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**An Evaluation of Focal Ablation Therapy using High-Intensity Focused  
Ultrasound in the Treatment of Localized Adenocarcinoma of the  
Prostate**

**PHASE II TWO CENTRE STUDY**

**CLINICAL STUDY PROTOCOL**

Short Title: High Intensity Focused Ultrasound Focal Ablation of Localised Prostate Cancer

Test Product: Sonablate® 500 (Focused Surgery, Indianapolis, IN)

Protocol Code: ISRCTN

Version: 3

Date: 7<sup>th</sup> January 2008

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**Clinical Study Protocol  
Summary**

Study Title	An Evaluation of Focal Ablation Therapy using High-Intensity Focused Ultrasound in the Treatment of Localized Adenocarcinoma of the Prostate
Protocol Code	Will be registered with ISRCTN
Objectives	This study seeks to evaluate the patient acceptability, feasibility, side effect profile and early efficacy of HIFU Focal Ablation in men with organ-confined, MRI and histologically proven adenocarcinoma of the prostate
Phase	II
Study Design	Two centre, prospective
Study Population	Men between 45-80 years of age with organ-confined, histologically proven adenocarcinoma of the prostate
Sample Size	42 patients
Duration of Observation	12 months follow-up observation period following treatment
Planned Clinical Start	3Q 2007
Planned Clinical End	2Q 2009
Test Product	Sonablate® 500 (Focus Surgery, Indianapolis, IL)
Sponsor	UCLH NHS Foundation Trust, London, UK
Examination Dates	Screening Visit (pre-op) Treatment Day (Baseline) Follow-up visits at 5-10 days, 10-20 days and 1, 3, 6, 9 and 12 months
Primary Variables	To determine: <ul style="list-style-type: none"> <li>i. feasibility</li> <li>ii. patient acceptability</li> <li>iii. side-effect profile.</li> </ul>
Secondary Variables	To determine the early effectiveness of therapy to control cancer by: <ul style="list-style-type: none"> <li>i. Exclusion of cancer on <ul style="list-style-type: none"> <li>- MRI and prostate biopsies at 6 months</li> </ul> </li> <li>iii. Recording the need for secondary or adjuvant treatment following treatment</li> </ul>
Analysis of Safety	<ul style="list-style-type: none"> <li>i. Adverse events</li> <li>ii. Laboratory parameters</li> <li>iii. Vital signs</li> </ul>

## TABLE OF CONTENTS

<b>1</b>	<b>GENERAL INFORMATION</b>	<b>6</b>
1.1	Title of the Study	6
1.2	Sponsor	6
1.3	Authorized Trial Personnel and Responsibilities	6
<b>2</b>	<b>BACKGROUND INFORMATION</b>	<b>8</b>
2.1	General Information on Prostate Cancer	8
2.2	Current Treatment Strategies for Organ-confined Prostate Cancer	8
2.3	Rationale for Focal Ablation in the Treatment of Organ-Confined Prostate Cancer	8
2.4	Description of Medical Device: High Intensity Focused Ultrasound	13
2.5	Known and Potential Risks of High Intensity Focused Ultrasound	13
2.6	Magnetic Resonance Imaging in Prostate Cancer	14
2.7	Description of Transperineal Biopsy of the Prostate	14
2.8	References	16
<b>3</b>	<b>STUDY OBJECTIVES</b>	<b>19</b>
3.1	Primary Objectives	19
3.2	Secondary Objectives	19
<b>4</b>	<b>TRIAL DESIGN</b>	<b>20</b>
4.1	Recruitment	20
	4.1.1 Localisation of Cancer	
	4.1.2 Treatment using Focal-HIFU	
4.2	Eligibility	20
	4.2.1 Inclusion Criteria	
	4.2.1 Exclusion Criteria	
4.3	Evaluation Process	21
4.4	Stage 1 – Localisation Technique	21
	4.4.1 Magnetic Resonance Imaging in Prostate Cancer Localisation	
	4.4.2 Transperineal ultrasound-guided template-directed prostate biopsy	
	4.4.2 Histopathology criteria for prostate biopsy	
4.5	Stage 2 – Treatment with Focal-HIFU	24
	4.5.1 General HIFU Treatment Protocol	
	4.5.2 Specific Protocol for Focal-HIFU	

4.6	Follow-up Schedule	26
4.6.1	Study Events Flow Chart	
4.6.2	Study Visits and Schedule	
4.7	Follow-up Details	28
4.7.1	ms-MRI	
4.7.2	Prostate biopsy	
4.7.3	Concomitant therapies	
<b>5</b>	<b>EVALUATION OF EFFICACY</b>	<b>30</b>
5.1	Primary Endpoints	30
5.2	Secondary Endpoints	30
<b>6</b>	<b>EVALUATION OF SAFETY AND TOLERABILITY</b>	<b>31</b>
6.1	Adverse Event Monitoring	31
6.2	Adverse Event Definitions	31
6.3	Adverse Event Information Collection	32
6.4	Serious Adverse Events reporting	32
<b>7</b>	<b>EVALUATION OF TUMOUR RESPONSE</b>	<b>33</b>
7.1	No Evidence of Disease	33
7.2	Local Failure	33
7.3	Distant Failure	33
7.4	Biochemical Failure	33
7.5	Disease Free Interval	33
<b>8</b>	<b>DISCONTINUATION OF STUDY</b>	<b>34</b>
8.1	Study Discontinuation by the Sponsor	34
8.2	Study Discontinuation by the Chief Investigator	34
8.3	Discontinuation of Study for an Individual Patient	34
<b>9</b>	<b>STATISTICAL CONSIDERATION</b>	<b>35</b>
9.1	Statistical Analysis	35
9.1.1	Patient Characteristics	
9.1.2	Safety and Tolerability Assessment	
9.2	Stopping Rule for Adverse Events	35
<b>10</b>	<b>ETHICAL AND REGULATORY CONSIDERATIONS</b>	<b>36</b>
10.1	Ethical Principles	36
10.2	Ethics Committee Approval	36
10.3	Protocol Amendment Procedure	36
10.4	Patient Identification	36
10.5	Patient Information Sheet and Informed Consent	36
10.6	Confidentiality	37

10.7	Disclosure of Data	37
10.8	Publication	37
10.9	Patient Risks and Benefits	37
	10.9.1 Patient Risks	
	10.9.2 Patient Benefits	
10.10	Liabilities and Insurance	38
10.11	Quality Assurance	38
<b>11</b>	<b>DATA HANDLING</b>	<b>39</b>
11.1	Case Report Forms	39
11.2	Retention of Study Records	39
<b>11</b>	<b>APPENDIX</b>	<b>40</b>
11.1	Appendix 1: Sample Patient Information Sheet	
11.2	Appendix 2: Sample Informed Consent	
11.3	Appendix 3: Patient Questionnaires	
	11.3.1 IPSS	
	11.3.2 IPSS-QoL	
	11.3.3 IIEF-15	
	11.3.4 UCLA-EPIC Incontinence	
	11.3.5 FACT-P	
11.4	Appendix 4: Case Report Form (CRF)	
11.5	Appendix 5: World Medical Association Declaration of Helsinki	
11.6	Appendix 6: Research Governance Framework (version 2)	
11.7	Appendix 7: Sonablate® 500 User Guide	
11.8	Appendix 8: Sonablate® 500 Liability Insurance	

## **1 General Information**

### **1.1 Title of the Study**

**An Evaluation of Focal Ablation Therapy using High-Intensity Focused Ultrasound in the Treatment of Localized Adenocarcinoma of the Prostate**

### **1.2 Sponsor**

University College London Hospitals NHS Trust  
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### **1.3 Authorized Trial Personnel and Responsibilities**

The following persons are authorized to sign the protocol and the protocol amendments. All persons listed are responsible for this study to be conducted in compliance with the protocol, good clinical practice and the applicable regulatory requirements.

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## **2 Background Information**

### **2.1 General Information on Prostate Cancer**

Prostate cancer is the second commonest cause of cancer related death in the USA. It accounts for 3% of all male deaths in the USA [National Cancer Institute, USA, 1999]. This translates to 179,300 new cases of prostate carcinoma diagnosed in the United States in 1999 [Landis et al, 1999]. In the year 2000, 92,000 men over 65 years of age were diagnosed with prostate cancer in the European community [Boyle et al, 1994], where prostate cancer will account for 12% of all new male cancer diagnoses [Esteve et al, 1993]. In the current era of prostate specific antigen (PSA) testing, cancers are being detected at an earlier stage in younger men with lower Gleason grade and lower volume cancers [Cooperberg et al, 2005].

### **2.2 Current Treatment Strategies for Organ-Confined Prostate Cancer**

Although prostate cancer is one of the most commonly diagnosed cancers in men, the ideal treatment for early organ-confined disease remains unclear. In general, the accepted treatments include active surveillance or radical treatment (radical prostatectomy, radical radiation therapy) [D'Amico et al, 2003; Zelefsky et al, 1998]. For many patients a policy of active surveillance is suitable, especially when life expectancy is limited or the risk of disease progression or a prostate cancer related death is low [Klotz et al, 2003]. For a significant number of patients the treatment options will be limited to only some of those listed above. The grade of tumour, the stage of disease in addition to a number of other patient factors make some treatments more suitable than others because the presence or absence of these characteristics confers different probabilities of benefit versus harm. On current standards of evidence it is difficult to emphatically recommend one treatment over another. With little if any grade I evidence available the treatment alternatives are considered by most to be options that men, together with their care givers and medical advisers, are required to choose between based on the probabilities of likely benefit versus possible harm. Given that it is generally assumed there is little difference between treatments in terms of cancer control much of the decision making process that governs treatment allocation is based on the differences in the side-effect profiles associated with the various treatments.

### **2.3 Rationale for Focal Ablation in the Treatment of Organ-Confined Prostate Cancer**

#### 2.3.1 The problem

Men with localised prostate cancer are forced to choose between two extremes of care - active surveillance versus radical therapy [Zeliadt et al, 2006]. The best evidence we have shows that the difference between these two very distinct approaches is not that substantial in terms of preventing an individual from dying of prostate cancer within a 10 year period - 14% mortality for watchful waiting compared to 9% for men who had radical prostatectomy [Bill-Axelsen et al, 2005]. It is worth commenting that the real difference between the two treatment strategies, were the study to be repeated in a contemporary setting with PSA as the principal method of diagnosis, is likely to be considerably less than that reported in the study given the lead time of approximately 7-10 years conferred by PSA diagnosis [Parker, 2005]. In other words,

this study looked at a group of men who had a diagnosis of prostate cancer clinically and not with an abnormal high age-specific PSA. In addition, modern active surveillance with selective delayed intervention is very different to the watchful waiting protocol instituted by that Scandinavian trial.

So, on the other hand we know that the side effects of radical treatments are high – they include amongst others, deterioration in urinary, sexual and bowel function [Steineck et al, 2002; Penson et al, 2005]. The profile and probability of these harmful outcomes depend to a large extent on the type of radical treatment, but all occur as a consequence of damaging tissue or structures that exist outside the prostate gland – the rhabdo-sphincter, the neurovascular bundles and the rectal mucosa, respectively. Refinements in the traditional radical therapies (conformal or intensity modulated radiation therapy on the one hand versus laparoscopic or robotic radical prostatectomy on the other) have had little impact on the key treatment related morbidities [Khoo, 2005; Hoznek et al, 2005]. The reason for this is that despite the refinements in the treatment their essential premise remains the same. The premise being that the whole gland is treated irrespective of the volume or position of the tumour [Al Barqawi and Crawford, 2005].

Our study challenges the prevailing assumption that all men need to have their whole gland and the surrounding structures treated irrespective of the volume and location of their prostate cancer. In other words, if treatment is limited to areas of cancer with a margin of surrounding normal tissue (focal ablation), is the treatment associated with a low rate of treatment-related adverse effects in addition to acceptable levels of cancer control?

In summary, radical radiotherapy on average causes moderate to severe recto-anal toxicity and urinary problems in 5-20% of patients, with nearly all suffering minor short term symptoms. Surgery causes less damage rectally, but a third suffer chronic urinary symptoms. Importantly, on average both modalities give rise to impotence in well over half of men. Our study would therefore be aiming to demonstrate rates of toxicity of the following order: (1) incontinence (10%) and (2) erectile dysfunction (20%). If these were achieved, a larger multicentre trial evaluating long-term 5-10 year efficacy (biochemical failure, long term recurrence rates, survival) would be justifiable.

