardisation of mpMRI sequences and reporting across all centres.

6.4.4 HistoScanning™

HistoScanning™ (Advanced Medical Diagnostics, Waterloo, Belgium) is a novel form of diagnostic imaging currently under evaluation for its ability to detect and localize clinically significant prostate cancers. The technique relies on the differing backscatter produced by tissue of altered morphology i.e. tumours, compared with normal tissue.
Algorithms are applied that convert backscatter signals into interpretable results indicating the presence or absence of disease. Retrospective analyses using radical prostatectomy specimens as the reference standard have demonstrated that Histoscan can reliably detect clinically significant lesions of at least 0.5cc in volume\textsuperscript{104, 105}. We propose a prospective assessment of this technique in the characterisation and localization of clinically significant prostate cancers, using template biopsies as the reference standard.

6.5 High Intensity Focused Ultrasound (HIFU)

6.5.1 Description of the Medical Device

HIFU works by focusing and depositing a large pulse of high-energy ultrasonic waves on a single area, thereby increasing the temperature to a point whereby, it causes coagulative necrosis. Focused ultrasound waves are emitted from a transducer and are absorbed in the target area of approximately 3x3x10mm of tissue. The result is a targeted thermal effect without damage to the tissue in the path of the ultrasound beam\textsuperscript{106}.

The clinical applications of HIFU in organ-confined prostate cancer are continually being updated with the technique being used throughout the world. Two commercially available devices exist for HIFU therapy: Ablatherm (Edap- Technomed, Lion, France) and Sonablate (Focus Surgery, Indianapolis, IN, USA). This study will use the Sonablate device, which has a combined therapy-imaging transducer of different focal lengths, allowing precise control of energy delivery by each pulse.

International results\textsuperscript{107, 108} show no cancer detected in between 87-94\% of men biopsied after whole gland ablation. Our own results have shown that we can ablate prostate cancer effectively in a whole-gland and focal manner\textsuperscript{109, 110}

6.5.2 Known and Potential Risks of Whole-gland High Intensity Focused Ultrasound

The HIFU procedure does not breach the skin or mucosal surfaces and is therefore considered safer than other minimally invasive techniques such as cryotherapy and photodynamic therapy. Morbidity associated with the latest generation Sonablate HIFU is as follows:

- Urinary symptoms- reported by most during the first 2 months after treatment
- Symptomatic urinary tract infection (UTI): 5\%
- Urethral Stricture: 10\%
- Retrograde ejaculation: 3\%
- Epididymitis: 3\%
- Urinary retention requiring surgery: 2\%
- Impotence: 25-30\%
- Incontinence (transient): 0-2\%
- Recto-urethral fistula: <0.5\%
6.6  Focal Therapy Trials

6.6.1 Focal therapy case series
Focal therapy involves locating and destroying the areas of cancer only whilst leaving the majority of prostate tissue untreated. To date, focal therapy case series have evaluated hemiablation of unilateral disease (Gleason \( \leq 7 \), PSA \( \leq 15 \), \( \leq T2bNoMo \)) using cryosurgery and one using HIFU\(^{111}\). These have demonstrated impotence rates of approximately 15% with little to no incontinence\(^{112, 113, 114, 115, 116}\). These have used a variety of methods to identify unilateral disease from Doppler TRUS biopsies, TRUS alone and template biopsies and have generally shown poor reporting standards due to their retrospective nature with short follow-up and generally small numbers of patients (tables below).

Table 4: Focal Therapy HIFU Retrospective Series

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Therapy</td>
<td>Hemiablation</td>
<td>Hemiablation</td>
</tr>
<tr>
<td>Biopsy</td>
<td>TRUS Biopsy</td>
<td>TRUS Biopsy</td>
</tr>
<tr>
<td>Mean PSA (ng/ml)</td>
<td>5 (range 2-25)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Gleason Score</td>
<td>( \leq 8 )</td>
<td>( \leq 7 )</td>
</tr>
<tr>
<td>Potency</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Not reported</td>
<td>0%</td>
</tr>
<tr>
<td>Disease Control</td>
<td>76.5% (biopsy)</td>
<td>58% (10 years)</td>
</tr>
</tbody>
</table>

Table 5: Focal Therapy Cryosurgery Series

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>112</td>
<td>60</td>
<td>25</td>
<td>31</td>
<td>100</td>
<td>795</td>
</tr>
<tr>
<td>Therapy</td>
<td>Hemi</td>
<td>Hemi</td>
<td>Hemi</td>
<td>Hemi</td>
<td>Focal</td>
<td>‘Focal/Partial’</td>
</tr>
<tr>
<td>Biopsy</td>
<td>TRUS</td>
<td>TRUS+Doppler</td>
<td>TRUS+Doppler</td>
<td>TRUS+Doppler</td>
<td>Template</td>
<td>TRUS</td>
</tr>
<tr>
<td>Mean PSA (ng/ml)</td>
<td>8.3</td>
<td>7.2 +/- 4.7</td>
<td>6 (range 1-13)</td>
<td>4.95</td>
<td>5.2 +/- 4.1</td>
<td></td>
</tr>
<tr>
<td>Gleason Score</td>
<td>( \leq 6 )</td>
<td>( \leq 8 )</td>
<td>( \leq 7 )</td>
<td>( \leq 8 )</td>
<td>( \leq 7 )</td>
<td>( \leq 8 )</td>
</tr>
<tr>
<td>Potency</td>
<td>85%</td>
<td>70.6%</td>
<td>70.8%</td>
<td>89%</td>
<td>83%</td>
<td>65%</td>
</tr>
<tr>
<td>Incontinence</td>
<td>0%</td>
<td>3.6%</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
<td>2.8%</td>
</tr>
<tr>
<td>F/U (mean, months)</td>
<td>43.2</td>
<td>15.2</td>
<td>28</td>
<td>70</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Disease control</td>
<td>93% NED</td>
<td>76.7% (biopsy)</td>
<td>88% (&gt;50% nadir reduction)</td>
<td>96% (biopsy) (ASTRO)</td>
<td>97% (biopsy at 12/12)</td>
<td>4.5% (36/295) 25% (36/199) 83% (ASTRO)</td>
</tr>
</tbody>
</table>
6.6.2 Prospective Studies in Focal Therapy

Three UK single-arm, phase II, prospective IRB-approved and independently audited studies are close to completion at University College London (NCT00988130, NCT00561314, NCT00561262). Two of these are National Cancer Research Network approved. These trials have evaluated the side-effect profile of various forms of focal therapy using high intensity focused ultrasound (HIFU) in men with low-intermediate risk prostate cancer (Gleason ≤4+3, PSA≤15, T2cNoMo):

1. Hemiablation of unilateral PCa (20 patients treated and follow-up completed, accepted for publication in Journal of Urology) (Hemi-HIFU)
2. Focal ablation of only the cancer areas, whether unilateral or bilateral (43/43 recruited, in follow-up stage) (Focal-HIFU)
3. Index lesion(s) ablation of multifocal/bilateral prostate cancer (54/56 recruited) (Lesion Control-HIFU)

The first two trials have localised disease using 5mm-spaced transperineal template prostate mapping biopsies whilst the lesion control trial localises disease either with template biopsies or a combination of TRUS and multi-functional MRI. Such trials suggest that focal therapy can be delivered safely as a day-case procedure with most men discharged 3-5 hours after treatment.

**Quality of life**
Outcomes measured using validated questionnaires show (tables below):
1) urinary incontinence  \( \leq 5\% \)
2) erectile dysfunction (erections insufficient for intercourse) 5-10%
   (with return to baseline scores by 6-9 months)
3) preservation of wet ejaculation 50%
4) bowel dysfunction  \( \leq 5\% \)

**Early Cancer Control**
Biopsy of treated areas at 6 months
- absence of any cancer: 82-89%
- absence of clinically important cancer:
  (Gleason \( \leq 3+3 \) and/or Max CCLI \( \leq -2\)mm)
**Table 6: Hemi-HIFU Trial Outcomes**  (UK National Cancer Research Network approved; Cancer Research UK endorsed; MRC funded)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Follow-up (months)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Erections sufficient for penetration (&gt;=2 Q2 on IIEF-15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>100% (20/20)</td>
<td>86.7% (13/15)</td>
<td>80% (12/15)</td>
<td>83.3% (15/18)</td>
<td>94.4% (17/18)</td>
<td>95% (19/20)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>86.7% (13/15)</td>
<td>80% (12/15)</td>
<td>83.3% (15/18)</td>
<td>94.4% (17/18)</td>
<td>95% (19/20)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>80% (12/15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continence (pad-free)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>100% (20/20)</td>
<td>85% (17/20)</td>
<td>95% (19/20)</td>
<td>95% (19/20)</td>
<td>95% (19/20)</td>
<td>95% (19/20)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>85% (17/20)</td>
<td>95% (19/20)</td>
<td>95% (19/20)</td>
<td>95% (19/20)</td>
<td>95% (19/20)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>95% (19/20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continence (leak-free, pad-free)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>100% (20/20)</td>
<td>85% (17/20)</td>
<td>75% (15/20)</td>
<td>90% (18/20)</td>
<td>90% (18/20)</td>
<td>90% (18/20)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>85% (17/20)</td>
<td>75% (15/20)</td>
<td>90% (18/20)</td>
<td>90% (18/20)</td>
<td>90% (18/20)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>75% (15/20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PSA (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.3</td>
<td>2.1</td>
<td>1.5</td>
<td>1.4</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>7.3</td>
<td>2.1</td>
<td>1.5</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of clinically significant cancer in treated side on TRUS biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>95% (19/20) (one refused)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continence (pad-free)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>89% (17/19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 7: Focal-HIFU Trial Outcomes (Interim)**  (UK National Cancer Research Network approved; MRC funded)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Follow-up (months)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Erections (hard for penetration) &gt;=2Q2 IIEF-15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70% (9/13)</td>
<td>73% (11/15)</td>
<td>85% (11/13)</td>
<td>100% (7/7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>70% (9/13)</td>
<td>73% (11/15)</td>
<td>85% (11/13)</td>
<td>100% (7/7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>73% (11/15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Continence (Pad-Free)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>86% (18/21)</td>
<td>94% (17/18)</td>
<td>100% (15/15)</td>
<td>100% (7/7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>86% (18/21)</td>
<td>94% (17/18)</td>
<td>100% (15/15)</td>
<td>100% (7/7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>94% (17/18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Continence (Leak-Free, Pad-free)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76% (16/21)</td>
<td>89% (16/18)</td>
<td>93% (14/15)</td>
<td>100% (7/7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>76% (16/21)</td>
<td>89% (16/18)</td>
<td>93% (14/15)</td>
<td>100% (7/7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>89% (16/18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of clinically significant cancer in treated side on biopsy &lt;=3mm &amp; Gleason pattern &lt;=3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>88% (15/17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of any cancer in treated side on biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>82% (14/17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>82% (14/17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.7 Outcomes in Focal Therapy Trials