### 2.3.2 The research question

Do men with early localised prostate cancer (T2c N0 M0 or less), when treated with focal ablation of all cancer foci and a margin of 5mm normal tissue, using the HIFU Sonablate® 500, experience less harm (fewer treatment related toxicities) when compared to conventional whole gland therapies (either radical radiation therapy or surgery). In addition, is treatment in a focal manner feasible (as laid out in the treatment protocol below) in a manner that allows destruction of those cancer areas.

### 2.3.3 Defining the population

Defining where the cancer is localised in a cohort of men is the first challenge that we encounter. Men whose standard (sextant or more) transrectal (TRUS) prostate biopsies alongside PSA (<15ng/mL) and other investigations demonstrate early localised, low grade disease (Gleason 7 or less) will be the targeted group. These

criteria thus avoid focal therapy in men who are more likely to benefit from whole-gland radical treatment in terms of cancer control and survival [Hardie et al, 2005]. Active surveillance policies exclude Gleason grade 7 as this is a moderate risk group. The reason to include Gleason 7 is that this trial offers a form of treatment and need not therefore adhere to active surveillance protocol inclusion criteria.

There will be no limit on number of positive biopsies nor extent of biopsy involvement, as a full evaluation of the localisation of disease will occur using the verification technique we have discussed. The eligibility criteria for HIFU treatment will also be applied (maximum Anterior-Posterior distance of less than 40mm, minimal calcification, no prior rectal fistulae or moderate to severe inflammatory bowel disease). Men who have had previous hormonal treatment for prostate cancer (in the last 6 months), those who have had previous prostate treatments (radiotherapy, brachytherapy, surgery, laser therapy, cryosurgery) are excluded. Those having TURP in the last 5 years are also excluded. Those who are unable to have an MRI scan (severe claustrophobia, metallic implants) will also be excluded.

How can we be as sure as we can that men offered focal ablation have had all cancer foci located? Equally important, how can we ascertain 3-dimensional information on the margins of each focus of cancer in order to guide treatment. Prior to inclusion in this trial, men will undergo multi-sequence Magnetic Resonance Imaging (ms-MRI) and template-guided transperineal 5mm spaced prostate biopsies (under regional or general anaesthesia) using a standardised protocol to sample all areas of the gland, with number of cores dependent on size of the prostate. Those men who have undergone these procedures and have an interest in the trial will be assessed as to their suitability for focal ablation (see guidelines for focal ablation below). If suitable, these men will be counselled as to the trial objectives and informed consent taken for participation.

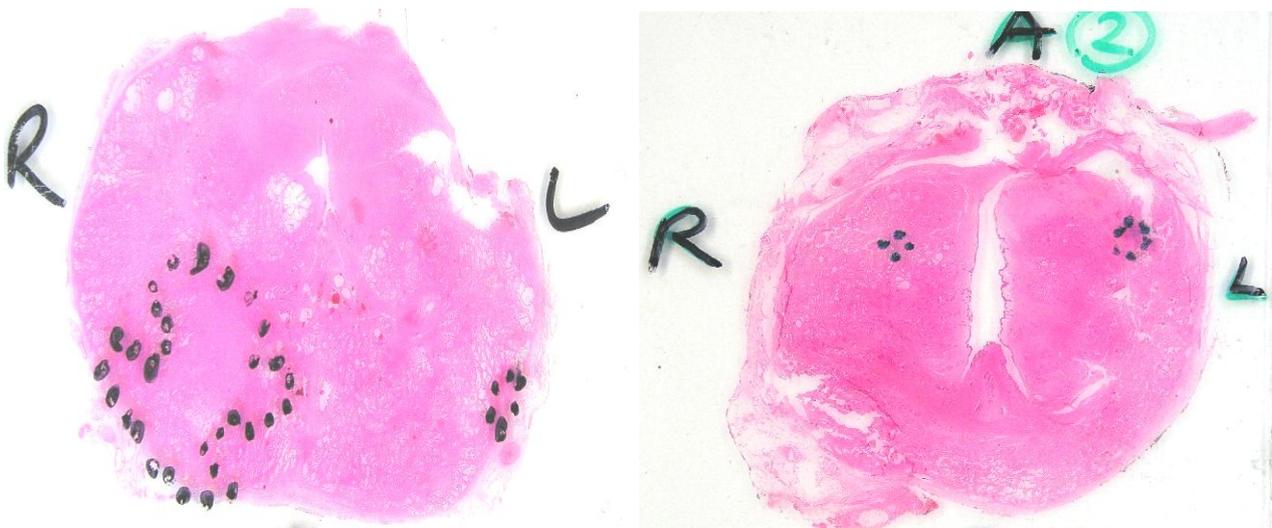
How sure will we be that the areas of the prostate that are declared to be free of disease are indeed free of disease? Our estimate comes from series that look at cancer detection rates in men who have multiple biopsies or so called saturation biopsies. Men who have two negative sets of biopsies (with between 12-18 cores in total) have a residual prostate cancer detection rate of between 5-10%. In other words, this gives a true negative rate in excess of 90% [Djavan et al, 2005]. As template-guided transperineal biopsy will take more cores and sample areas that traditional biopsy techniques do not reach (midline, apex and anterior regions) accuracy rates of approximately 90-95% have been demonstrated in the literature [Furono et al, 2002; Crawford et al, 2005].

As this is the first trial looking at focal ablation using HIFU the occurrence of adverse effects is particularly important but difficult to predict. Only two other groups have looked at partial treatment of the prostate. These groups looked at hemiablation using cryotherapy in men with unilateral disease verified by transperineal biopsies [Onik et al, 2005; Bahn et al, 2006]. Importantly, they showed side-effect profiles lower than standard whole-gland cryosurgery – impotency rates were between 11% and 15%. In addition, recent data has shown that up to 40% of men may actually have unifocal disease [Sirma-Chiang et al, 2006; Ohori et al, 2006]. However, the benefits of focal therapy may not only be limited to men with unilateral or unifocal disease. Those men who have bilateral cancer but whose pre-treatment parameters demonstrate low risk disease - i.e., low PSA (<10ng/mL) and low grade (total Gleason

≤7) - may equally benefit from focal therapy to all areas of cancer foci, in terms of lower toxicity.

A treatment planning meeting will occur to ensure that each individual man will have approximately 50% tissue gland ablation. We have set an arbitrary figure of approximately 50% of total gland tissue destruction to coincide with the ethically approved hemiablation trial (currently running as of 22<sup>nd</sup> September 2006). This trial's treatment protocol allows for destruction of the half of the gland with proven unilateral disease. As this focal ablation trial is the first of its kind looking at focal ablation, there is no previous evidence to guide us as to the threshold amount of tissue destruction that will eventually lead to toxicity. Equally, a man whose disease is mainly anterior and would require more than 50% tissue destruction, but still allow avoidance of the postero-lateral areas (alongside which the neurovascular bundles run) may still benefit from focal ablation in terms of potency. The 50% tissue destruction will therefore be flexible provided the treatment planning meeting between the investigators deems the patient suitable for focal ablation.

The figures below illustrate radical prostatectomy whole-mount specimens of disease foci that may be suitable for focal therapy using the protocol of HIFU treatment outlined in this protocol (~50% tissue destruction with avoidance of damage one or both neurovascular bundles).



The data derived from this study will then be used to both design and power a randomised Phase II/III study in which the control would be radical therapy involving whole gland treatment.

The decision to proceed to Phase III will incorporate the following:

- recruitment rate
- low incidence of erectile dysfunction (<40% participants at 6 months)
- low incidence of urinary incontinence (<10% participants at 3 months)

Some qualitative work would be desirable in order to be as sure as we can that men would be willing to accept randomisation between HIFU and an alternative intervention. This work is not part of this trial proposal.

International data show that HIFU can destroy tissue. Results in whole gland treatment show no cancer detected in 85-95% using HIFU [Uchida et al, 2006; Blana et al, 2004]. Therefore, the issue as to whether biopsies should be taken after treatment is an important one. The objectives of the trial are feasibility and safety of focal therapy. Can post-treatment biopsies at the 6 months contribute to these objectives? We believe there are two questions that post-treatment biopsy could answer. First, was focal treatment (in the manner set out in the protocol) of the cancer areas successful? Second, are there de novo and/or missed areas of cancer in the untreated areas?

The first question is certainly pertinent to feasibility. We know that even in whole-gland treatment, a proportion of men have positive biopsies after treatment. So for this trial, was our method of localising and then ablating in a focal manner effective in treating those areas of cancer that we know are present in the gland? It is our opinion that histological confirmation of this is necessary. This question does not require repeat transperineal biopsies at 6 months and certainly the extra morbidity of transperineal biopsies is not justified nor ethically sound. As we have information on these specific areas with pre-treatment mapping and post-treatment imaging we can target them by TRUS biopsies. Our radiologist, Dr Clare Allen, has extensive experience in TRUS targeted biopsies of suspicious lesions seen on pre-biopsy MRI and we are confident that this method will be valid.

The second question relates to untreated areas. This in itself can be divided into two aspects:

- 1) Is there de novo cancer in the untreated areas (a surveillance issue)? This is not a trial evaluating long-term efficacy nor is it one of surveillance of untreated areas. A trial addressing this would need to be larger and run for at least a decade.
- 2) Have we missed cancer using transperineal biopsies prior to treatment (a quality control issue as well as one of surveillance)? The peer reviewer is correct in stating that since TRUS biopsies have limited accuracy it is unlikely that these biopsies will detect the approximate 5% of lesions missed by transperineal biopsies. Therefore, TRUS biopsies are not warranted. Repeat transperineal biopsies would be able to answer this question. However, as we have stated earlier, repeat transperineal biopsies would constitute excess risk and potential morbidity (three general anaesthetics within 8 months, toxicity of biopsies) which is ethically unacceptable. However, since these men will go onto 'active surveillance' of their untreated areas, these small number of small lesions are likely to be detected by active surveillance regimens if clinically significant and so this not having a strategy within the trial for trying to pick up the 5% of missed lesions on the untreated side does not pose a major ethical issue either.

In summary, we believe that TRUS biopsies of treated areas, but not of untreated areas are important and therefore form a part of this protocol.

#### 2.3.4 Sample size calculation

The issue of sample size is problematic when no other trial of this kind has been performed and one of the primary objectives is to ascertain event rates. Considering

erectile dysfunction as the primary toxicity of concern, we would regard the erectile dysfunction rate as the primary factor on which to base power calculations.

The current rate of erectile dysfunction after whole-gland HIFU is between 25-50% [Uchida et al, 2006; Blana et al, 2004]. Our own results (as yet unpublished) demonstrate rates of erectile dysfunction of 54% at 6 months and 30% at 9 months for whole gland therapy. The only estimates we have of erectile dysfunction following a prostate preserving approach are from published non-trial single centre or pooled experience. These estimates come from two groups [Uchida et al, 2005; Bahn et al, 2006] using cryotherapy as a form of hemi-ablation. In these two reports, rates of erectile dysfunction were 11-15% with an overall follow-up of between 12-70 months.

Our initial calculations for sample size were based on the hemiablation trial that is currently recruiting. The hemi-HIFU trial is treating 20 patients with an aim to reduce erectile dysfunction rates from 40% to 5%.

However, in this focal-HIFU trial, we are treating areas bilaterally in a prostate preserving manner (focal therapy as we have defined it). Therefore, a more conservative estimate of a clinically significant and important reduction in the rate of occurrence of erectile dysfunction would be a relative risk reduction of about 50% in men undergoing focal therapy. Or put another way, an absolute risk reduction of 25%, if we assume rates of erectile dysfunction to be 40% at 12 months with whole gland therapy (less than our current observed rate) and rates of erectile dysfunction of 15% at 12 months with focal ablation (a rate higher than the reported rate in the literature for hemiablation). Therefore, we would require 33 patients with a power of 90% ( $p_0=0.4$  and  $p_1=0.15$ ,  $\alpha=0.05$ , 1-sided test).

Baseline erectile dysfunction is likely to be present in about 25% of cases so this adjustment would require that we recruit 42.

**Therefore, we calculate that the trial would require 42 patients to be treated in a focal manner.**

## **2.4 Description of Medical Device: High Intensity Focused Ultrasound**

High intensity focused ultrasound (HIFU) works by focusing and depositing a large pulse of high-energy ultrasonic waves on a single area. This increases the temperature to a point whereby it induces coagulative necrosis. Focused ultrasound waves are emitted from a transducer and are absorbed in the target area of about 3x3x10mm of tissue. This leads to mechanical effects, cavitation and thermal effects without damage to the tissue in the path of the ultrasound beam [Huber et al, 1996]. Treatment is accomplished by systematically pulsing energy throughout the target area until the entire the whole area is destroyed. The potential anti-tumour effect of HIFU has been shown on treated rats with two implanted sublines of Dunning tumour [Chapelon et al, 1992].

The clinical applications of HIFU in organ-confined prostate cancer are continually updated. The technique has been used throughout the world, mainly in Europe and Japan. Two commercially available devices exist in delivering the HIFU technology: Ablatherm® (Edap-Technomed, Lion, France) and Sonablate® (Focus Surgery, Indianapolis, IN, USA). This study will use the latest generation Sonablate-500®

which has a combined therapy-imaging transducer, the ability to use two focal length (30mm and 40mm) to increase the resolution of the treatment plan and precise control of energy delivery by each pulse.

The latest international results show no cancer detected in between 87-94% of men biopsied after whole gland ablation with 5 years follow-up [Uchida et al, 2006; Blana et al, 2004]. Through our extensive experience using Sonablate® 500 HIFU to treat organ-confined prostate cancer we have shown we can treat men safely when ablating the whole gland [Illing et al, 2006].

## **2.5 Known and Potential Risks of High Intensity Focused Ultrasound**

The HIFU procedure does not breach the skin or mucosal surfaces and is considered safer than other techniques such as cryosurgery and photodynamic therapy. Morbidity associated with the latest generation Sonablate® 500 HIFU is as follows:

- Most patients report urinary symptoms (frequency, urgency, difficulty in urination) during the first two months after treatment
- Symptomatic urinary tract infection 5%
- Urethral stricture 10%
- Retrograde Ejaculation 3%
- Epididymitis 3%
- Urinary retention requiring surgery 2%
- Impotence 25-30%
- Incontinence (transient) 0-2%
- Recto-urethral fistula <0.5-5%

The Ablatherm® device seems to cause a higher rate of impotence (45-100%) and incontinence (1-23%).

## **2.6 Magnetic Resonance Imaging in Prostate Cancer Localisation**

The use of MRI to locally stage prostate cancer has been well documented. However, using MRI to detect cancer foci and accurately localise them is essential for the success or otherwise of focal therapy. T2-weighted MR can detect well over 60% of prostate cancers, and the addition of dynamic gadolinium enhancement significantly improves both detection and delineation of disease without substantially decreasing specificity. Spectroscopy is useful in detecting recurrent disease in treated glands and may improve detection, but at the expense of specificity. Current multi-sequence MRI using T2-weighted sequences, dynamic enhanced scans and spectroscopy has the potential to detect most clinically significant cancer and is certainly more sensitive than TRUS biopsy [Heenan et al, 2004; Kirkham et al, 2006; Villers et al, 2007; Ahmed HU et al, 2007].

MRI after a biopsy is confounded by post-biopsy artefact due to haemorrhage. This shows up as an area of low signal on T2-weighted sequences that can be indistinguishable from cancer. Studies have shown that tumour presence and extra-capsular extension can be significantly overestimated when MRI is carried out within 3 weeks [White et al, 1995]. MR spectroscopy can also help distinguish questionable areas increasing accuracy [Kaji et al, 1998]. Therefore, this trial uses MRI scanning before transperineal biopsy.

## 2.7 Description of Transperineal Biopsy of the Prostate

Prostate cancer is usually diagnosed using a TRUS probe to biopsy the prostate in men with risk factors for developing the disease. TRUS biopsy is carried out with injection of local anaesthetic prior to tissue sampling. This technique usually takes between 6 and 12 cores of tissue. Therefore, by virtue of sampling error, TRUS biopsy has an overall cancer detection rate of just over 40%, but only if 12 or more cores are taken [Presti et al, 2000; Kawata et al, 2003].

We propose to carry out transperineal ultrasound (TPUS) guided biopsy after multi-sequence MR-Imaging of the prostate in order to localize areas of prostate cancer. TPUS has been shown to carry no extra risk of complications than TRUS [Miller et al, 2005]. TPUS biopsies have a greater cancer detection rate by taking more samples of tissue - between 30-40 cores of tissue in a 40cc sized gland. The exact number of cores is dependent on the size of the prostate. This technique also samples areas that TRUS cannot - midline of peripheral zone, apex and anterior zones [Furuno et al, 2002]. The procedure is carried out under general anaesthetic or regional anaesthesia with a transrectal ultrasound probe attached to a brachytherapy stepping unit with a standard 5mm brachytherapy template positioned over the perineum. Systematic biopsies are then taken through the perineum guided through template holes [Bott et al, 2004].

Studies have shown TPUS to be effective in detecting cancer. One group showed that if biopsies are taken every 10mm on the template with an average of 20 cores (+/-4) from prostates with a mean volume of 42ml (+/- 20ml), the cancer detection rate was 51%. This was carried out in men who had no previous biopsies but a high PSA (between 4.0 and 10.0ng/ml) [Demura et al, 2005]. The study's weakness lay in that whole-mount prostatectomy histology was not available as a comparator. This would be difficult as only a proportion of these men would go onto radical surgery.

In order to overcome this weakness, another group elegantly demonstrated the effectiveness of TPUS biopsy with the use of computer modelling of radical prostatectomy histology whole-mount slices [Werahera et al, 2004]. This group also modelled prostates taken at post-mortem that also had cancer. Using 10mm spaced biopsies the cancer detection rate was 61% in the post mortem group and 95% in the radical prostatectomy group. Taking 5mm spaced biopsies gave a detection rate of 86% in the autopsy group and 100% in the radical prostatectomy group. When they analysed the two methods with respect to number of cancer foci, 10mm biopsies detected 45% and 5mm detected 76% of total cancer foci in autopsy patients with similar results in the radical prostatectomy group [Crawford et al, 2005]. The mean number of cores taken with 10mm and 5mm biopsies was 12 (range 5-27) and 54 (range 23-108) respectively.

	Biopsy Method	
	10mm	5mm
Sensitivity	78%	95%
Specificity	66%	30%
Positive Predictive Value	43%	31%
Negative Predictive Value	90%	95%

The group in Florida carrying out hemiablation of prostate glands using cryosurgery now evaluate all patients who present with unilateral disease – as demonstrated by TRUS biopsy - with 5mm TPUS biopsies. They have found that just over 50% of these men have true unilateral disease [Onik et al, 2005].

Current best practice therefore suggests TPUS biopsies with 5mm spacing on the template should be carried to locate most cancer foci in the prostate. All men will have undergone these procedures before entry into this trial.

## 2.8 References (alphabetical order)

- Ahmed HU, et al. Comment on: Villers et al. Dynamic Contrast Enhanced, Pelvic Phased Array Magnetic Resonance Imaging of Localized Prostate Cancer for Predicting Tumor Volume: Correlation With Radical Prostatectomy Findings. *J Urol* 2006;176.
- Al Barqawi and Crawford D. Focal Therapy in prostate cancer: future trends. *BJU Int.* 2005; 95: 273-280.
- Bahn, Silverman, Lee et al. Focal Prostate Cryoablation: Initial Results Show Cancer Control and Potency Preservation. *J Endourol.* 2006; 20(9): 688-692
- Bill-Axelsen A, Holmberg L, Mirrja Ruuth et al. Watchful waiting and prostate cancer. *NEJM* 2005;352: 1977-1984.
- Blana A Walter B, Rogenhofer S, Wieland WF. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. *Urology.* 2004;63(2):297-300.
- Bott SR, Henderson A, McLarty E, Langley SEM. A brachytherapy template approach to standardize saturation prostatic biopsy. *BJUI* 2004; 93: 629-630.
- Bott SR, Freeman AA, Stenning S, Cohen J, Parkinson MC. Radical prostatectomy: pathology findings in 1001 cases compared with other major series and over time. *BJU Int.* 2005;95(1):34-9.
- Boyle P. Prostate cancer 2000: Evolution of an epidemic of unknown origin; In: *Prostate Cancer 2000*, Denis L Ed., Springer-Verlag, Heidelberg, 1994, 5-11.
- Chapelon JY, Margonari J, Vernier F, et al. In vivo effects of high-intensity ultrasound on prostatic adenocarcinoma Dunning R3327. *Cancer Res.* 1992; 52: 6353-6357.
- Cooperberg MR, Moul JW, Carroll. The changing face of prostate cancer. *J Clin Onc* 2005;23(32):8146-8151.
- Crawford DE, Wilson SS, Torkko KC, et al. Clinical staging of prostate cancer: a computer-simulated study of transperineal prostate biopsy. *BJUI* 2005; 96: 999-1004.
- D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol.* 2003; 21(11): 2163-72.
- Demura T, Hioka T, Furuno T, Kaneta T, et al. Differences in tumor core distribution between palpable and nonpalpable prostate tumors in patients diagnosed using extensive transperineal ultrasound-guided template prostate biopsy. *Cancer* 2005; 103: 1826-32.
- Djavan B, Milani S, Remzi M. Prostate biopsy: who, how and when. An update. *Can J Urol.* 2005 ;12 Suppl 1:44-8.

Esteve J, Krickler A, Ferlay J, Parkin DM (eds). Facts and figures of cancer in the European Community. IARC, Lyon, 1993.

Furuno T, Demura T, Kaneta T et al. Difference of cancer core distribution between first and repeat biopsy: in patients diagnosed by extensive transperineal ultrasound guided template prostate biopsy. *The Prostate* 2002; 58: 76-81.

Gonzalvo ML, Bastian PJ, Mangold LA, et al. Relationship between primary Gleason pattern on needle biopsy and clinicopathologic outcomes among men with Gleason score 7 adenocarcinoma of the prostate. *Urology*. 2006;67(1):115-9.

Hardie C, Parker C, Norman A, et al. Outcomes of active surveillance for localized prostate cancer. *BJUI* 2005;95(7):956-60.

Heenan SD. Magnetic resonance imaging in prostate cancer. *Prostate Cancer Prostatic Dis*. 2004; 7(4):282-8.

Hoznek A, Menard Y, Salomon L, Abbou CC. Update on laparoscopic and robotic radical prostatectomy. *Curr Opin Urol*. 2005 May;15(3):173-80.

Huber P, Debus J, Jenne J, et al. Therapeutic ultrasound in tumor therapy: principles, applications and new developments. *Radiologe* 1996; 36: 64-71.

Illing RO, et al. Visually directed HIFU for organ confined prostate cancer – a proposed standard for the conduct of therapy. *BJUI* 2006

Kaji YJ, Kurhanewicz J, Hricak H, et al. Localizing prostate cancer in the presence of postbiopsy changes on MR images: role of proton MR Spectroscopic imaging. *Radiology*. 1998; 206: 785-790.

Kawata N, Miller GJ, Crawford ED et al. Laterally directed biopsies detect more clinically threatening prostate cancer: computer simulated results. *Prostate* 2003; 57: 118-28.

Kirkham A, Emberton M, Allen C. How Good is MRI at Detecting and Characterising Cancer within the Prostate? *Eur Urol* 2007.

Khoo VS. Radiotherapeutic techniques for prostate cancer, dose escalation and brachytherapy. *Clin Oncol (R Coll Radiol)* 2005 Oct;17(7):560-71.

Klotz L. Active surveillance with selective delayed intervention: a biologically nuanced approach to favorable-risk prostate cancer. *Clin Prostate Cancer*. 2003 Sep;2(2):106-10. Review.

Landis SH, et al. Cancer statistics, 1999. *CA Cancer J. Clin*. 1999, 9.

Miller J, Perumalla C, Heap G. Complications of transrectal versus transperineal prostate biopsy. *ANZ J Surg*. 2005;75(1-2): 48-50.

National Cancer Institute, SEER Cancer Statistics Review 1973–1999.

Onik G. Focal Cryoablation for Prostate Cancer. Abstract. Society of Interventional Radiology. 30th Annual Scientific Meeting (2005, New Orleans).

Onik G. 3D global biopsy mapping. (Abstract 525). Society of Interventional Radiology. 30th Annual Scientific meeting (2005).

Ohuri M, Eastham JA, Koh H, et al. Is focal therapy reasonable in patients with early stage prostate cancer (CAP) – an analysis of radical prostatectomy (RP) specimens. AUA Annual Meeting, Atlanta 2006. Abstract 1574.

Parker C. The Scandinavian Prostate Cancer Group Study: the case for conservative management. BJUI 2005; 96(7): 952-3.

Penson et al. 5 year urinary and sexual outcomes following radical prostatectomy. J Urol 2005; 173 (4): 451

Presti JC Jr, Chang JJ, Bhargava V, Shinohara K. The optimal systematic prostate biopsy should include 8 rather than 6 biopsies: results of a prospective clinical trial. J Urol. 2000; 163: 163-7.

Simma-Chiang V, Hom JJ, Simko JP, Chan JM, Carroll PR. Increased prevalence of unifocal prostate cancer in a contemporary series of radical prostatectomy specimens: implications for focal ablation. AUA Annual Meeting, Atlanta 2006. Abstract 1163.