There are no validated or agreed outcome measure other than prostate cancer related deaths or rate of metastatic disease that would serve as a meaningful clinical outcome measure across the therapies of focal therapy, active surveillance, radical prostatectomy and radical radiotherapy. However, in this focal therapy trial with a very low expected rate of death and metastatic progression in this sub-set of low-intermediate risk patients, some 10-15 years would have to pass after treatment before sufficient events were accrued in order to gain meaningful results on which to base the outcomes of this therapy. Furthermore, a trial would require 2000-3000 patients. Therefore, other outcomes will be required in the short to medium-term to serve as surrogate secondary outcome measures. These can be categorized into four groups.

- The first relates to treatment related side-effects and can be relatively well captured using validated questionnaires. These are principally directed at genito-urinary and bowel associated outcomes. In focal therapy studies reported to date, stability in terms of functional health status is achieved between 3 to 6 months following the intervention. This domain of outcome can therefore be derived relatively early.

- The second relates to a more global assessment of quality of life. Some are generic, and some designed specifically for the evaluation of patients with prostate cancer.

- The third, and most problematic area relates to the type and timing of the surrogate cancer related outcomes used (PSA, biopsy, imaging, additional therapy). This area needs some consideration in this proposal. The problem arises since radical therapies use very different outcome measures based on PSA kinetics with little consensus across different modalities of treatment. No such outcome measures have been validated for focal therapies. Indeed, focal therapy will be further problematic in this respect as tissue is left untreated – this tissue will inevitably give rise to PSA increases with time as the man ages. The table below illustrates which outcomes will be available on which group of patients at any given time point.

- The fourth relates to the costs of care and incorporates cost-effectiveness, cost utility and cost benefit. Apart from cost minimization exercises nested on the intervention versus known costs of alternative intervention, most economic analyses will require that cancer outcomes are derived as well as functional status and quality of life.
We propose the primary outcome measures detailed below (section 7.3.1). Prostate cancer has a long natural history with minimal expected impact on mortality rates over the time-scale of this trial. In addition, we need to establish the impact that this therapy may have on the patients’ daily quality of life. In respect to radical therapies, erectile dysfunction and urinary incontinence are the most common side effects encountered. These aspects will be assessed as part of the secondary outcome measures.

Erectile function, although multifactorial in aetiology, declines as part of the ‘normal’ aging process with a significantly greater prevalence of dysfunction in men over 70 years compared to those in their 50’s or 60’s\textsuperscript{117}. Baseline erectile function is an important measure to establish in order to know the true impact of a therapy. Unfortunately, relatively few studies report on this. The range of reported erectile function rates is large. A review of the epidemiology of erectile function showed a prevalence of 5-20\% of moderate to severe ED across all age groups. However, this prevalence ranged from 2-30\% in the <50 year old age group to 38-57\% in men of 70-79 years\textsuperscript{118}. Salomon et al. reported dysfunction ranging from mild to severe on IIEF score in 48\% of 1330 men with localized prostate cancer awaiting radical prostatectomy\textsuperscript{119}. Whether there is a decline in continence function as part of normal aging is less certain but out of 3810 men within the ERSPC study, up to 9\% of men had urinary leakage several times a week\textsuperscript{117}.

The trifecta metric is a summary statistic that has been proposed as a useful measure of therapeutic success following radical surgery for men with early prostate cancer in which the rate varies between 45-62\%. It incorporates the three domains that matter to patients – freedom from prostate cancer, erectile function and continence status\textsuperscript{120, 121, 122}. We will evaluate trifecta outcomes as a secondary outcome. However, we are aware that this measure is subject to population bias as it will select out those men with continence and normal erectile function at baseline.
6.8 The Rationale for a Multicentre Prospective Single Arm Intervention Study

Verification of a new therapy as favourable, or equivalent, in outcome to ‘standard’ care is ideally sought through comparison with another matched control group. Randomised controlled trials (RCTs) offer the best method for minimising systematic bias and revealing the true effect of an intervention or drug. However, RCTs involving treatments of localised prostate cancer have had a historically poor patient uptake, as the reference ‘gold’ standard of care is not known. In addition, RCTs are expensive to run and involve huge infra-structural support. A number of trials in the USA have been forced to close due to lack of recruitment. The ProStart trial in the UK has also had to close for the same reason. It has been acknowledged by the Food and Drug Agency in the USA that comparative randomized trials will be problematic in this area due to lack of physician and patient equipoise. A randomized trial may be feasible if a pragmatic design is adopted but prior to acceptance of such a design, the number of centres with expertise in this complex intervention (mp-MRI, TTPM, focal HIFU) will need to be increased.

Observational studies are a commonly used alternative to ascertain the effectiveness of a treatment. They are used to observe a treatment effect in a selected group of patients who are presumed to derive benefit from the treatment given. Although methodologically not as robust, and therefore prone to bias, they have some benefits over RCTs. The principal ones are those of enhanced external validity (many patients do not wished to be randomised and therefore refuse participation), and more rapid accrual compared to a randomised design.

For this reasons, a single arm medium term follow-up cohort intervention study has been designed.

At the time of writing the safety and tolerability aspects of focal therapy by HIFU are known as a result of the Phase I/II studies carried out at UCLH. The results have been presented and exist in the public domain in abstract form but have not yet been published (presented in tables above). These early studies were powered to detect a change in the proportion of men who could obtain an erection sufficient for penetration compared to their status prior to their treatment. The very low event rate for both erectile dysfunction and incontinence indicates that the ‘proof of concept’ has been demonstrated for focal therapy. Moreover, we can be relatively confident that, in expert hands, focal HIFU is safe.

Therefore, a multi-centre study is now required involving a larger group of patients for the following reasons:

1) To evaluate medium term cancer control using histological parameters.

2) To confirm that focal therapy can lead to low rates of genitourinary and rectal toxicity and minimal impact on quality of life within a large and more representative cohort of patients (greater precision around outcome measures).

3) To demonstrate that the skills (characterization through template prostate mapping and MRI as well as the treatment related skills) acquired by the team at UCLH are indeed
transferable to other providers.

4) To calculate costs of care and to model potential cost-effectiveness in comparison to alternative therapies.

If this single arm intervention study demonstrates acceptable outcomes to support the findings of the Phase I/II studies, it is anticipated that this preliminary study will lead onto a Phase III evaluation of focal therapy, prior to more widespread use of this technology.

6.9 Cost Effectiveness Modelling

Development of a cost effectiveness model for focal therapy outcomes could evaluate pre-treatment, treatment and post-treatment costs (blood tests, mpMRI, biopsies, management of side-effects, re-treatment of failures, recurrent costs), quality of life, and potential impact on survival. The benefits, costs and savings in using a quick treatment that utilises fewer resources (capital and recurrent), and achieving fewer side-effects through a reduction in the therapeutic burden using focal therapy, needs to be assessed against the greater costs incurred as a result of a requirement to characterise the disease accurately at the outset. A decision analytic disease model will become available to determine the place of focal therapy in relation to other treatment options for prostate cancer, including radiotherapy, surgery and active surveillance. 123

This objective will utilise validated questionnaire data that is available from existing studies led by Erasmus MC, Rotterdam, the Netherlands. Such data will be used in the comparative modelling of the current diagnostic and therapeutic pathways. Details of the model to be used are specified in section 15.2.

In order to gain an understanding of how patient outcomes relate to other similar patient groups to derive incremental cost-effectiveness ratios, we are seeking to make direct outcome comparisons against other trials that have incorporated current standard care. Most single arm intervention observational studies of prostate cancer therapies use erectile function, urinary continence, and cancer control as outcome measures. We propose a retrospective analysis of data collected from other cohorts of men with similar disease risk profiles i.e. localised low-intermediate risk prostate cancer, and baseline characteristics e.g. age, who have undergone ‘standard’ prostate cancer treatments.

A number of statistical methods can be used in order to reduce bias effects in observational studies. For example, propensity score matching uses a scoring system applied to study subjects, in order to ‘balance’ known confounding factors between exposed and non-exposed groups 124. This method is thought to provide a more robust matching technique and can be applied where baseline characteristics differ between groups. This statistical analysis will enable us to model cost effectiveness.
### 7. Specific Aims of the Study

#### 7.1 Research Question

In men with localised prostate cancer, can focal ablation using High Intensity Focused Ultrasound, lead to acceptable medium term cancer control?

#### 7.2 Objectives

##### 7.2.1 Primary objectives

1. To determine the proportion of men who are free of any prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU

2. To determine the proportion of men who are free of clinically significant prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU

To further explain, we would wish for a man to undergo the following transitions from baseline to 36 month TTPM in order to meet either primary objective 1 or 2

<table>
<thead>
<tr>
<th>Treated area</th>
<th>Untreated area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-focal</td>
<td></td>
</tr>
<tr>
<td>Green</td>
<td>Amber</td>
</tr>
<tr>
<td>Red</td>
<td>Green</td>
</tr>
<tr>
<td>White</td>
<td>Green</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Objective 1</th>
<th>White</th>
<th>White</th>
<th>White</th>
<th>AND</th>
<th>Green</th>
<th>White</th>
<th>White</th>
<th>Green</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Primary Objective 2</th>
<th>Green</th>
<th>Green</th>
<th>Green</th>
<th>AND</th>
<th>Green</th>
<th>White</th>
<th>White</th>
<th>Green</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>White</td>
<td>White</td>
<td>White</td>
<td></td>
<td>White</td>
<td>Green</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- histological outcomes in the treated and untreated areas at 12 months and 36 months
- proportion of men achieving trifecta status at 36 months
- rate of secondary prostate cancer intervention (prostatectomy, radiotherapy, androgen ablation, whole-gland HIFU or cryosurgery)
- risk factors for failure defined as a) presence of any cancer and b) clinically significant cancer at study end

To analyse the following outcome parameters following focal therapy using HIFU:
- biochemical (PSA) kinetics including determining the optimal biochemical definition of failure
- describe composite outcomes of failure

2. To determine the costs of treatment and model potential cost effectiveness using comparative cancer control and functional outcomes at 36 months compared to other cohort trials involving the management of localized prostate cancer

3. To determine the clinical validity (sensitivity, specificity, negative and positive predictive values, inter-observer variability (MRI only)) of:
- multi-parametric MR-imaging to predict presence of clinically significant prostate cancer on template transperineal prostate mapping biopsies prior to focal therapy
- MR-imaging changes to predict presence of residual/recurrent clinically significant prostate cancer on biopsy
- HistoScanning™ to predict presence of clinically significant prostate cancer on template transperineal prostate mapping biopsies prior to focal therapy
- HistoScanning™ to predict presence of residual/recurrent clinically significant prostate cancer on biopsy

4. To determine the following using MR-TRUS registration (UCLH only):
- Number of patients in whom the planned treatment volume was increased as a result of image registration
- Volume change between initial and registration-informed treatment plans
- Time required to plan the treatment manually versus registration-based planning alone or a combination of the two methods (as proposed in this protocol).
- Volume overlap between target volumes, as defined by the HIFU treatment plan, and the regions of necrosis visible in post-operative MR images.

### 7.3 Outcome Measures

#### 7.3.1 Primary Outcomes

**Cancer control**

1. The proportion of men who are free of any prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU
2. The proportion of men who are free of clinically significant prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU

7.3.2 Secondary Outcomes

To determine the following after focal therapy using HIFU:

**Sexual outcomes**
- The presence of severe erectile dysfunction at 12 and 36 months, as measured by the IIEF-15 questionnaire with or without the use of phosphodiesterase-5 inhibitors, in those with absence of severe erectile dysfunction at baseline
- 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.
- Time to return of erectile function (absence of severe ED on IIEF-15 questionnaire)
- Need for phosphodiesterase-5 inhibitors to maintain erectile function sufficient for penetration at 36 months
- The presence of ejaculatory function at 12 and 36 months as measured by the orgasmic function domain of the IIEF-15 questionnaire
- The presence of orgasmic function at 12 and 36 months as measured by the orgasmic function domain of the IIEF-15 questionnaire
- Presence of pain during intercourse requiring premature cessation of intercourse i.e. prior to climax, at 36 months

**Urinary incontinence**
- 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
- Presence of urinary incontinence (requiring any pad usage) as determined by the UCLA-EPIC urinary continence questionnaire at 12 months and 36 months
- Time to return of urinary continence (as determined by UCLA-EPIC Urinary domain questionnaire)

**Other functional outcomes**
- Grading of lower urinary tract symptoms as determined by IPSS scores at 12 months and 36 months
• Presence of bowel toxicity as determined by the UCLA-EPIC Bowel questionnaire at 12 months and 36 months

• Anxiety levels as measured by the Memorial Anxiety Scale for Prostate Cancer

• General and prostate health related quality of life as measured using EQ-5D and FACT-P Version 4.

**Cancer control/ disease progression outcomes**

• 12 months histology
  
  o Absence of any prostate cancer on TRUS biopsy in the treated area
  
  o Absence of clinically significant prostate cancer on TRUS biopsy in the treated area

• 36 months histology: of men who had clinically significant cancer in the treated area, the absence of clinically significant cancer in the treated area

• 36 months histology: of men who had no cancer at baseline TTPM in the untreated area,
  
  o Absence of any prostate cancer on TTPM histology in the untreated area
  
  o Absence of clinically significant prostate cancer on TTPM histology in the untreated area

• 36 months histology: of men who were free of clinically significant cancer at baseline TTPM in the untreated area,
  
  o Absence of clinically significant prostate cancer on TTPM histology in the untreated area
  
  o Absence of any prostate cancer on TTPM histology in the untreated area

• Biochemical (PSA) kinetics and the optimal biochemical definition of failure

• Composite end-point on cancer control as defined by time to failure defined on histological OR biochemical OR clinical parameters
  
  o Histological failure (presence of clinically significant prostate cancer on any biopsy: Gleason pattern >/=4 and/or 4mm maximum CCLI)
  
  o Clinical progression (clinical T3, prostate cancer metastases, prostate cancer related death)
  
  o Biochemical (using known parameters)
    
    velocity >1 ng/ml/year OR
    
    doubling time </=3 years OR
    
    nadir >XX% of baseline PSA or PSA rise to >XX% of baseline PSA after nadir achieved
    
    XX% defined by:
    
    \[
    \frac{\text{volume of residual prostate tissue on 12 month MRI}}{\text{volume of prostate tissue on pre-treatment MRI}} \times 100
    \]
Three composite endpoints will be reported representing each of the biochemical parameters outlined above.

- Achievement of trifecta status (no severe ED, pad-free leak-free continence, cancer control with absence of clinically significant cancer) at 36 months in those men with good baseline function

- Time to initiation of secondary prostate cancer intervention (prostatectomy, radiotherapy, androgen ablation, whole-gland HIFU or cryosurgery) as a result of:
  - Histological burden greater than Gleason pattern 3 and/or max CCLI >=3mm
  - Rising PSA* (*needs TSC validation of clinical, pathological and case report form review to verify reason)

- Time to initiation of secondary prostate cancer intervention (prostatectomy, radiotherapy, androgen ablation, whole-gland HIFU or cryosurgery) for any cause

- Evaluation of risk factors predictive of failure as defined by
  - Presence of any cancer or
  - Presence of clinically significant cancer at study end

**Cost effectiveness**

- Development of a healthcare economic model to evaluate the cost-effectiveness of focal therapy using a comparison of genitourinary and cancer control outcomes against matched groups from existing studies evaluating standard of care (active surveillance and radical therapies).

**Imaging**

- The clinical validity (sensitivity, specificity, negative and positive predictive values, inter-observer variability) of MR-imaging changes to predict presence of residual/recurrent clinically significant prostate cancer on biopsy

- To determine the clinical validity (sensitivity, specificity, negative and positive predictive values, inter-observer variability) of multi-parametric MR-imaging to predict presence of clinically significant prostate cancer on template transperineal prostate mapping biopsies prior to focal therapy

- The clinical validity (sensitivity, specificity, negative and positive predictive values) of HistoScanning™ to predict presence of clinically significant prostate cancer on template transperineal prostate mapping biopsies prior to focal therapy

- The clinical validity (sensitivity, specificity, negative and positive predictive values) of HistoScanning™ to predict presence of residual/recurrent clinically significant prostate cancer on biopsy

**MR-TRUS Imaging Registration (UCLH only)**

- Proportion of patients in whom the planned treatment volume was increased as a result of image registration
• Volume change between initial and registration-informed treatment plans
• Time required to plan the treatment manually versus registration-based planning alone or a combination of the two methods (as proposed in this protocol).
• Volume overlap between target volumes, as defined by the HIFU treatment plan, and the regions of necrosis visible in post-operative MR images.

8. Study Design

8.1 Verification stage

8.1.1 Evaluation Process

• Approved written informed consent
• History and Physical Examination, including digital rectal examination
• Completion of validated patient questionnaires
• Serum blood tests: PSA, renal function, full blood count
• TRUS to determine prostate volume, presence of intra-prostatic calculi
• Attendance at Pre-assessment clinic to assess fitness for general anaesthetic

8.1.2 Identifying the disease by multi-parametric MRI

mpMRI will be the non-invasive investigation on which the presence of ‘clinically significant’ lesions amenable to focal ablation will be identified.

For men referred from other centres who would not have had a mpMRI prior to a TRUS prostate biopsy, a mpMRI scan will be performed. The mpMRI will be performed at least 6 weeks after the original biopsy performed at the referring centre to limit biopsy artefact being seen on MRI. They will also have a radio-isotope bone scan to rule out macroscopic evidence of metastatic disease as appropriate according to local cancer network guidelines for staging.

Pre-Focal HIFU, 12 month and 36 month mpMRI protocol

Pre-operative and all post-HIFU imaging will be performed using either a 1.5 Tesla or 3 Tesla scanner and a pelvic phased array receiver, with a pelvic coil. A full protocol of T1 and T2 weighted turbo-spin echo images and a dynamic post gadolinium volume acquisition will be used for both pre-operative diagnostic and planning scans and post-operative assessment of HIFU. The protocol will be standardised as below:

• T2 weighted axial of pelvis: to detect lymphadenopathy and other pelvic pathologies
  T2 axial small field of view prostate: cancer detection and volume estimation
  T2 small FOV coronal: for cancer detection and to accurately determine the position of prostatic apex and external sphincter
  T1 axial small FOV: to detect haemorrhage
  Total time= 20 minutes

• Dynamic contrast-enhanced FLASH sequences with scans before and after every 20 seconds after contrast administration for 1.5 Tesla scanner or after every 10 seconds for 3 Tesla scanner, for 4 minutes: for tumour enhancement.
• Post contrast small FOV fat saturated T1 axis: high-resolution images of enhancement
  Total time= 10 minutes

• Diffusion weighted axial scans of prostate: to detect restricted diffusion in tumour
  Total time= 5 minutes

• The scoring system agreed as a result of the European consensus meeting will be used to report the probability of malignancy from the images. The results will be conveyed in diagrammatic, number and written form using a standardised proforma. The prostate will be divided into 27 Regions of Interest for scoring.