Steineck, G. et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 347, 790-6 (2002).

Uchida T, Ohkusa H, Nagata Y et al. Treatment of localized prostate cancer using high-intensity focused ultrasound. BJU Int. 2006; 97(1):56-61.

Villers et al. Dynamic Contrast Enhanced, Pelvic Phased Array Magnetic Resonance Imaging of Localized Prostate Cancer for Predicting Tumor Volume: Correlation With Radical Prostatectomy Findings. J Urol 2006;176.

Werahera PN, Miller GJ, Torkko K, et al. Biomorphometric analysis of human prostatic carcinoma by using three-dimensional computer models. Human Pathol. 2004; 35: 798-807.

White S, Hricak H, Forstner R, et al. Prostate cancer: effect of postbiopsy hemorrhage on interpretation of MR images. Radiology. 1995; 195(2):385-90.

Zelevsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome of prostate cancer. *Int J Radiat Oncol Biol Phys*. 1998, 41:491-500.

Zeliadt SB, Ramsey SD, Penson DF, Hall IJ, Ekwueme DU, Stroud L, Lee JW. Why do men choose one treatment over another?: a review of patient decision making for localized prostate cancer. Cancer 2006;106(9): 1865-74.

### **3 Study Objectives**

#### **3.1 Primary Objectives**

To determine patient acceptability, feasibility, and side-effect profile by evaluating:

- ◇ Recording of Adverse Events
- ◇ Urinary symptoms and Erectile function will be assessed at each visit with the following:
  - Questionnaires
  - International Index of Erectile Function-15 [IIEF-15]
  - International Prostate Symptom Score [IPSS] and IPSS-QoL
  - Functional Assessment of Cancer Therapy – Prostate (FACT-P)
  - Continence questionnaires

#### **3.2 Secondary Objectives.**

To determine the effectiveness of therapy by:

- ◇ post-treatment biopsies of treated areas at 6 months
- ◇ post-treatment MRI to evaluate area of necrosis within two weeks and at 6 months and 12 months
- ◇ measurement of PSA at each follow-up visit and estimated measurement of time to PSA nadir
- ◇ recording the need for secondary or adjuvant treatment following therapy
- ◇ trifecta outcomes (continence, potency, cancer control)

## **4 Trial Design**

This is a single centre, phase II, 12 months follow-up clinical trial. Although it is the intention to follow every patient until death, this protocol is limited to the first year of follow-up after HIFU Focal Ablation. However, Office for National Statistics flagging will also be used.

### **4.1 Recruitment**

Patients who show an interest in participation will be briefed on the details of the study and given an approved information sheet. They will then be offered an appointment for a screening and consent visit. At this stage eligibility to study participation will be formally assessed and if still eligible, details of the study will be explained and any questions answered. In particular the patient will be briefed about the commitment and intensity of the follow-up schedule. They will be alerted to the personal nature of the replies required by the questionnaires. They will be informed of their rights regarding participation in the proposed research study, including their right to refuse participation or to end participation at any time without adversely affecting continuing medical management of their disease. The patient will have the treatment stage of the trial particularly highlighted.

Patients need to have had both multi-sequence MRI and TPUS template guided biopsies as per the protocol below to be eligible for the trial. The data from both these investigations will be reviewed to determine suitability for focal ablation before recruitment. If the patient is happy to proceed he will be asked to sign an approved consent form indicating his formal consent to participation in the study. Consent for the Focal-HIFU will be taken as per standard of care under the NHS.

### **4.2 Eligibility**

#### 4.2.1 Inclusion criteria

- 4.2.1.1 Men aged 45-80 years
- 4.2.1.2 Histological diagnosis of prostate adenocarcinoma
- 4.2.1.3 Gleason grade total 7 or less (patterns 3+4 or 4+3 or less acceptable)
- 4.2.1.4 Cancer prostate-confined only (bilateral or unilateral)
- 4.2.1.5 Serum PSA  $\leq$  15 ng/mL
- 4.2.1.6 A life expectancy of 5 years or more
- 4.2.1.7 Prostate volume  $\leq$ 40cc or maximum anterior-posterior length  $\leq$  40mm
- 4.2.1.8 Has had ms-MRI and transperineal template 5mm spaced biopsies in the 6 months prior to recruitment
- 4.2.1.9 All malignant areas are treatable by focal ablation so that approximately 50% of prostate tissue is destroyed and at least one neurovascular bundle is preserved
- 4.2.1.10 Signed informed consent form by patient

#### 4.2.2 Exclusion criteria

- 4.2.2.1 Men who have received androgen suppression within previous 6 months
- 4.2.2.2 Men who have had previous radiation therapy for prostate cancer
- 4.2.2.3 Men treated with chemotherapy for prostate cancer
- 4.2.2.4 Men with evidence of metastatic disease
- 4.2.2.5 Men with latex allergies
- 4.2.2.6 Men who have undergone prior significant rectal surgery preventing insertion of transrectal probe
- 4.2.2.7 Men with intraprostatic calcifications making HIFU of focal areas of cancer untreatable
- 4.2.2.8 Men who have undergone previous transurethral resection of the prostate or laser prostatectomy in the 5 years prior to recruitment
- 4.2.2.9 Men who have undergone previous HIFU, cryosurgery, thermal or microwave therapy to the prostate at any point prior to recruitment
- 4.2.2.10 American Society of Anesthesiology grades III-IV
- 4.2.2.11 Men not fit for general anaesthesia or regional anaesthesia as assessed by Consultant Anaesthetist
- 4.2.2.12 Men unable to have MRI scanning (e.g., severe claustrophobia, permanent cardiac pacemaker, metallic implant likely to contribute significant artefact to images)

### **4.3 Evaluation Process**

- 4.3.1.1 Approved written, informed consent
- 4.3.1.2 History and Physical Examination, including digital rectal exam
- 4.3.1.3 Completion of the IIEF-15, IPSS, IPSS-QoL, FACT-P and ICS questionnaires
- 4.3.1.4 Serum PSA; serum sodium, potassium, urea and creatinine; haemoglobin, white cell count, platelet count; alkaline phosphatase
- 4.3.1.5 TRUS to determine prostate volume (prolate ellipsoid method: length x width x height x 0.52), intraprostatic calculi if information not available from previous TRUS

### **4.4 Stage 1 – Localisation technique**

Patients will enter into this stage of the trial if they meet all inclusion and exclusion criteria and written informed consent has been taken to participate in this stage of the trial. All of our patients will have had TRUS biopsy, ms-MRI and transperineal template biopsies before recruitment. The standards of these investigations must meet the criteria below.

#### 4.4.1 Multi Sequence Magnetic Resonance Imaging

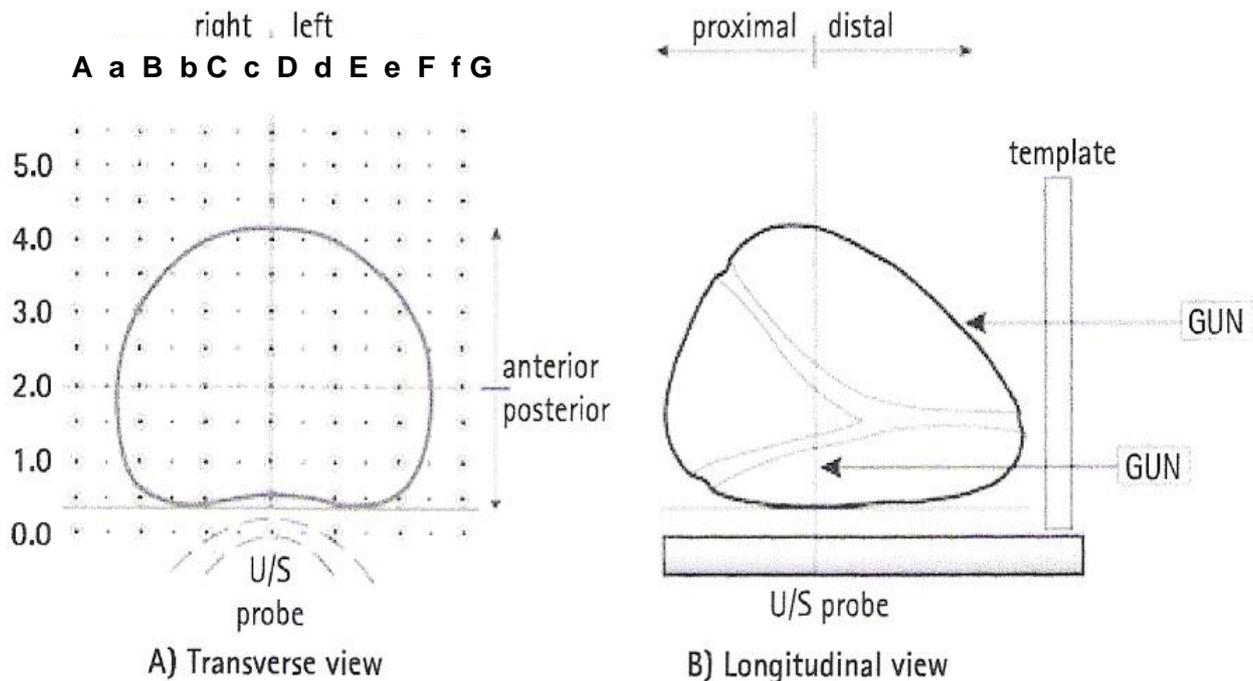
A full protocol of T1 and T2 weighted turbo-spin echo images and a dynamic post gadolinium volume acquisition will be used for both preoperative diagnostic and planning scans and postoperative assessment of HIFU. The MRI protocol will be as follows:

- 4.4.1.1 T2 weighted axial wide field of view of pelvis: to detect pelvic lymphadenopathy and other pelvic pathologies  
T2 small field of view prostate: cancer detection and volume estimation  
T2 small FOV coronal: for cancer detection & to accurately determine the position of prostatic apex & external sphincter  
T1 axial small FOV: to detect haemorrhage  
Total Time = 20 minutes
- 4.4.1.2 Dynamic contrast-enhanced FLASH sequences with scans before and every 30 seconds after contrast for 4 minutes: for tumour enhancement  
Post contrast small FOV fat saturated T1 axials: high resolution images of enhancement  
Total Time = 10 minutes
- 4.4.1.3 Diffusion weighted axial slices of prostate: to detect restricted diffusion in tumour  
Total time = 5 minutes
- 4.4.1.4 Spectroscopy of whole prostate with voxel sizes of approximately 0.3ml  
Total time = 20 minutes

#### 4.4.2 Transperineal ultrasound-guided template-directed prostate biopsy

A discussion of this procedure is warranted, even though it is not part of the trial as data from this procedure will guide focal ablation. With the patient in the lithotomy position the perineum is prepared with shaving of hair if necessary and cleaning with sterile povidone-iodine solution or chlorhexidine solution. A brachytherapy stand with stepping unit will be set up with a transrectal biplanar ultrasound probe. A standard 5mm brachytherapy template is positioned over the perineum. A Foley catheter is placed to allow visualisation of the urethra.

The template has scales of 'A' to 'G' with 10mm intervals and intervening 'a' to 'b' with 10mm intervals (sequence A-a-B-b-C-c-D-d-E-e-F-f-G-g, 5mm intervals) on the x-axis. The y-axis has a scale of 1.0 to 7.0 along 5mm intervals (sequence 1.0-1.5-2.0-2.5-3.0-3.5-4.0-4.5-5.0-5.5-6.0-6.5-7.0). Grid-point 'A-0' was located on the patient's right side at the bottom of the template.



The prostate is scanned from base to apex. The prostate is aligned so that the posterior aspect lies on the '1.5' row and the urethra on the 'D' column. The prostate is divided into right and left portions by the 'D' column. Systematic biopsies are then taken using the template at 5mm points through the perineum using an 18-gauge core biopsy needle and firing biopsy 'gun'. Each core is 23mm in length. Two or more biopsies will be taken from the same grid-point when a single biopsy is not sufficient to sample the length, apex to base, of the prostate. In these cases the biopsies will be denoted 'apical' or 'base' (cranial and caudal, respectively) after their grid reference. The apical (caudal) end will be inked with blue ink so that the specimen can be orientated (this does not affect histopathological analysis). In the unlikely event that any areas that are suspicious for cancer on ms-MRI and which have not been biopsied, these areas will separately targeted transperineally. The following parameters should be recorded at the time of biopsy:

- Grid reference for every biopsy
- Apical or base (if two biopsies taken at a particular grid ref)
- Electronic or hard copies of all biopsies taken on an axial plane image of the prostate with a superimposed 5mm grid (a laptop computer will be attached to the ultrasound scanner so that electronic images can be retained and analysed for correlation with MRI images)

These data will aid in the focal treatment planning stage.

#### 4.4.2 Histopathology criteria for prostate biopsy

For each prostate core biopsy the following dataset will need to be recorded to guide focal therapy:

4.4.2.1	Grid-point reference	
4.4.2.2	Cancer present	- yes/no
4.4.2.3	Location	- proximal, middle, distal
4.4.2.4	Length of tumour/length of core	
4.4.2.5	Geason score	
4.4.2.6	PIN present	- yes/no
4.4.2.7	Location of PIN	- proximal, middle, distal
4.4.2.8	Perineural invasion	- yes/no

### 4.5 Treatment with Focal-HIFU

#### 4.5.1 General HIFU Treatment Protocol

Signed informed consent will be taken for Focal-HIFU of the Prostate.

Patients will be admitted the evening prior to or on the day of therapy. A phosphate enema will be administered on the morning of surgery to ensure a clear rectum. Type of anaesthetic (general or regional with or without sedo-analgesia) will depend on anaesthetic opinion and discussion with the patient. The procedure chosen should as far as possible eliminate potential patient movement. The patient is placed in the lithotomy position. Prophylactic antibiotic is given (intravenous gentamicin 2mg/kg).

The HIFU probe and machine is prepared as per manufacturer's instructions (see Appendix for Sonablate® 500 Userguide). The HIFU probe is covered with a latex protector and primed with degassed water. The HIFU probe is then placed within the rectum using an appropriate amount of degassed lubricant gel used specifically for ultrasound. Views of the prostate are then obtained to ensure that images are of a high quality and that therapy is technically feasible (i.e. anterior gland is accessible, absence of acoustic shadowing). Once satisfied, a treatment plan will be selected by the operator and treatment commenced (see 4.5.2).

A long term urinary catheter is placed at the end of the procedure either urethral or supra-pubic. Patients are transferred to a recovery area and then the ward. Discharge home is usually on the same day if deemed appropriate after medical team review and once they are confident in catheter management. Patients are given appropriate post-operative antibiotics (ciprofloxacin 500mg twice daily for 7 days). Appropriate analgesia such as co-dydramol 10/500 (dihydrocodeine tartrate 10mg; paracetamol 500mg) or suitable alternative is given on an 'as required' basis (maximum two tablets four times daily).

Catheter withdrawal will occur under antibiotic cover and take place between 5 to 14 days after treatment in a clinic setting. The patient will be taught intermittent self-catheterisation (ISC) at this time for use during voiding problems. If the patient fails to void and ISC is unsuccessful the catheter will be replaced urethrally and the procedure repeated at weekly intervals until successful.

#### 4.5.2 Specific Protocol for Focal-HIFU

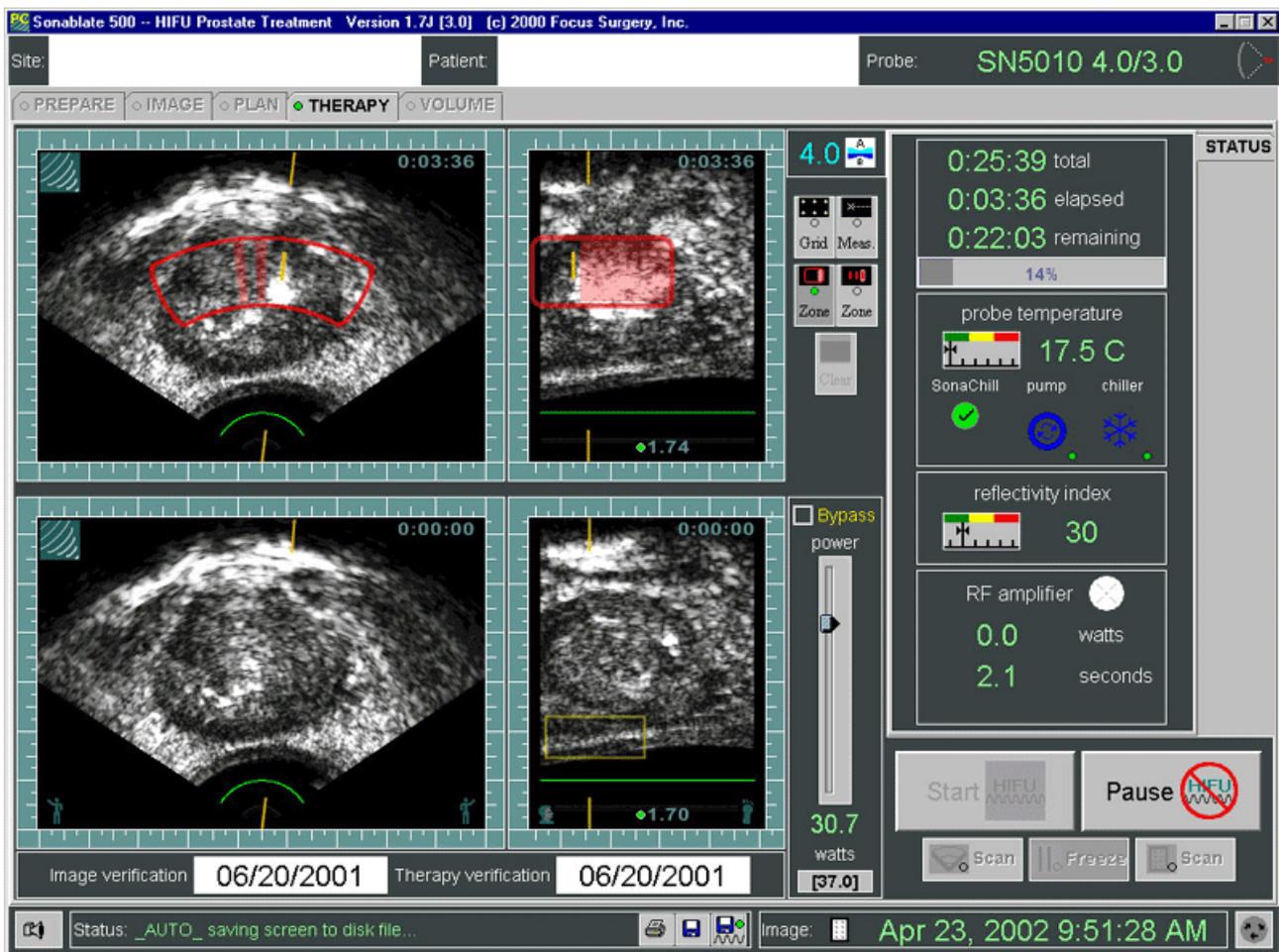
Focal ablation by HIFU will be tumour foci dependent rather than destroying pre-defined zones of the prostate. This is to ensure that a circumferential 5mm margin around each focus of cancer is possible. Such ablation will be carried out in the following way:

4.5.2.1 Each focus will have its margins defined by the most lateral/medial and most anterior/posterior positive biopsies on TPUS biopsies (the marginal positive biopsies or MPB).

4.5.2.2 Each MPB's axial coordinates ('x' and 'y' i.e., grid reference) will be located on the Sonablate 500 HIFU screen ('V' scan) by simple measurements from the midline-posterior point (which by standard will be D,1.5). The device has a grid to facilitate this.

4.5.2.2 As it is difficult without image-referencing software to localise the z coordinate accurately, treatment will proceed with an entire cylinder of tissue treated from apex to base. This will be carried with each foci of tumour and ensure 5mm margin of normal tissue is also treated.

#### Screen capture of Sonablate 500 HIFU 'Image' phase



## 4.6 Follow-up Schedule

### 4.6.1 Study events flow chart

Procedure	Screening	HIFU Focal ablation	Follow-up Visits						
VISITS	1	2	3	4	5	6	7	8	9
DAYS	Day -28 to Day -22	Day 0	Day 5-10	Day 10-20	1 M	3 M	6 M	9 M	12 M
Informed Consent	√	√							
Medical History	√								
Physical/Clinical Examination	√				√	√	√	√	√
Digital rectal examination	√				√	√	√	√	√
Transrectal Ultrasound Biopsy							√		
Inclusion Criteria	√	√							
Exclusion Criteria	√	√							
PSA Level	√				√	√	√	√	√
Urine culture	√				√	√			
Laboratory Evaluations									
- Na, K, Ur, Cr	√				√				
- Full blood count	√				√				
ms-MRI				√			√		
HIFU treatment		√							
Removal of catheter				√					
Adverse Events		√	√	√	√	√	√	√	√
Questionnaires									
- IPSS	√				√	√	√	√	√
- IPSS QoL	√				√	√	√	√	√
- FACT-P	√				√	√	√	√	√
- EPIC continence	√				√	√	√	√	√
- IIEF-15	√				√	√	√	√	√
Concurrent Disease		√		√	√	√	√	√	√
Concurrent Medications		√		√	√	√	√	√	√

### 4.6.2 Study visits and schedule

Patients who have been diagnosed with histologically proven prostate cancer with low to intermediate risk characteristics (as defined by the inclusion criteria above) which has not been previously treated will be approached for this study. Patients will be given as much time as is necessary to decide whether they wish to participate.

Once the patient has indicated a willingness to be considered a screening assessment will be carried out. The following schedule of visits is based on the start of HIFU treatment at visit 2 designated as Day 0, so any visits prior to this are given approximate negative ranges in the table above:

#### 4.6.2.1 *Visit 1 – Screening and Inclusion*

Informed consent must be signed by the patient before any implementation of study-related procedures.

The screening assessment will consist of:

- ◇ Full Medical History
- ◇ Physical/Clinical Examination (cardiovascular, respiratory, abdominal)
- ◇ Digital Rectal Examination
- ◇ Review of biopsy and ms-MRI
- ◇ Review of previous laboratory investigations (biochemistry, haematology, PSA)
- ◇ Review of Urinalysis
- ◇ Transrectal ultrasound if information on HIFU suitability not available from prior TRUS
- ◇ Assessment of inclusion/exclusion criteria

If the patient is eligible to join the study, signed informed consent will be taken and the following carried out on this visit:

- ◇ Patient questionnaires (IPSS, IPSS-QoL, EPIC continence, FACT-P, IIEF-15)
- ◇ PSA
- ◇ Other laboratory investigations (biochemistry, haematology, urinalysis) to update routine pre-operative assessment

If he agrees to proceed in the trial, a convenient date for Focal ablation HIFU will be organised in discussion with the patient

#### 4.6.2.2 *Visit 2 – Focal ablation HIFU*

Signed informed consent will be obtained. Focal ablation HIFU will be carried out as outlined in section 4.5. Discharge will usually be on the same day with a urethral catheter.

#### 4.6.2.3 *Visit 3 – Day 5-10: Post Focal-HIFU*

- ◇ Catheter removal under antibiotic cover.
- ◇ Patient will be taught clean intermittent self-catheterisation
- ◇ Adverse events reporting

#### 4.6.2.4 *Visit 4 – Day 10-20: Post Focal-HIFU*

- ◇ A follow-up MRI scan will be carried out to assess area of necrosis.
- ◇ Adverse events reporting

#### 4.6.2.5 *Visit 5 – 1 month: Post Focal-HIFU*

- ◇ Adverse events reporting
- ◇ Physical Examination
- ◇ DRE
- ◇ Urinalysis
- ◇ PSA level, biochemistry and haematology
- ◇ Laboratory investigations (biochemistry, haematology)
- ◇ Concurrent disease and Concurrent medication

- ◇ Patient questionnaires (IPSS, IPSS-QoL, EPIC continence, FACT-P, IIEF-15)

**4.6.2.6**      *Visit 6 – 3 months: Post Focal-HIFU*

- ◇ Adverse events reporting
- ◇ Physical Examination
- ◇ DRE
- ◇ Urinalysis
- ◇ PSA level, biochemistry and haematology
- ◇ Concurrent disease and Concurrent medication
- ◇ Patient questionnaires (IPSS, IPSS-QoL, EPIC continence, FACT-P, IIEF-15)

**4.6.2.7**      *Visit 7 – 6 months: Post Focal-HIFU*

- ◇ Adverse events reporting
- ◇ Physical Examination
- ◇ DRE
- ◇ Urinalysis
- ◇ PSA level, biochemistry and haematology
- ◇ Multi-sequence MRI to assess for recurrence
- ◇ Prostate Biopsies (Transrectal ultrasound guided biopsies under Local Anaesthetic) (with signed informed consent)
- ◇ Concurrent disease and Concurrent medication
- ◇ Patient questionnaires (IPSS, IPSS-QoL, EPIC continence, FACT-P, IIEF-15)

**4.6.2.8**      *Visit 8 – 9 months: Post Focal-HIFU*

- ◇ Adverse events reporting
- ◇ Physical Examination
- ◇ DRE
- ◇ Urinalysis
- ◇ PSA level, biochemistry and haematology
- ◇ Concurrent disease and Concurrent medication
- ◇ Patient questionnaires (IPSS, IPSS-QoL, EPIC continence, FACT-P, IIEF-15)

**4.6.2.9**      *Visit 9 – 12 months: Post Focal-HIFU*

- ◇ Adverse events reporting
- ◇ Physical Examination
- ◇ DRE
- ◇ Urinalysis
- ◇ PSA level, Biochemistry and Haematology
- ◇ Concurrent disease and Concurrent medication
- ◇ Patient questionnaires (IPSS, IPSS-QoL, EPIC continence, FACT-P, IIEF-15)

**4.7**            **Follow-up Details**

**4.7.1**            Post-Treatment MRI

This will be carried out within 10-20 days after treatment to evaluate the extent and volume of necrosis of the prostate. Another MRI will be carried out before

the 6 month prostate biopsy in order to evaluate for recurrence. All volume measurements will be by planimetry of contiguous 3mm slices, a technique that has been validated in the kidney. T2 images will be used for measurement of prostatic volume. The necrosis volume will be measured using the final dynamic post gadolinium image, allowing the use of the dynamic series and enhancement curves to confirm that an area was 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 dynamic 3D FLASH) from the total volume of prostate on the T2 sequence.