**Scoring System**

1 - Clinically significant disease is highly unlikely to be present
2 - Clinically significant cancer is unlikely to be present
3 - The presence of clinically significant cancer is equivocal
4 - Clinically significant cancer is unlikely to be present
5 - Clinically significant disease is highly likely to be present

(Clinically significant disease defined as Gleason >= 4+3 +/- lesions >= 0.5cc)

**A Twenty-Seven Regions of Interest Scheme**

Pre-Focal HIFU, 12 and 36 month HistoScanning™ protocol
HistoScanning™ will be performed in those centres that already have the device. Histoscanning™ will be performed at baseline either prior to the initial disease localization template biopsies, or just prior to HIFU treatment, on the same visits and under General Anaesthetic (for patient convenience to reduce the number of visits required, not because this investigation requires anaesthesia). Histoscanning™ imaging will also be performed at 12 months prior to TRUS biopsies (under local anaesthetic), and prior to the 36-month template biopsies (under the same general anaesthetic). A standardised reporting protocol will be used for communicating the results. This protocol is currently being formulated and will be available prior to commencement of the trial.

8.1.3 Disease Localisation: Prostate Mapping Biopsies

The process by which the specified distribution of cancer will be verified is primarily by using transperineal template 5mm spaced prostate mapping biopsies. This uses biopsies taken every 5mm from the prostate using a brachytherapy grid placed over the perineal skin whilst the man is in the lithotomy position. 3-dimensional data on the location and specific grade for each focus of cancer is available and focal ablation planning based on this information. The following format will be used to report all template biopsies:
The diagnosis will be established on Transperineal template prostate biopsy (Gleason grade). Areas of Green as defined by the method above will be deemed clinically insignificant.

Histopathologists from each site will need to reach consensus on the quality control issues surrounding both TRUS and Transperineal biopsies. The format for this will be decided amongst the pathologists involved from each centre prior to the commencement of the trial. Centralised double reporting of baseline TRUS biopsies can be requested.
prior to enrolment to ensure eligibility for inclusion.

8.2 **Intervention Stage**

8.2.1 **Treatment with HIFU focal ablation procedure**

Signed informed consent will be taken for the focal ablation procedure using HIFU therapy. Patients will 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 contraindications 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.

The treatment will cover the side of the gland in which the clinically significant lesion(s) have been identified by a combination of MRI and biopsy as follows:

1. Max 50-60% tissue ablation

2. Tissue will be ablated in the entire lobe affected (i.e. hemi-ablation of the prostate) for the first 20 cases of each centre that is conducting focal HIFU for the first time. This will standardize treatments for the initial phase of the study when the learning curve is most pronounced.

Following this initial period, the treatment protocol will be as follows:

Tissue will be ablated in the entire lobe affected provided more than one half of the lobe is affected.

OR

Tissue will be ablated in the entire affected quadrant of the prostate provided that less than one half of the lobe is affected.
3. Treatment will reach the urethra and may cross the midline by up to 5-10 millimeters if the disease is close to the midline (minimum 5mm margin over midline) or crosses over (minimum 10mm margin over midline) (anterior or posterior ‘dog-leg’), provided that the treatment does not cross the para-sagittal plane on that side (usually 10mm from midline).

4. At least one neurovascular bundle must be avoided by ensuring a minimum distance of ablation zone to contralateral NVB of 10mm. This would usually require preservation of the contralateral lobe but the 10mm rule ensures that in patients in whom the dog-leg is used the contralateral NVB avoids damage.

5. When cancer is seen at the extreme apical limit on mp-MRI the patient should be excluded.

6. Absence of clinically significant cancer in untreated areas (up to and including 3mm cancer core length and Gleason pattern ≤3). The maximum number of cores with this amount of cancer core length or Gleason grade should not exceed 50% of the total biopsy volume from that corresponding side. If this number is exceeded, that lobe must be considered as equivalent to clinically significant disease.

7. In men in whom both lobes meet criteria for clinically insignificant cancer (≤3mm and absence of Gleason pattern 4), the lobe with the dominant disease burden will be treated. This will be evaluated primarily on biopsy results (combined TRUS guided biopsy histology and TTPM histology). If these show identical bilateral disease burden, the side with the highest score for probability of malignancy on MRI will be treated. If this is also equivalent, a second review of the biopsies will be requested by the trial centre’s pathologist and the dominant side treated. Only those patients with exactly equivalent disease bilaterally following these three reviews will be excluded from the trial.

8. One redo-HIFU to treated side is permissible, as per current protocols and standard practice for HIFU, if either 12 months TRUS biopsies of treated side OR ‘for-cause’ biopsies are positive. If redo focal HIFU is required on the basis of a positive 36 month TTPM, the re-treatment will be considered and given outside of the trial protocol, as considered appropriate by the treating clinician but the case treated as a failure according to primary outcome measure 1.

The following diagrams demonstrate the types of treatments that are possible within these rules:
A new software-based image registration technique has been developed by a UCL team at the Centre for Medical Imaging Computing. This can ‘fuse’ MR-images taken before focal therapy to the ultrasound images taken at the time of focal therapy. Such a procedure may improve the treatment by helping the surgeon to decide whether (s)he has covered the entirety of the cancer that (s)he wants to treat.

Demonstration software has been developed specifically for use with the Sonablate 500 HIFU therapy device. This enables the surgeon to register one or more prostate tumour locations based on radiological analysis of MR images with 3D transrectal ultrasound (TRUS) images obtained by the device. A novel feature of the software is that it compensates for gland deformation between the MR and TRUS images. The registration software runs independently of the Sonablate software, but on the computer that forms part of the device. The software will allow MR-image-derived targets to be accurately located with respect to the TRUS guidance images provided by the system, thus helping to guide and target the HIFU ablation.

We propose integrating image registration within the INDEX trial at the UCLH site only within the INDEX study by adopting this software. The corresponding workflow is as follows:

Pre-operative Treatment Planning
- Pre-operative MR images will be assessed for visible lesions by a trained uro-radiologist.
- Manual contouring will be performed on the prostate capsule and the boundary of visible lesions (suspected to be cancerous tumours) using special-purpose software. The lesions will be delineated by the uro-radiologist, but the capsule boundary may be delineated by another trained clinician to reduce the load on the radiologist.
- Base and apex points will be identified manually and marked on the MR images.
- Concordance for positive histology of contoured lesions will be verified on template mapping biopsies (TPM) by another co-investigator (i.e. not the uro-radiologist reporting the pre-operative MR images).
- Part of the UCL registration software will generate a patient-specific computer model of the prostate gland (based on MR-derived contours), which deforms in a physically realistic way to reflect the expected deformation of the gland during a HIFU procedure. This model will contain information on the location of the prostate with respect to the rectum, and the location and extent of MR-visible tumours identified by the uro-radiologist.

Peri-operative Image Registration
Firstly, a standard set-up procedure will be performed with the Sonablate device, prior to HIFU treatment. This will include acquisition of a 3D TRUS volume, which is saved to the device hard drive. The area to be treated will then be planned manually by the operating surgeon using the standard Sonablate treatment planning software, according to usual procedure; i.e. according to pre-operative MRI and TPM findings and pre-operative discussion between the operating surgeon and the uro-radiologist. Treatment plans will be stored on the device and visualised as a graphical overlay, superimposed onto views of the 3D TRUS volume saved in the previous step.

Secondly, the previously generated computer model of the prostate will be registered (i.e. spatially aligned) with the saved 3D TRUS volume using the UCL registration
software. This procedure is fast, taking only 2-3 minutes per procedure. The accuracy of the alignment will be visually inspected by the surgeon and information of the registered location of the tumour targets saved to a file, which can then be loaded into the Sonablate device planning software and visually compared with the regions to be treated as defined in the initial treatment plan. At this stage, the surgeon may adapt the treatment plan based on the information from the registration software in way that can only add to but not decrease the initial planned treatment volume, subject to the constraint that the final image-registration-informed treatment volume may not exceed 60% of the overall prostate volume. This will ensure that the cancer control capability of the standard clinical treatment method is not compromised in the situation when a smaller tissue volume would otherwise be treated if the new plan was based entirely on information provided by the registration software. The final treatment plan will be stored electronically on the Sonablate device. The operating surgeon will be free to reject the information provided by using the registration software if (s)he believes that this may compromise the patient treatment in any way. In this case, the surgeon will record the reasons, which will be stored with the other data collected as part of the study. A further 3D TRUS image will be acquired and saved by the Sonablate system at the end of the procedure for the purposes of post-operative analysis.

Post-operative Image Registration
Using the same method described above, the UCL registration will be used to register post-operative MR images with the 3D TRUS volume acquired at the end of the procedure. The spatial distribution of the treated tissue (i.e. necrosis), visible in the MR images, will then be compared with the treatment plan and the treated tissue determined by analysing the final 3D TRUS image.

Of the approximately 60 patients we intend to treat at UCLH, approximately 70% are expected to have MR-visible lesions therefore approximately 42 patients will be eligible for image-registration-aided treatment planning in addition to standard manual planning.