#### 4.7.2 TRUS prostate biopsy

This will be carried out using a standard technique to biopsy the prostate gland under local anaesthetic in order to exclude cancer. Antibiotic prophylaxis (ciprofloxacin 500mg twice daily) will be given for a period of 5 days. Signed informed consent will be obtained.

The specimen will be processed according to standard protocol and examined by a named Consultant Histopathologist (Dr. Alex Freeman). For each core the following features will be noted:

4.7.1.1	Presence of adenocarcinoma	- yes/no
4.7.1.2	Gleason score	
4.7.1.3	Length of cancer and length of core	
4.7.1.4	Perineural invasion	
4.7.1.5	Presence of PIN	- yes/no

Biopsies will be targeted to ablated areas only unless the ms-MRI at 6 months demonstrates suspicious lesions that were not seen in the pre-treatment MRI.

#### 4.7.3 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), Transurethral Resection Prostate (TURP)
- ◇ Androgen suppression in any form, radiation therapy to prostate in any form, cryotherapy, radical prostatectomy.
- ◇ Repeat treatment with HIFU
- ◇ Alpha blockade, 5 alpha reductase inhibitors, anti-muscarinic medication

## **5 Evaluation of Efficacy**

### **5.1 Primary Endpoints**

This study will primarily determine the feasibility, patient acceptability and side effect profile of Focal-HIFU to treat histologically confirmed, organ-confined low-risk prostate cancer. This will be by monitoring:

#### 5.1.1 Adverse Events

#### 5.1.2 Patient acceptability, urinary symptoms and erectile function assessment:

- ◇ Patient questionnaires
  - Functional Assessment of Cancer Therapy – Prostate (FACT-P)
  - International Prostate Symptom Score (IPSS)
  - IPSS – Quality of Life (IPSS-QoL)
  - EPIC continence questionnaire
  - 15-Item International Index of Erectile Function (IIEF-15)

### **5.2 Secondary Endpoints**

This study will secondarily aim to determine the effectiveness of Focal-HIFU to control prostate cancer as expressed by:

#### 5.2.1 Recording of PSA kinetics measurement of PSA at each follow-up to determine:

- ◇ measurement of time to PSA nadir

#### 5.2.2 Exclusion of cancer on:

- ◇ MRI at 10-20 days and at 6 months
- ◇ Transrectal prostate biopsies of treated areas at 6 months

#### 5.2.3 Recording the need for secondary or adjuvant treatment for prostate cancer following treatment

## **6 Evaluation of Safety and Tolerability**

### **6.1 Adverse Event Monitoring**

Each patient must be carefully monitored for adverse events. 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 hemiablation treatment. The following procedures will be in place:

- 6.1.1 Serious adverse effects will be monitored and reported on a continual basis.
- 6.1.2 Overall safety analysis will be carried out monthly by a subcommittee of the Trial Steering Committee comprising investigators in the trial.
- 6.1.3 Expected adverse effects and cancer failures will be recorded and analysis carried out after 10 patients have undergone treatment and then at end of treatment stage (20 patients).
- 6.1.4 Treatment related toxicities will be analysed when all 20 patients have undergone 6 months, 12 months and 24 months follow-up.

### **6.2 Adverse Event Definitions**

#### 6.2.1 Adverse Event

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

#### 6.2.2 Adverse Reaction

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

#### 6.2.3 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)

#### 6.2.4 Serious Adverse Event/Reaction (SAE/SAR)

Any untoward medical occurrence that:

- 6.2.4.1 Results in death
- 6.2.4.2 Is life-threatening (this term refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe)
- 6.2.4.3 Requires hospitalisation or prolongation of existing hospitalisation
- 6.2.4.4 Results in persistent or significant disability or incapacity
- 6.2.4.5 Is a congenital anomaly or birth defect
- 6.2.4.6 Is otherwise considered medically significant by the investigator

#### 6.2.5 Suspected Unexpected Serious Adverse Reaction

All suspected adverse reactions related to the intervention that are both unexpected and serious

### **6.3 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:

#### 6.3.1 Unrelated

An adverse event which is definitely not related to the intervention.

#### 6.3.2 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.

#### 6.3.3 Possible

An adverse event which 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.

#### 6.3.4 Probable

An adverse event which 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).

#### 6.3.5 Very likely

An adverse event, which 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 dechallenge and rechallenge).

#### 6.3.6 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.

### **6.4 Serious Adverse Events Reporting**

All serious adverse events must be reported to the sponsor (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.

## **7 Assessment of Tumour Response**

Long term cancer control is not possible in this trial of feasibility. However, some of the following will be assessed as early parameters of interest.

### **7.1 No Evidence of Disease**

No evidence of residual cancer, demonstrated by:

- ◇ Stable PSA (no three consecutive rises)
- ◇ Negative TRUS biopsies at 6 months
- ◇ Negative post-treatment MRI
- ◇ No clinical or radiological evidence of metastatic disease

### **7.2 Local Failure**

Local failure or lack of control will be demonstrated by:

- ◇ Rising PSA.
- ◇ Positive post-treatment biopsy
- ◇ No clinical or radiological evidence of metastatic disease

### **7.3 Distant Failure**

Distant relapse as demonstrated by:

- ◇ Clinical or radiological evidence of metastatic disease

### **7.4 Biochemical Failure**

In the follow-up of this trial, biochemical failure cannot be evaluated since follow-up of a minimum of 3-5 years is needed. The study is powered for early toxicity and early failure at 6 months.

### **7.5 Disease Free Interval**

Some data will be recorded for this, although due to the short follow-up interval, complete data on this would not be obtained. Measured from the date of therapy to the date of local or distant failure or until the time of death.

## **8 Discontinuation of Study**

### **8.1 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:

- 8.1.1 The investigator is non-compliant with the protocol
- 8.1.2 The investigator is non-compliant with the regulatory requirements
- 8.1.3 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)
- 8.1.4 The CRF completion or drug accountability is inadequate

### **8.2 Study Discontinuation by the Chief Investigator**

- 8.2.1 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.
- 8.2.2 If the positive biopsy rate post-treatment exceeds acceptable limits (i.e., greater than 50% after treating 15 patients) the trial will be closed. Each enrolled patient with negative biopsy results will be followed for the planned follow-up period and as per standard of care. Enrolled patients with positive biopsy results will be offered therapeutic options including active surveillance, radiation therapy, radical prostatectomy, cryoablation or repeat HIFU treatment to the whole gland.

### **8.3 Discontinuation of Study for an Individual Patient**

The criteria for discontinuing the study in the case on individual patients are:

#### 8.3.1 Intercurrent illness

Any illness, which in the judgment of the investigators would affect the assessments of clinical status to a significant degree

#### 8.3.2 Request by the patient

It is the patients 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.

#### 8.3.3 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.

## 9 Statistical Considerations

### 9.1 Statistical Analysis

The statistical analysis of patient characteristics, clinical and biological safety and tolerability profiles will be performed by the Investigator. The statistical analysis will consist of individual data listings, descriptive statistics and graphics (e.g., box-whisker plots) for the following parameters of interest:

#### 9.1.1 Patient characteristics

Patient characteristics will be evaluated using demography, medical history, previous and concomitant treatment, histological and blood parameters.

Disease risk categories and biopsy parameters (PSA, stage, Gleason, number positive, total number, focality)

#### 9.1.2 Safety, Tolerability and early outcomes Assessment

This will be evaluated as outlined in sections 5.1 and 6.1-6.4

Hospital stay

Early toxicity on adverse event reporting

Erectile function defined by erections sufficient for penetration and total IIEF-15 erectile domain scores and total scores. Other domain on IIEF-15 total scores summarised

Continence defined by specific questions on EPIC questionnaire to determine pad-free, leak-free and pad-free only rates as well as total scores evaluated by standardised analysis of EPIC scores

FACT-P total scores and individual domain scores summarised chronologically

Dichotomised scores to determine genitourinary functional outcomes

Biopsy outcomes and burden of positive biopsies

Imaging outcomes on MRI

Trifecta outcomes at 12 months (continence, potency, cancer control on biopsy and imaging)

The paired 2-sided Student t test to be used to evaluate differences between continuous variables (PSA and questionnaire scores) measured at baseline and at each follow-up visit.

Categorical patient reported functional outcomes were dichotomized into none to moderate or severe. McNemar's test to be applied to assess whether marginal proportions are significantly different from each other between baseline and at each follow-up. Statistical significance set at  $p \leq 0.05$

## **9.2 Stopping Rule for Adverse Events**

An early termination of the trial will occur if the rectal injury rate is unacceptably high. A rectal fistula rate of 2 at any point in the trial will be considered unacceptable and the trial stopped.

## **10 Ethical and Regulatory Considerations**

### **10.1 Ethical Principles**

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

### **10.2 Approval by Ethics Committee**

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

### **10.3 Protocol Amendment Procedure**

With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the documented approval of the Sponsor.

The LREC which granted the original approval for the study must be notified of all changes in the protocol and must provide documented approval of any change or deviation which may increase the risk to the patient and/or which may adversely affect the rights of the patient or validity of the investigation. This stipulation does not apply to those changes made to reduce discomfort or undue risk to the patients.

In the event of any emergency, the Chief Investigator shall perform all medical procedures which he deems appropriate. However, all such procedures must be promptly reported to the Sponsor.

### **10.4 Patient Identification**

The assignment of number and code for patient identification is based on the need for anonymity. Patients will be numbered consecutively in the order of their inclusion in the study. This will be pseudoanonymised.

### **10.5 Patient Information Sheet and Informed Consent**

The risks and benefits of participating in the study will be explained to each potential patient prior to entering into the study. The patient information sheet and consent form will be written in a language readily understood by the patient. The patient information sheet and consent form will be approved by the LREC prior to the initiation of the study and performance of any study procedure. The Chief Investigator or his designee must obtain a signed Informed Consent Form for each patient. Receipt of the signed Informed Consent Form will be documented in the Case Report Form and a copy retained in the Trial Master File. The original will be filed in the medical. A copy of the signed Informed Consent Form will be given to each patient. Refer to Appendix 1 for a sample of Patient Information Sheet and appendix 2 for a copy of the consent form.

## **10.6 Confidentiality**

The following strategies will be used to ensure patient confidentiality:

- 10.6.1 Each researcher will be trained to understand the need for absolute confidentiality with explicit instructions not to discuss any of the data or the identities of the subjects.
- 10.6.2 Failure to maintain confidentiality will be grounds for immediate termination.
- 10.6.3 Data will be coded using unique identifiers.
- 10.6.4 Hard copy interview forms will be stored in a locked research office (National Medical Laser Centre, 67 Riding House Street, London).
- 10.6.5 No individual's identity can be determined from encoded data.

## **10.7 Disclosure of Data**

The Chief Investigator, Co-investigators and any employee or agent involved in this study shall not disclose or use for any purposes other than the performance of the study any patient data, records, or other information disclosed to the Chief Investigator or his/her employees or agents.

However, for the purpose of flagging or tracing the patient after the study period, registration of patient identifiable data with the Office for National Statistics via the National Health Service Central Register (NHSCR) will be carried out. Informed consent will taken for this and a relevant clause is on the Patient Consent Form.

## **10.8 Publication**

The investigators shall be free to publish, present or use any results arising out of the performance of the study for their own instructional, research or publication objectives.