8.2.2 Post Focal HIFU

Post-treatment the suprapubic catheter will be attached to a catheter bag on free drainage. This will be changed the following day to a flip-flow valve thereby allowing the patient to return to a normal voiding pattern sooner.

From the operating theatre the patient will be taken to a recovery area and thence to the ward. Discharge will be nurse-led and on the same day as deemed appropriate. Catheter care advice will be given to the patient prior to discharge. Analgesia (such as co-dydramol 10/500, paracetamol or diclofenac), antibiotics (quinolones for 1 week) and laxatives will be provided as part of post-operative care.

Suprapubic catheter withdrawal will occur under antibiotic cover in a clinic setting 5-14 days after treatment at the treating centre or locally by a practice nurse or district nurse. If the patient fails to void, he will be taught CISC. Failure to void requiring hospitalisation is an expected side-effect of HIFU therapy and will not be reported as a serious adverse event that requires reporting to the sponsor or the Ethics Committee.
8.3 Training and Quality Control

The success or otherwise of a new intervention will be heavily dependent on the training and quality control for new users. This needs to be both comprehensive and flexible to fit in with clinical practice. With these factors in mind, the following pragmatic clinical training programme has been written for the purpose of delivering the interventions within this trial.

8.3.1 Multi-parametric MRI

All radiologists from non-UCH UK centres will attend UCH for a training day on the conduct and reporting of pre-treatment MRI and post-treatment early contrast MRI and late mpMRI. This training day will comprise:
- 20 pre-treatment diagnostic sets of mpMRI with their corresponding pathology (Template biopsy or radical whole-mount)
- 5 training sets of early contrast MRI
- 10 late post-treatment diagnostic mpMRI

mpMRI from the first 5 patients will be double reported by a radiologist expert in prostate MRI as a quality control measure. Discrepancies will be dealt with by an arbitrating third radiologist expert in prostate MRI.

Only radiologists attending the training day (or other approved training programme if they cannot attend the training day) will be approved for reporting MRIs within this trial.

8.3.2 HistoScanning™

Clinicians from centres performing HistoScanning™ who are not already familiar with the technique to the required trial standards, will have a training session prior to the commencement of the trial. This may be arranged at the host centre or at the centre concerned and will be led by a member of Advanced Medical Diagnostics.

A proportion of the trial scans will be reviewed externally by a member of the Advanced Medical Diagnostics group experienced in the use of HistoScanning™. All data collected, in the form of still ultrasound images, will be available for review by the sponsor centre and Advanced Medical Diagnostics, for quality control and data collection purposes. Data collection will conform to the required standard of conduct for confidentiality, including anonymity of data sets.

3-dimensional radiofrequency datasets will be archived in the Sponsor facilities.

8.3.3 Template Biopsies

All clinicians carrying out template biopsies will be required to carry out template biopsies to the standard laid down in this protocol.

1. Any number of clinicians at each centre may carry out this procedure
2. Each clinician carrying out template biopsies will need to observe a minimum of 2 template biopsies at a training centre (Basingstoke or UCH).
3. Each clinician will then need to be proctored for the first two cases by an approved expert proctor. This may be extended at the discretion of the proctor.

Clinicians will be signed off for non-proctored cases by an expert proctor. Only clinicians approved through this programme can conduct template biopsies for the purpose of this trial.

8.3.4 **TRUS guided biopsy**

There will be no formalised specific training programme for clinicians carrying out TRUS biopsies but all clinicians will be required to conduct the TRUS biopsies after focal therapy as laid down by the trial protocol. There will be no minimum requirement on the study entry TRUS biopsy as men will undergo a detailed TTPM biopsy procedure.

8.3.5 **Pathology**

There will be a specialist pathology meeting prior to the trial commencement in order to discuss the requirements for standardised pathology reporting and all pathologists will be required to report the biopsies as laid down by the trial protocol. However, there will be no other formalised specific training programme for pathologists.

8.3.6 **Focal-HIFU**

Clinicians will undergo training and proctoring to ensure treatment is delivered to a standard laid down by the reference centre, UCL/UCH.

1. Clinicians with or without previous HIFU experience will be required to visit a training centre (UCH or Basingstoke) on at least two occasions and observe at least 3 cases of focal HIFU.

2. Clinicians with previous HIFU experience will be required to undergo proctoring for their first 5 cases on any number of visits. This number may be extended at the discretion of the proctor. Thereafter, either in-person or remote video-linked training will be delivered by an expert proctor and HIFU technician for the next 5 cases. This number may be extended at the discretion of the proctor.

3. Clinicians with no previous HIFU experience will be required to undergo proctoring for their first 10 cases on any number of visits. This number may be extended at the discretion of the proctor. Thereafter, either in-person or video-linked training will be delivered by an expert proctor and HIFU technician for the next 5 cases. This number may be extended at the discretion of the proctor.

Clinicians will be signed off for non-proctored cases once the first 10 or 20 cases for that clinician has undergone review, including against post-treatment early contrast MRI. This review will be conducted in an iterative manner so treatments conducted below the standard required will lead to remedial action in the next treatment for that centre. The reviews will be carried out by an expert proctor.

The specified number of proctoring visits should be considered as a minimum. Clinicians undergoing proctoring are encouraged to request further proctoring visits at any time if required following the minimum number of cases. If more than a 3 month period elapses since the end of the proctoring to the first treatment due to be given by the surgeon, a refresher proctoring session will be required.
Only approved clinicians will deliver the treatment within this trial. This may be urologists or non-urologists dependent on the individual centre’s preference. At the initiation of the trial, only one clinician per site will be proctored until competent to perform focal HIFU independently. If after this point, another clinician from a centre wishes to take part in performing focal HIFU, availability of a reference centre for proctoring will be considered at that point.

Each trial centre is required to treat at least 5 patients within the trial period to ensure that the required HIFU treatment skills are maintained.

Any re-do focal HIFU treatments performed within the trial period should be proctored with an expert proctor and/or HIFU technician present.

9. Study Group

Patients who have histologically confirmed prostate cancer, which has not been treated and meeting the entry criteria will be approached for the study. They will be given as much time as they need to consider whether or not they wish to participate (minimum 24 hours). Patients who wish to participate after reading the patient information sheet will undergo a screening visit (visit 1) to ascertain whether or not they are eligible for the trial. If they are eligible following mpMRI and template biopsies (visits 2 and 3), and undergo HIFU treatment (visit 4), they will be seen at further follow-up visits (visits 5-14).

9.1 Eligibility

9.1.1 Inclusion Criteria

The population studied will be those patients who have:

- Histologically proven prostate cancer on trans-rectal or transperineal template prostate biopsies
- TRUS biopsy: up to burden bilateral disease with maximum 3mm one biopsy on non-dominant side is allowable.
- Template biopsy:
  - unilateral disease any burden
  - bilateral disease
    - presence of clinically significant cancer on only one side (as determined by histological rules described above) Gleason $\leq 7$, OR
    - clinically insignificant disease with a burden of $>50\%$ of biopsy cores taken on that side, OR
    - bilateral clinically insignificant disease and $<50\%$ of biopsy cores positive on any one side but with dominant disease burden on one side
- Stage T1-T2cN0M0 disease, as determined by local guidelines (radiological T3a permitted)
- Serum PSA $<=$15
- Life expectancy of $>=$ 10 years
- Signed informed consent by patient
- An understanding of the English language sufficient to understand written and verbal information about the trial and consent process
9.1.2 **Exclusion Criteria**

- Men who have had previous radiation therapy
- Men who have had androgen suppression/hormone treatment within the previous 12 months for their prostate cancer
- Men with evidence of metastatic disease or nodal disease outside the prostate on bone scan or cross-sectional imaging
- Men with an inability to tolerate a transrectal ultrasound
- Men with latex allergies as the HIFU probe is covered with a latex condom sheath prior to insertion into the back passage
- Men who have undergone prior significant rectal surgery preventing insertion of trans-rectal HIFU probe (decided on the type of surgery in individual cases)
- Men who have had previous HIFU, cryosurgery, thermal or microwave therapy to the prostate.
- Men who have undergone a Transurethral Resection of the Prostate (TURP) for symptomatic lower urinary tract symptoms within 6 months. These patients may be included within the trial if deferred from consenting and screening until at least 6 months following the TURP.
- Men not fit for major surgery as assessed by a Consultant Anaesthetist
- Men unable to have pelvic MRI scanning (severe claustrophobia, permanent cardiac pacemaker, metallic implant etc likely to contribute significant artefact to images)
- Presence of metal implants/stents in the urethra
- Presence of prostatic calcification and cysts (on transrectal ultrasound) whose location will interfere with effective delivery of HIFU therapy
- Men with renal impairment with a GFR of <35ml/min (unable to tolerate Gadolinium dynamic contrast enhanced MRI).
10. Trial Flow

1. Men with Low-Intermediate Risk Prostate Cancer
   - Refused to participate, n/a...
   - Consent
     - MR-MRI and Template Transperineal Prostate Mapping Biopsies
     - Refused to participate, n/a...
     - Ineligible for focal therapy, n/a...
   - Focal Therapy
    - 1-3 weeks: Dynamic Contrast MRI
    - 1-2 weeks: SPC removal
    - 6 weeks post-Focal: questionnaires, PSA
    - 3, 6 & 9 months post-Focal: questionnaires, PSA
    - Refused biopsy, n/a...
    - 12 months post-Focal: MP-MRI and TRUS biopsy, questionnaires, PSA
      - If positive, allow one redo Focal-HIFU
    - 18, 24, and 30 months post-Focal: questionnaires, PSA
      - For cause biopsy
    - 36 months: questionnaires, PSA, mp-MRI, template biopsy
      - Refused biopsy, n/a...
    - 38 month post-Focal: Exit from trial
      - If positive, allow one further focal HIFU to treated or untreated areas
11. Individual Study Visits

Patient questionnaires will be in two packs:
Pack 1 = All questionnaires except FACT-P and Memorial Anxiety Scale score.
Pack 2 = FACT-P and Memorial Anxiety Scale score questionnaires.

11.1 Visit schedule

<table>
<thead>
<tr>
<th>Visit number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-2W</td>
<td>6W</td>
<td>3M</td>
<td>6M</td>
<td>9M</td>
<td>12M</td>
<td>18M</td>
<td>24M</td>
<td>30M</td>
<td>36M</td>
<td>38M (Exit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full blood tests</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA blood test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire Pack 1</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire Pack 2</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRUS (assess prostate)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>X</td>
<td>(X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HistoScanning</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRUS biopsy</td>
<td>(X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Template biopsy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal HIFU</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter removal</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case Report Form</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event reporting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Re-treatment HIFU may be required at those points marked by an arrow (→), or following ‘for cause’ biopsies at any other point after the primary HIFU treatment.

Shaded areas represent the follow-up visits that may be performed via telephone consultations plus PSA checks with the general practitioner (at the trial centre clinician’s discretion).

PSA blood tests will also be required at 15, 21, 27 and 33 months and can be taken at the patient’s general practitioner or trial centre.
11.1.1 Visit 1: Screening Visit

- Informed consent will be signed before implementation of any study-related procedure.
- The screening assessment will consist of:
  - Full medical history
  - Digital rectal examination
  - Review of prostate biopsy
  - Review of previous laboratory investigations (biochemistry, PSA and full blood count)
  - PSA if not available within 60 days prior to entry
  - Review of urinalysis
  - Assessment of inclusion/exclusion criteria

If they are eligible to participate in the study the following will be carried out during this visit:

- Sign informed consent form
- Patient questionnaires packs 1 and 2
- PSA level

If previous template biopsy and mpMRI have already been carried out to the standards described in this protocol within 12 months of screening visit, these will be reviewed to determine eligibility. If eligible, the next trial visit will be the focal-HIFU treatment (Visit 4). Otherwise, men will proceed to mpMRI and Template biopsies as follows.

11.1.2 Visit 2. Multi-parametric MRI

Minimum of 6 weeks after TRUS biopsy. Protocol outlined in section 8.1.2

11.1.3 Visit 3. Template Transperineal biopsies

Protocol outlined in section 8.1.3
HistoScanning™ may also be performed at this time (in specified centres) according to the protocol in section 8.1.2.
Following the results of the mpMRI and template transperineal biopsies, the patient will be informed of whether he is eligible for focal-HIFU treatment. If so, the next visit will occur. If not, the patient will be withdrawn from the trial and offered standard care treatments as determined by local practice.

11.1.4 Visit 4: HIFU Treatment Day

Minimum 6 weeks after TTPM in order to allow inflammation to resolve.
HistoScanning™ may also be performed at this time (in specified centres) according to the protocol in section 8.1.2.
Signed informed consent for the procedure will be obtained. HIFU treatment will be carried out as outlined in the HIFU treatment section (8.2.1). Discharge is expected to be on the same day or the following day with a suprapubic catheter.
11.1.5 Visit 5: 1-2 Weeks Post HIFU Ablation

A follow-up MRI scan will be carried out to assess the area of necrosis in at least the first 5 cases per centre (for quality control purposes). Protocol for this is outlined in section 11.2.3

Suprapubic catheter removal under antibiotic cover (can be carried out in local centre or in treating centre as appropriate).Patients will be taught CISC, if appropriate.

11.1.6 Visit 6: 6 Weeks Post HIFU Ablation

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires pack 1
• Case report forms

11.1.7 Visit 7: 3 Months Post HIFU Ablation

(This visit may be performed via a telephone consultation and arrangement for blood tests via the patient’s family practitioner at the clinician’s discretion)

• Adverse event reporting
• Blood tests: PSA (locally with family practitioner is possible)
• Patient questionnaires pack 1
• Case report forms

11.1.8 Visit 8: 6 Months Post HIFU Ablation

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires packs 1 and 2
• Case report forms

11.1.9 Visit 9: 9 Months Post HIFU Ablation

(This visit may be performed via a telephone consultation and arrangement for blood tests via the patient’s family practitioner at the clinician’s discretion)

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires pack 1
• Case report forms

11.1.10 Visit 10: 12 Months Post HIFU Ablation

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires packs 1 and 2
• Case report forms
• Multi-parametric MRI, HistoScanning™ (in some centres), and TRUS prostate biopsy of treated area

If the 12 month transrectal prostate biopsy identifies the presence of cancer in the treated area of ablation then the patient will be offered a second treatment (re-treatment) with focally delivered HIFU and the follow-up visits for the re-treatment HIFU will be the same as the primary HIFU treatment.

11.1.11 Visit 11: 18 Months Post HIFU Ablation

(This visit may be performed via a telephone consultation and arrangement for blood tests via the patient’s family practitioner at the clinician’s discretion)

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires pack 1
• Case report forms

11.1.12 Visit 12: 24 Months Post HIFU Ablation

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires packs 1 and 2
• Case report forms

11.1.13 Visit 13: 30 Months Post HIFU Ablation

(This visit may be performed via a telephone consultation and arrangement for blood tests via the patient’s family practitioner at the clinician’s discretion)

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires pack 1
• Case report forms

11.1.14 Visit 14: 36 Months Post HIFU Ablation

• Adverse event reporting
• Blood tests: PSA
• Patient questionnaires packs 1 and 2
• Case report forms
• Multi-parametric MRI
• HistoScanning™ (in some centres)
• Transperineal template prostate biopsy of both treated and untreated areas
11.1.15 Visit 15: 38 Months Post HIFU Ablation

- Adverse event reporting
- Case report forms
- Transperineal template prostate biopsy result to patient

If the transperineal template prostate biopsy identifies the presence of cancer in the treated or untreated area of ablation then the patient can be offered re-treatment as per the local or clinician's guidance standard, outside of the trial. The presence of residual or recurrent disease will be reported as a histological outcome failure as per the trial protocol.

Other blood tests

PSA blood tests at 15, 21, 27 and 33 months will be taken either by the patient's family practitioner or at the treating centre unless clinically indicated otherwise.

Additional diagnostic tests

Subject to securing future funding, additional tests will be included on visits baseline, 12 months and 36 months for evaluation of the translational objectives in this study:
Post DRE urine
Serum/blood and germ line DNA: for biobanking and analysis of biomarkers.

Patients can opt out of any or all of these additional tests, if they wish, without compromising the overall primary objectives of the study. However, as the burden of these tests is low and men usually undergo them as part of standard care, we expect a low opt-out rate from these tests.

11.2 Follow-up details

11.2.1 TRUS Prostate Biopsy

12 month biopsy: This will be carried out using a standard technique to biopsy the prostate gland to exclude the presence of cancer. Local anaesthetic will be given during the procedure along with antibiotic prophylaxis (ciprofloxacin 500mg twice daily) for 5 days. Informed consent will be obtained by the individual performing the procedure.

Biopsies of the treated area only will be taken in order to assess under treatment, and hence treatment failure. Due to the density and volume of the residual tissue, a minimum of 1 biopsy per 1-2 ml of prostate volume is deemed sufficient. However, a biopsy density of less than 1 biopsy per 2ml will be considered inadequate and a protocol breach. Documentation of biopsy site will take the form of a 6 zone diagrammatic representation of the prostate (protocol to be finalized prior to trial commencement). The practitioner will mark those boxes that correlate with the area of the prostate that the biopsies were taken from. This will aim to standardize conduct.

Biopsy of the untreated area will only be carried out if a new suspicious lesion is detected on the 12 month MRI which was not present in that area in the pre-treatment
MRI. If this occurs, a minimum of 5 biopsies will be taken of the untreated side to reflect standard systematic TRUS biopsy protocols.

A biopsy will be offered to those men who have undergone redo HIFU treatment 4-6 months after redo focal HIFU. This will follow the same protocol as that of the 12 month biopsy.

11.2.2 ‘For Cause’ Tests

**Biopsy:** Clinicians can biopsy the prostate between primary focal HIFU and 36 months if there is a clinically significant rise in PSA (‘for cause’ biopsy) (template or TRUS biopsy permissible). This will need to be documented (using a reporting sheet explaining the rationale) and consensus approval by a Study Investigators Group (minimum 3 investigators for quorum) will be necessary prior to ‘for cause’ biopsy.

If the untreated area is biopsied, the specimens will be individually identified according to location as determined by a standard protocol.

The specimen will be processed according to standard protocol and examined by a Consultant Histopathologist to note the following features for each core taken.
- Presence of adenocarcinoma
- Gleason score
- Length of cancer and core length
- Perineural or lymphovascular invasion

**Additional Tests:** ‘For cause’ additional tests such as ultrasound, multi-functional MRI, CT scan, bone scan or PET scan will be permissible as per local centre practice.

**Template biopsy at 36 months:** This will be carried out and reported in the same format as the pre-treatment template biopsies. Areas that are absent within the 20 zone protocol will be omitted.

**HistoScanning™ at 12 and 36 months:** This will be performed at University College Hospital London and other specified centres as described in section 8.1.2. The HistoScanning™ results will not contribute towards any decision about whether a patient requires re-treatment or further biopsies.

11.2.3 Post-Treatment MRI

**1-2 week:** This will be used to verify that the treatment has been delivered appropriately according to plan with all areas planned for coverage ablated as well as determining whether appropriate energy has been delivered. It will therefore be carried out in the first 5 patients per centre (at least) as a quality control measure.