## **10.9 Patient risks and benefits**

- 10.9.1 The risks of this study to the patient are those that are involved in any in-situ prostate cancer therapy. Complications may include incontinence, urinary obstruction, urinary retention, impotence and rectal injury. The cancer may not be completely treated, especially if it has already spread beyond the prostate or the localisation techniques used have not completely excluded cancer foci in the untreated areas. Minimization of this risk is attempted by the patient selection criteria outlined with selection parameters supported by the literature. The localisation techniques also have a high level of accuracy and this issue should be minimised. The ultimate effect of this risk is decreased by the ability to give other therapies or even repeat HIFU to the whole gland if the cancer recurs. In the event of cancer recurrence the patient will be transferred to standard practice of care.

- 10.9.2 Patient Benefits  
The patient may benefit from entering this study by being exposed to a lower complication rate than that reported by more invasive prostate cancer therapies.

#### **10.10 Liabilities and Insurance**

In case of any damage or injury occurring to a subject in association with trial interventions, the Sponsor (UCLH Foundation NHS Trust) has contracted an insurance policy for negligent harm as covered by the Secretary of State for Health and NHS Indemnity.

#### **10.11 Quality Assurance**

This study will be conducted in compliance with the principles of Good Clinical Practice as laid down by the Declaration of Helsinki and will comply with the Research Governance Framework (version 2) (see Appendices 6 and 7).

## **11 Data Handling**

### **11.1 Case Report Forms**

Case report forms will be used by the Investigators and they will be responsible for the timeliness, completeness and accuracy of the information in the case report form. A case report form will be completed for each patient who signed the informed consent form.

Data will be entered according to the chronological sequence provided for in the case report form. All entries must be legibly recorded in ink, with corrections initialled and dated, by the investigator or a member of the investigator's authorised staff.

After completion, case report forms will be signed and dated at the end of each visit by the Investigator or the Co-investigator.

Original completed CRFs will be retained at one site along with the supporting source documents. Copies of the radiologist's, histologist's or urologist's report, laboratory reports, patient questionnaires and other relevant documents may be collected. Provision will be made for all documentation to be kept at the following site:

National Medical Laser Centre, 67 Riding House Street, London, W1P 7PN.

### **11.2 Retention of Study Records**

The Chief Investigator must be ready to meet and cooperate with any auditor designated by the Sponsor, to ascertain the performance of the study according to Good Clinical Practices. Archiving will be carried out at the clinical sites in an appropriate room designed for records retention. This room will be locked around the clock, and includes fire-detection monitoring.

The Chief Investigator will retain originals of the approved project protocol, original and a copy of the completed case report forms, patients' participation agreements, relevant source documents (patient CRFs and protocol files, protocol documents) and all other supporting documentation related to the project. These files must be made available for inspection upon reasonable request by an authorized representative of the Sponsor or the regulatory authorities.

All study-related records, including source documents, CRFs, and regulatory documents, must be retained for at least 2 years after the last patient has had their last visit. These documents should be retained for a longer period if demanded by regulatory requirements or by an agreement with the Sponsor. The Chief Investigator is responsible for the retention of all study documents for the appropriate period, and must inform the Sponsor in writing of any change in the status of these documents.

## 12 Appendix

### 12.1 Appendix 1: Sample Patient Information Sheet

#### Part 1

#### High Intensity Focused Ultrasound Focal Ablation of Localised Prostate Cancer

***You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.***

- ***Part 1 tells you the purpose of this study and what will happen to you if you take part.***
- ***Part 2 gives you more detailed information about the conduct of the study.***

***Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.***

#### **1. What is the purpose of the study?**

Men with localised prostate cancer have to choose between two extremes of care - active surveillance versus radical therapy. The best evidence we have shows the difference between these two very different approaches is not large in terms of preventing an individual from dying of prostate cancer within a 10 year period – 14% mortality for active surveillance, compared to a rate of 9% for men who had radical prostatectomy. On the other hand, we know that the side effects of radical treatments are high – they include, amongst others, deterioration in urinary, sexual and bowel function. It is these harms of therapy that many men are keen to avoid.

Could there be some way in which the benefits of treatment could be conferred on an individual without exposing him to the harms traditionally associated with radical therapies? We believe there is, at least for some men. Our focal-ablation (destruction of cancer areas only) study using high intensity focused ultrasound (HIFU) addresses this precise point. In other words, if we are as sure as we can be that cancer is confined to certain areas in the gland, then why not treat just those areas and monitor the untreated areas? If we can do this it is likely the cancer will be controlled and side effects kept to an absolute minimum. This trial will assess whether we correct in this theory.

#### **2. What is High-intensity Focused Ultrasound?**

HIFU works by generating sound waves which make the prostate tissue heat up and die. The treatment areas can be carefully located within the prostate and avoid the delicate organs that lie next to the prostate gland. It does not involve any needles into the prostate or any cuts to the skin.

HIFU therapy for prostate cancer has been in use for about 5 years. Studies are either under way or have been completed in the United States, Europe and Japan. Over 3000 patients have been treated so far. Studies have shown that HIFU therapy is at least as safe as other treatments for early prostate cancer and may have fewer side effects. It also appears to be effective at controlling prostate cancer, though the studies that show this are relatively new. This means that the longest period of time between HIFU therapy and assessment of side effects and cancer control is 5 years. Whilst this may sound like quite a long time it is generally agreed that 10 to 15 years needs to pass before we can be reasonably sure that any one prostate cancer treatment is as effective as any other. These studies show that HIFU, in the short term, appears to be a promising treatment. Depending on the study, and exactly how success was measured, reports have shown that HIFU therapy was effective at controlling prostate cancer in 80% to 95% of men treated, up to five years after the patient received the treatment.

#### **3. Why have I been chosen?**

You have been chosen because you have had a diagnosis of prostate cancer. The cancer seems to not have spread outside the prostate and it seems to be localised to only areas of the prostate gland that have been mapped by an MRI scan and prostate mapping biopsies under general anaesthesia. The

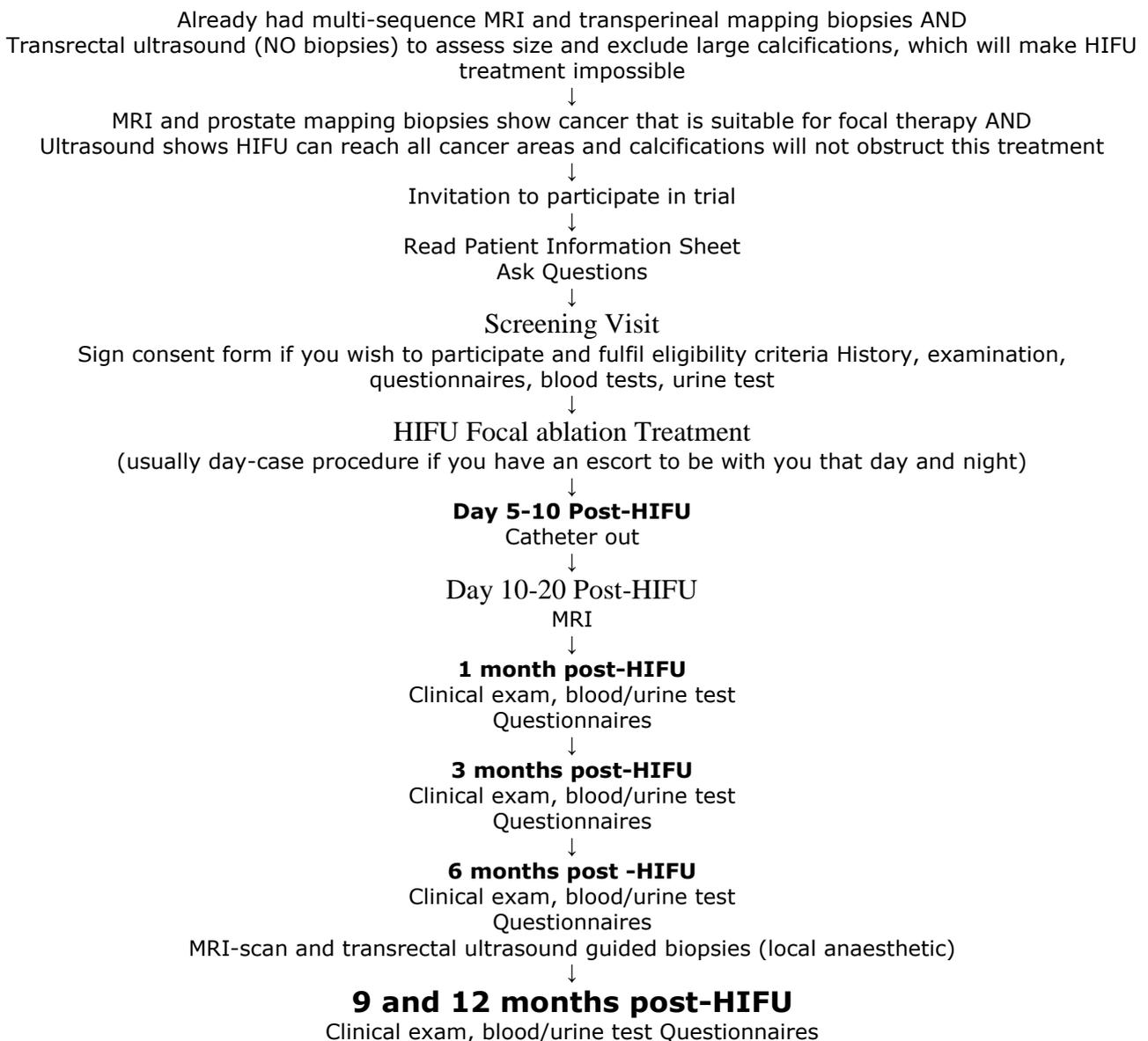
research team, upon looking at your results, think they can destroy only those areas of the prostate with cancer and leave non-diseased areas alone. Also, they believe they can preserve at least one of the nerves that runs alongside the prostate that supplies the penis for erection function. In radical treatments both nerves are usually damaged.

#### 4. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

#### 5. What will happen to me if I take part?

The flowchart gives a summary of what this study involves.



If you decide to take part in the trial, you will be asked to attend in trial visits over the course of the next one year. The precise commitment this will involve is laid out below. After this period, your care will continue in the same way as if you had not taken part in the study. Your progress and condition will be

monitored by your doctors in the urology or oncology clinic in the same way that it would have been if you had not decided to take part in the trial.

## **6. What happens exactly at each visit is outlined below**

### **Visit 1: Screening Visit**

Your research doctor will see you as an outpatient, explain the procedure to you, and answer any further questions that you might have. You will be asked to sign a consent form before we carry out anything further as part of the study. Once you have done this, you will have your full medical history taken and a physical examination carried out of your chest, heart and abdomen.

We will ask for the following things as well:

- 4 questionnaires to complete. These will include questions of a personal nature relating to erectile/sexual function, urinary flow/continence and your quality of life. You will be free to complete these in privacy.
- Blood sample for baseline tests and for anaesthetic pre-assessment [prostate specific antigen (PSA), full blood count (FBC), kidney function test (urea, creatinine, electrolytes)]. The amount of blood taken will be 10mls. This is about the same as a tablespoon of blood.
- A chest x-ray and a heart tracing (ECG) may also be required.

### **Visit 2: HIFU Focal Ablation Treatment**

- You will be asked to not eat anything for at least 6 hours before the procedure. You should drink anything for at least 4 hours before the procedure. On the morning of the procedure you will be given an enema to clear your rectum. This allows us to have clearer ultrasound pictures during HIFU treatment.
- An anaesthetist will explain the anaesthetic options available to you and make sure that your preferred option is both appropriate and safe. The anaesthetic will usually be a general anaesthetic (which puts you into a deep sleep during which you cannot feel anything. This is so that you do not move during the procedure so that the HIFU treatment is effective. The HIFU focal ablation will use a probe, slightly larger in size to the one used when you had your very first prostate biopsies taken, that is placed into the rectum. The treatment normally takes between 1<sup>1/2</sup> to 2 hours.
- After the treatment, a urinary catheter (a tube that drains urine from the bladder) is placed in the bladder. This is usually placed through the skin directly into the bladder rather than through your penis. Once this has been done your anaesthetist will wake you up. Most men will be able to have their treatment and go home about three hours later, provided there is someone else at home and suitable transport can be arranged. Occasionally, there will be the need for an overnight stay after treatment if your medical team think it is safer.
- You will be taught all about your catheter and how to look after it. Mild pain killers and a course of antibiotics and a contact number if you have any problems at home are given.