This will be performed within 1-3 week post-HIFU treatment to evaluate the extent and volume of necrosis of the prostate. T2 images will be used for measurement of prostatic volume. The necrosis volume will be measured using the final dynamic post gadolinium image, using the dynamic series and enhancement curves to confirm that an area is not enhancing. Haemorrhage will be measured on the pre-contrast FLASH sequence, and the
enhancing rim post-treatment on post Gadolinium T1-axial spin echo images. The volume of persistently enhancing prostate tissue on the follow-up scan will be calculated by subtracting the necrotic volume (measured on the dynamic 3D FLASH) from the total volume of prostate on the T2 sequence.

12 and 36 month mpMRI: This will follow the same protocol as the mpMRI pre-treatment and reported in the same manner (see section 8.1.2).

11.2.4 Concomitant therapies

Concomitant therapies and medications will be assessed and recorded during each follow-up visit. These include:

- Urethral dilatation, cystoscopy, bladder neck incision (BNI), and transurethral resection of the prostate (TURP)
- Androgen suppression in any form, radiation therapy to the prostate in any form, cryotherapy, whole-gland HIFU and radical prostatectomy
- Alpha blockade, 5 alpha-reductase inhibitors, anti-muscarinic medication

12. Evaluation of Safety and Tolerability

12.1 Adverse Event Monitoring

Each patient must be carefully monitored for adverse events and reported to the Competent Authority according to Regulation 16(10)(a) of the Medical Device Regulations 202 (SI618) and Annex X of the Medical Devices Directive 93/42. This includes abnormal laboratory values. An assessment must be made of the seriousness, intensity and relationship to the interventions undertaken in the trial as well as the HIFU treatment. The following procedures will be in place:

- Serious adverse effects will be monitored and reported on a continual basis.
- Overall safety analysis will be carried out 3-monthly by the Trial Coordinator through collation of adverse event reporting forms
- Treatment related toxicities will be analysed when all patients have undergone 6 months, 12 months, 24 months and 36 months follow-up.

12.2 Adverse Event Definitions

Adverse Event
Any untoward medical occurrence in a subject including occurrences, which are not necessarily caused by or related to the intervention

Adverse Reaction
Any untoward and unintended response in a subject, which is related to the intervention

Unexpected Adverse Reaction
An adverse reaction, the nature and severity of which is not consistent with the intervention’s applicable product information (investigator’s brochure)
Serious Adverse Event/Reaction (SAE/SAR)
Any untoward medical occurrence that:
• Led to a death
• Led to a serious deterioration in the health of the patient, user or others and includes:
  1. A life threatening illness or injury
  2. A permanent impairment to a body structure or function
  3. A condition requiring hospitalisation or increased length of existing hospitalisation (except redo HIFU treatment, elective intervention for urethral stricture, hospitalisation for planned admission unrelated to the intervention, urinary retention requiring catheterisation, planned admission for transperineal biopsies at 12 months instead of TRUS guided biopsies)
  4. A condition requiring otherwise unnecessary medical or surgical intervention and which might have led to death or serious deterioration in health had suitable action or intervention not taken place. This includes malfunction of the device (Sonablate 500) such that it has to be monitored more closely or temporarily or permanently taken out of service.
• Led to foetal distress, foetal death or a congenital abnormality or birth defect
• Might have led to any of the above

Suspected Unexpected Serious Adverse Reaction
All suspected adverse reactions related to the intervention that is both unexpected and serious

12.3 Adverse Events Information Collection
All adverse events regardless of severity or causal relationship with the intervention observed by the Investigator or reported by the patient and occurring during the study period will be recorded in the Case Report Form (CRF). The date of onset, intensity, action taken due to the event, duration, date of resolution of the event, outcome, and relationship to the study intervention will be recorded. The definitions used to describe the relationship between the adverse event and the study interventions are the following:

Unrelated
An adverse event that is definitely not related to the intervention.

Unlikely
An adverse event for which an alternative explanation is more likely e.g. concurrent drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event that might be due to the intervention. An alternative explanation e.g. concurrent drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.
Probable
An adverse event that might be due to the intervention. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely e.g. concurrent drug(s), concomitant disease(s).

Very likely
An adverse event, that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation e.g. concurrent drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by de-challenge and re-challenge).

Unassessable
It is not possible to assign the reaction to any of the above categories because of insufficient, pending or contradictory information. Further information is requested in order to lead to an attribution of causality.

12.4 Serious Adverse Events (SAE) Reporting

All serious adverse events must be reported to the sponsor (UCL/UCLH Foundation NHS Trust) within 24 hours of the Investigator’s knowledge of the event except for those that are identified in the protocol as not needing immediate reporting. The sponsor or Chief Investigator must also notify the Main Research Ethics Committee for the trial within 15 days of the Chief Investigator becoming aware of the event, using the appropriate SAE report form. As the Sonablate 500 is a CE marked medical device, any Serious Adverse Device Effects (SADE) and any suspected unexpected SADE must also be reported to the MHRA (to the Devices Adverse Incident Centre) and the manufacturer of the device.

Those events arising from all participating centres will be reported on a three monthly basis in a summary format, to include:
• The number of serious adverse events from all participating centres in a tabular format laying out the percentages of each type of serious events with an indication as to how many of those are thought to be device related or non-device related
• The total number of patients recruited during that same 3 month period and in total

13. Data collection

Responsibility for data collection will be taken by a nominated individual at each centre. Data will be collected in paper form in the first instance. Data will be collected in both electronic and paper form. Data will be stored in two places – at the individual centre and centrally by the sponsor centre. The data will be reviewed regularly by the TSC. Data ‘cleaning’ and database entry will also be performed by the trial administrator, with overall supervision and responsibility by the trial manager. An external audit of data will be performed according to standard operating procedures of the sponsor or their delegated body.

Data will be held according to the Data Protection Act 1998 and pseudo-anonymised as necessary. Each participant will be given a study number and this will be used on all of their study records. The patient number will be known to Professor Mark Emberton, Mr
Hashim Ahmed, and Miss Louise Dickinson, and a designated person from each of the other participating centres. All clinic visit information including questionnaires, scans, biopsy results and blood results will be kept in study records and analysed at the end of the study. Questionnaires will be sent to all trial patients centrally and the responses kept confidentially at the sponsor centre and access will be available by the relevant trial centre. The records will be kept in a secure manner in the research offices with access available to named individuals from the study group only. All imaging data (MRI and ultrasound) will be held confidentially and processed by the named investigators for the purpose of image registration analysis, including the use of secure computer software for video linked proctoring between sites. The paper records will be retained for a minimum of 10 years after the end of the study, according to UCL guidelines. Any information that is transferred between trial centres or from general practitioners surgeries will be anonymised.

14. Discontinuation of Study

14.1 Study Discontinuation by the Sponsor

The Sponsor may terminate the study at any time if the following occur, and the investigator is unable to take corrective action in any of these cases:

- The investigator is non-compliant with the protocol
- The investigator is non-compliant with the regulatory requirements
- The investigator is non-compliant with the principles of Good Clinical Practice as outlined in the Declaration of Helsinki and the Research Governance Framework (version 2)
- The CRF completion or drug accountability is inadequate

14.2 Study Discontinuation by the Chief Investigator

If an unwanted effect is considered severe by the Chief Investigator and endangers the health of all patients, the study will be discontinued after agreement with the Sponsor.

14.3 Discontinuation of Study for an Individual Centre

The first ten HIFU treatments given at each centre will be assessed by the Chief and Co-Investigators at the sponsor centre via computerised recordings as and when treatments occur using patient outcomes and post-treatment MRI as quality control outputs. If the adequacy or safety of treatment given is not deemed of an appropriate standard, the sponsor will have the right to withdraw that centre from the study with immediate effect. A proctor visiting a centre will also have the right to report back any concerns to the sponsor centre, Chief Investigator or Trial Steering Committee for further investigation.

14.4 Discontinuation of Study for an Individual Patient

The criteria for discontinuing the study in the case on individual patients are:
Intercurrent illness
Any illness, which in the judgment of the investigators would affect the assessments of clinical status to a significant degree.

Request by the patient
It is the patient's right to request discontinuation of their participation in the study. If this request is made, it will be respected and will not affect the patient's ability to receive medical care from the investigators now or in the future.

Discontinuation of attendance at an investigating site.
Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients no longer attend the participating institution.

15. Statistical considerations

Primary outcomes – cancer control
1. The proportion of men who are free of any prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU

2. The proportion of men who are free of clinically significant prostate cancer in the treated area AND are free of clinically significant prostate cancer in the untreated area 36 months after focal therapy using HIFU

15.1 Sample size
In this phase II trial the primary objective is to estimate the proportions of patients with no evidence of clinically significant cancer and no evidence of cancer at 36 months in the treated areas (see definitions above). Evidence from a small single centre trial at UCLH has demonstrated event rates could be as high as 100% absence of clinically significant cancer and 90% absence of any cancer in the treated areas at 6 months following focal therapy\textsuperscript{126}. Clinical knowledge indicates that these rates are likely to be lower in a multicentre trial with further follow up. In calculating sample size for the current study we therefore assume 90% of patients will have no evidence of clinically significant cancer at 36 months and 80% will have no evidence of any cancer at 36 months in the treated area. Using a precision based calculation for 95% confidence intervals at least a sample size of 140 patients will be needed to estimate these proportions to within 7%\textsuperscript{127}. The sample size is further inflated to 154 patients in order to allow for an anticipated 10% drop out.

It is expected that across the 7 centres, 220 patients per year will be eligible for this trial following TTPM biopsies. Amongst these 75% are expected to consent. It is therefore estimated that the 154 patients required will be recruited within 12 Months.

15.2 Statistical analysis
A full and detailed statistical analysis plan will be produced prior to the commencement of the final analysis; a summary of this plan is provided here.
Baseline Data
Baseline demographic and clinical information will be summarised using standard summary statistics, graphs and charts (see below).

Primary Outcomes
The proportion of patients with evidence of clinically significant prostate cancer at 36 months and those with no evidence of cancer at 36 months (in the treated areas as per the outcome definitions above) will be estimated along with associated 95% confidence intervals.

Secondary Outcomes
Secondary outcomes will be reported as estimates with 95% confidence intervals calculated using standard statistical methods as appropriate for the type of outcome. For patient-reported outcomes with available baseline measurements, a comparison will be made with baseline values using paired analyses. Logistic regression will be used to investigate associations with potential risk factors for histological failure, considering PSA, Gleason score, cancer core length involvement (mm and %), number and % of positive biopsies for any cancer on TTPM and TRUS, stage and D’Amico risk group (low, intermediate, high). Sensitivity and specificity (with 95% confidence intervals) will be estimated in considering the use of standard PSA kinetics and thresholds for identifying clinically significant cancer. Modelling methods for serial measurements will be used to consider patterns of PSA change associated with subsequent positive biopsy.

Descriptive tables as shown below will be populated

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD, range)</td>
</tr>
<tr>
<td>Serum PSA (ng/ml), mean (SD, range)</td>
</tr>
<tr>
<td>Reason for PSA test and Biopsy, % (N)</td>
</tr>
<tr>
<td>PSA Screening (patient request)</td>
</tr>
<tr>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>Prostate Volume (ml), mean (SD, range)</td>
</tr>
<tr>
<td>PSA Density (ng/ml/ml), mean (SD, range)</td>
</tr>
<tr>
<td>Gleason (TRUS-guided Biopsy), % (N)</td>
</tr>
<tr>
<td>3+3</td>
</tr>
<tr>
<td>3+4</td>
</tr>
<tr>
<td>4+3</td>
</tr>
<tr>
<td>Gleason (TTPM)</td>
</tr>
<tr>
<td>3+3</td>
</tr>
<tr>
<td>3+4</td>
</tr>
<tr>
<td>4+3</td>
</tr>
<tr>
<td>TRUS Guided Biopsies, mean (SD, range)</td>
</tr>
<tr>
<td>Total Cores</td>
</tr>
<tr>
<td>Total Positive Cores</td>
</tr>
<tr>
<td>% Positive Cores</td>
</tr>
<tr>
<td>Risk category after TRUS guided biopsies (%), n</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>TTPM, mean (SD, range)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Total Cores</td>
</tr>
<tr>
<td>Total Positive Cores</td>
</tr>
<tr>
<td>% Positive Cores</td>
</tr>
<tr>
<td>Core density (biopsies/ml)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk category after TTPM (%, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
</tbody>
</table>

### Peri-operative Characteristics

| Procedure time (SPC and Hemi-HIFU) (minutes), mean (SD, range) |
| Discharge time from procedure end (hours), mean (SD, range) |
| Length of suprapubic catheterisation (days), mean (SD, range) |
| Dysuria (negative urine culture), % (n) |
| Duration (days), mean (SD, range) |
| Intermittent haematuria (start of stream only), % (n) |
| Duration (days), mean (SD, range) |
| Urinary debris, % (n) |
| Duration (days), mean (SD, range) |
| Urinary tract infection (positive urine culture) (%, n) |
| Stricture (%, n) |
| Recto-urethral fistula (%, n) |

### Histological Characteristics at 12 months TRUS Biopsy

| Number of cores taken, mean (SD, range) |
| Total length of cores taken (mm), mean (SD, range) |
| Residual tissue in treated side (ml), mean (SD, range) |
| Core density (cores per ml residual tissue in treated side), mean (SD, range) |
| Residual tissue (treated and untreated) (ml), mean (SD, range) |
| PSA Density (ng/ml/ml), mean (SD, range) |
| Absence of any cancer (%, n) |
| Absence of Gleason pattern 4 and/or maximum cancer core length involvement >3mm (%, n) |

### Histological Characteristics at 36 months TTPM Biopsy

| Number of cores taken, mean (SD, range) |
| Total Length of cores taken (mm), mean (SD, range) |
| Residual tissue in treated side (ml), mean (SD, range) calculated using planimetry on MRI with urethral cavity taken as midline. |
| Core density (cores per ml residual tissue in treated side), mean (SD, range) |
| Residual tissue (treated and untreated) (ml), mean (SD, range) |
| PSA Density (ng/ml), mean (SD, range) |
| Absence of any cancer (%, n) |
| Absence of Gleason pattern 4 and/or maximum cancer core length involvement >3mm (%, n) |
Cost effectiveness analysis

A cost-effectiveness model will be developed that describes the diagnostic process and therapeutic options for men with localized prostate cancer fulfilling the selection criteria for this study (PSA<=15ng/ml, Gleason score <=4+3, clinical stage <=T2cNoMo). The model structure will be defined based on a systematic review of previous decision analytic models for prostate cancer. A 'base case' will be used, that best represents a ‘typical’ patient with localised prostate cancer on which to base the modelling aspect of the analysis. The model will be populated from a review of secondary sources of epidemiological, clinical and economic evidence together with appropriately elicited expert opinion. Outcomes for the diagnostic element are defined by template biopsy and are available from this study. Outcomes for the therapeutic element will include functional outcomes and cancer control as defined under primary and secondary objectives.

Quality of life outcomes will primarily be assessed using the EQ-5D instrument as part of the main clinical study. The questionnaire was developed through a network of international, multi-lingual, multidisciplinary researchers, originally from seven centres in England, Finland, the Netherlands, Norway and Sweden. This is a widely used generic measure of health related quality of life (HRQoL) which can be used to derive Quality Adjusted Life Years (QALYs). It is available in a number of languages for use across the EU.

Analyses will include standard roll back for Markov models, probabilistic sensitivity analysis, and scenario analyses. We will develop a precision analytic model comparing radical prostatectomy, active surveillance, and focal therapy. The base case will be a 65 year-old man with focal (unilateral clinically significant) prostate cancer.
**Figure 2**: Markov model demonstrating impact of prostate cancer on life expectancy

Cost-effectiveness will be expressed as costs per QALY. A societal perspective will be used, implying that costs from all parties are considered (patient, hospital, insurer, society). The time horizon will be 3 years for medium term evaluations, and life-time for calculations of QALYs. With this cost-effectiveness model we may quantify the long-term implications of changes to the therapeutic pathway of prostate cancer that result from adoption of multifunctional MRI, and focal therapy in a variety of healthcare settings. A preliminary modelling phase will indicate the main sources of uncertainty associated with the outcomes of the new pathway. This will inform the final design of the cost-effectiveness model to inform this primary objective.

For the place of focal therapy, comparative data are required for alternative treatment options, including active surveillance, radical prostatectomy and radiotherapy, in order to model for treatment options. Data sources will include, but are not limited to series from the participating centres, and other series that the co-investigator, Ewout Steyerberg, will have access to.

The main phase of the project will provide a vehicle for the collection of relevant data to inform the cost-effectiveness model. These will include the costs of tests and treatments as well as the management of adverse events, and the HRQoL implications of any adverse events experienced with tests and treatments. On completion of the data collection for the main phase, the evidence synthesis and modelling undertaken in the first phase will be updated, and the evidence collected in the main study added to it. Ultimately, this work will provide an assessment of the implications of any change that the use of focal therapy has to the over-treatment of prostate cancer. These implications will be in terms of expected QALYs and long-term costs.

16. **Reporting and dissemination of results**

The data will be analysed submitted for peer reviewed journals for publication as full manuscripts. Abstracts to conferences will also be submitted for poster or podium presentation.

An interim analysis will be available for publication at 12 months using histological and genitourinary functional outcomes.

Individual centres cannot report data in the form of abstracts, posters or full manuscript publications without prior authorisation by the TSC.

Publications will have the names of the TSC committee members with all other investigators having co-authorship for the final publication(s) under the INDEX Study Group. The Principal Investigators will decide on first and senior authorship for each paper.

17. **Liabilities and Insurance**

In case of any damage or injury occurring to a subject in association with trial interventions, the UK Sponsor (University College London) has contracted an insurance policy for negligent harm as covered by the Secretary of State for Health and NHS
Indemnity. Each centre involved in the study should have their own insurance policy to cover such events.

18. Ethics

The study will be conducted in accordance with the principles of the Declaration of Helsinki, the Research Governance Framework (version 2) and local laws.

This Protocol, its associated Patient Information Sheet and Informed Consent form and any advertising must be reviewed and approved by the appropriate Main Research Ethics Committee (MREC). All protocol amendments must be approved by the MREC prior to their implementation. A copy of the letter signed by the Chairman of the MREC to the Chief Investigator indicating MREC approval of the protocol must be received by the sponsor and maintained in the study file prior to study initiation.
19. References

25 Pickles T, Ruether JD, Weir L, Carlson L, Jakulj F; SCRN Communication Team (2007) Psychosocial barriers to active surveillance for the management of early prostate cancer and a strategy for increased acceptance. BJU Int. 100(3):544-51.
42 Taneja SS, Tareen B. Targeting prostate cancer for focal destruction: can we find it? Cancer. 2008 Oct 1;113(7):1500-1.
64 Konety BR et al. (2005) Comparison of the incidence of latent prostate cancer detected at autopsy before and after the prostate specific antigen era. J Urol 174: 1785–1788
66 Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994 Feb 2;271(5):368-74.
68 Freedland SJ, Aronson WJ, Terris MK, Kane CJ, Amling CL, Dorey F, Presti JC Jr. The percentage of prostate needle biopsy cores with carcinoma from the more involved side of the biopsy as a predictor of prostate specific antigen recurrence after radical
prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Cancer. 2003 Dec 1;98(11):2344-50


76 Hu Y, Ahmed HU, Arumainayagam N, Freeman A, Hawkes DJ, Emberton M, Barratt DC. Comparison between transperineal and transrectal biopsy for the detection of prostate cancer to guide focal therapy. EAU Annual Congress April 2010, Barcelona


127 Machin D, Campbell M et al Sample size Tables for Clinical Studies, Wiley-Blackwell 2009