### **Visit 2 and 3: Removal of Catheter (5-10 days) and MRI scan (10-20 days) after HIFU Treatment**

The MRI scan will allow us to see how successful the destruction of prostate tissue was. Your catheter will be removed. This is a simple procedure that is usually not painful. Once the catheter has been removed you will be encouraged to drink and asked to try and pass urine. If you are unable to pass urine, a new catheter will be placed and you will be invited back a week later to have it removed. If at the second attempt at catheter removal, you are still unable to pass urine two things may happen. The first would involve teaching you the technique of Clean Intermittent Self Catheterisation (CISC). Although this may sound difficult to perform, most people learn it very quickly. It involves you passing a small slippery catheter into the bladder to empty it. You would only do this when you needed to. With time your bladder would start to work again and your need for CISC would become less and less.

If you cannot re-establish normal bladder emptying a cystoscopy (using a telescope to look into the bladder) will be carried out to investigate the cause. Some men, about 10-20%, may need this to be done. At the time a small procedure may be performed in order to promote normal bladder emptying. This might involve releasing some scar tissue in the prostate (formed as a result of the HIFU therapy) or cutting through the bladder neck in order to allow more efficient bladder emptying. Very occasionally some dead tissue or debris within the prostate would have to be removed. These procedures can be done using a telescope and should require no more than a one night stay in hospital.

### **Visits 4 and 5: 1 and 3 months after HIFU treatment**

- Blood tests to measure PSA, kidney function and haemoglobin level, white cell count and platelet count
- Urine test
- You will be asked about any symptoms that you experienced following the therapy.
- Complete the same 4 questionnaires that you completed prior to the HIFU therapy.

### **Visit 6: 6 months post treatment**

The only difference between this visit and visits 4 and 5 is that we will need to take further biopsies of the prostate as well as other items done in visits 6 and 7. Biopsies are taken to be as sure as we can that no cancer cells remain in the treated parts of the prostate. We will not biopsy the untreated areas unless the MRI shows a suspicious lesion that was not seen in your pre-treatment biopsy. It is done under local anaesthetic using a transrectal probe in a similar fashion to those biopsies you had before the trial to diagnose the cancer. You will not normally need to stay in hospital overnight. The procedure lasts for 15-20 minutes and you will be given a course of antibiotics to ensure infection does not develop.

### **Visits 9 and 10: 9 and 12 months after HIFU Treatment.**

These visits would be identical to visits 4 and 5.

### **7. What will happen once the trial finishes?**

Longer-term follow up will be carried out in the form of routine clinical appointments. This would be similar to the follow-up that you would expect to receive if you had chosen active surveillance at the outset.

### **8. What will happen to me if the treatment fails?**

The HIFU therapy will be assumed to have been effective unless one or both of the following occur. Firstly, if prostate biopsies (scheduled at 6 months) show prostate cancer cells in the treated areas. Secondly, if rises in PSA occur which indicate there may be cancer. If the PSA level rises in a way to suggest a recurrence you will be offered further prostate biopsies, even if previous biopsies did not reveal cancer at 6 months. If any biopsies show prostate cancer cells the HIFU focal ablation treatment will be deemed to have failed. Further treatments might include: surgery, radiotherapy, cryotherapy, hormonal treatment, photodynamic therapy or further HIFU treatment. You will be given detailed information on this.

### **9. What data will be collected?**

We will hold information about you without anything that could identify you to that data. You will be given a study number and this will be used on all your study records. The code for this number will be known to Mr Mark Emberton and Mr Hashim Uddin Ahmed so that the link between your name and the data we hold on you is not completely broken. All clinic visit information including questionnaires, scans, biopsy results and blood results will be kept in study records so that we can analyse how this HIFU treatment has performed.

### **10. What do I have to do?**

You may continue to take your regular medication or other prescribed over-the-counter drugs. You should not be involved in any other studies that involve the prostate gland. Normally, you should not be involved in any other type of study using drugs or medical devices. Please discuss this with your research doctors and they will advise you. It is important that you attend all visits, undergo all study investigations and agree to fill in all questionnaires before and after the treatment.

### **11. What is the device or procedure that is being tested?**

The procedure we are testing is destruction of the half of the prostate gland with prostate cancer using a device called the Sonablate® 500 HIFU machine. It uses a high energy focused ultrasound beam, which is directed across the wall of the back passage into the prostate to heat and destroy a very precise

volume of tissue at its focus. This study will help us to find out just how safe and well tolerated HIFU is in destroying only discrete areas of the gland.

## 12. What are the alternatives for diagnosis or treatment?

At the time of diagnosis, prostate cancer may be confined to the prostate itself, or may have spread to other sites within the body. If prostate cancer is confined to the prostate, there are a number of treatments available. The types of treatment that aim to destroy the whole prostate include surgery (radical prostatectomy), external beam radiotherapy, brachytherapy (small implanted radioactive seeds), cryosurgery (freezing) or HIFU. All these treatments can fail to cure prostate cancer. There are two main reasons why this may happen. First, the cancer within the prostate was not properly treated. In other words, some of the cancer cells survived. Second, although the prostate cancer was thought to be confined to the prostate this was not the case: some cancerous cells had spread to other areas and were therefore unaffected by the surgery, radiotherapy, or HIFU. The best result shows that radical prostatectomy reduces the risk of dying from localised prostate cancer by 5% compared to watchful waiting (where no treatment is given).

## 13. What are the side effects of any treatment received when taking part?

### Complications from HIFU using the Sonablate® 500 HIFU

Most patients report temporary urinary symptoms (frequency, urgency, difficulty in urination) during the first 2-3 months after treatment. Other complications are listed with the chances of them happening in brackets:

- Urinary tract infection (5 in 100)
- Urethral stricture (narrowing in the urine passage) (1 in 10)
- No semen produced during ejaculation (dry ejaculation) (most men)
- Epididymitis (infection of the tubes surrounding the testicles) (3 in 100)
- Urinary retention requiring surgery (2 in 100)
- Impotence (2 in 5)
- Urinary Incontinence (temporary) (0-2 in 100)
- Recto-urethral fistula (an abnormal connection between the rectum and urinary passage) (0-1 in 200)

These complications are from published results using HIFU to treat the whole gland. We believe that using HIFU to treat only some parts of the gland may mean less complications and this is what we want to prove. However, this is a theory and we will only know the true extent of complications after the study results have been analysed.

## 14. What are the other possible disadvantages and risks of taking part?

### Complications from the Contrast-agent Gadolinium during the MRI Scan

The use of gadolinium is very safe and widely used in clinical practice and not just for this study. Some complications occur and include:

- nausea and vomiting (less than 5 in 10,000)
- mild allergic reaction (e.g., rash, itching) (less than 4 in 1,000)
- moderate allergic reaction (less than 5 in 10,000)
- severe allergic reactions (breathing problems, face swelling) (less than 1 in 10,000)

1.1.

### 1.2. Complications from General Anaesthetic

1.3. There are risks associated with undergoing any anaesthetic procedure.

- Nausea/vomiting after anaesthetic (less than 1 in 10).
- Most men will have a dry cough for an hour or two and may experience a sore throat for 24 hours. This occurs because a mask and /or tube are placed in the throat during the anaesthetic.
- Minor bruises from intravenous catheters (drips) are common.
- Occasionally extensive bruising, temporary hardening of the vein (phlebitis) or infection can occur from intravenous catheters (1 in 20).
- The known risk of death under anaesthesia in the UK is 1 in 150,000 anaesthetics. To put this in perspective, if we anaesthetised a volunteer every day for 400 years there would be one death.

#### Complications from Transrectal Prostate Biopsies

These include:

- bloody urine and semen (less than 1 in 100)
- retention of urine requiring a temporary catheter (2 in 100)
- prostatitis (inflammation or infection of the prostate, less than 1 in 100)
- temporary pain in anal area (less than 1 in 200)
- infection (requiring admission and intravenous antibiotics, 0-1 in 100)

If, during the course of this trial, we were to discover a condition of which you were unaware, we will inform you, and if necessary, refer you to the relevant medical practitioner. If you have private medical insurance you should check with the company, before agreeing to take part in the trial, whether participation is considered a 'material fact' that should be reported. You will need to do this to ensure that your participation will not affect their medical insurance.

Please share this information with your partner if it is appropriate: it is not known if the study device will affect sperm or semen. It is possible that the sperm quality could be affected by participation in the study. You should not assume that you will be infertile as the majority will not be affected. We are hoping that ejaculation will be maintained.

#### **15. What are the possible benefits of taking part?**

The possible benefits from this treatment are that we can treat the prostate cancer and reduce the side-effects traditionally associated with other forms of prostate cancer treatment which affect your urinary, rectal and erectile function. We hope that you will personally benefit from HIFU therapy. However, this cannot be guaranteed. The information provided in this information sheet should help you to decide whether you wish to undergo this experimental form of HIFU treatment.

#### **16. What happens when the research study stops?**

When the research study is completed, the results will be analysed. If the treatment has been shown to be useful, the next step would be to compare the longer-term results of HIFU focal ablation treatment directly with surgery and radiotherapy. Your own care will continue regularly as it would with any other form of managing your disease.

It is also important for us to know how you are doing even after the period of the study has elapsed. For various reasons, we may be unable to contact you. For this reason, we will also obtain your consent for us to obtain information from the Office for National Statistics in the event that we are unable to contact you after the study period. In order for us to do this we provide identifiable information for us to trace you on the National Health Service Care Register (NHSCR).

#### **17. What if there is a problem?**

Any complaint about the way you have been dealt with during the study or any possible harm you might have suffered will be addressed. The detailed information on this is given in Part 2. A contact number for complaints is given in Part 2.

#### **18. Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

#### **19. Contact Details**

In the first instance, for further information or any concerns during the study, please contact  
Mr Hashim Uddin Ahmed  
Mobile: 07980 551 297  
E-mail: hashim\_uddin\_ahmed@hotmail.com

You may also contact Mr Mark Emberton via his office on  
Tel: 020 7380 9194

*In an emergency it is best to contact your local GP or go to your local Casualty department or dial 999 for an ambulance.*

**This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.**

## Part 2

### 20. What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

***Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.***

***If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.***

### 21. What will happen if I don't want to carry on with the study?

Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future medical care. All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

### 22. What if there is a problem?

*If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about this study, the normal National Health Service complaints mechanisms should be available to you.*

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top of this consent form.

Complaints Department

2<sup>nd</sup> Floor, Dorville House, The Middlesex Hospital, London W1T 3AA

Tel: 020 7380 9655

### 23. Will my taking part in this study be kept confidential?

***Our procedures for handling, processing, storage and destruction of their data are compliant with the Data Protection Act 1998.***

- Your data will be collected at each visit. Blood and biopsy results will be collected from UCLH NHS Trust computer database and your medical notes. The data will be held in paper form in one site and also held on secured laptop computers

- The data will be stored securely, in a coded manner so that no information that could identify you is held in study records. The controller for this data is UCLH NHS Trust. The custodian of this data who is responsible for the safety and security of the data is Mr Mark Emberton (Chief Investigator).
- The data will be analysed and any results may be published in medical journals. The data will also help us plan larger trials using this form of HIFU treatment if it is successful. If the data is to be used in any other way in future studies then approval will be sought from the local Research Ethics Committee.
- The following persons will have authority to view identifiable data:
  - Mr Mark Emberton (Chief Investigator)
  - Mr Hashim Uddin Ahmed (Clinical Research Fellow)
    - Miss Rebecca Scott (Research Nurse)
    - Dr Dean Barratt (Senior Research Fellow, UCL)
    - Professor David Hawkes (Professor of Computer Science, UCL)
    - Mr Dominic Morgan (PhD Student)
    - Mr Enrico deVita (Medical Physics Department, UCL)
    - Mr Alan Bainbridge (Medical Physics Department, UCL)
    - Dr Jan van der Meulen (Clinical Trial Monitor, Royal College of Surgeons)
  - UCLH NHS Trust designated officials

The data will be retained for 2 years after the end of the study. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

#### **24. Involvement of your General Practitioner/Family doctor (GP)/Other Doctors**

***With your consent, your GP and other doctors not involved in the research but looking after you in this or another hospital will be notified of your participation in this study. If you will not consent for this then we cannot enter you into the trial as it is important these doctors are aware what treatment you have had for the prostate.***

#### **25. What will happen to any samples I give?**

All blood samples will be processed in UCLH laboratories as part of routine anaesthetic work-up or for follow-up after treatment. Samples are not kept for more than 2 days in the laboratory and no further tests are carried out on them. All these blood tests would occur if you were to undergo surgery or radiotherapy and are not extra samples taken just for this study.

The prostate biopsies you have taken will be processed and reported by the Department of Histopathology at UCLH. After they are reported by a Consultant Histopathologist, this study will make no further use of the samples. We view your samples as a 'gift' which are stored in the Histopathology department with your hospital number, name and date of birth.

Future studies can only be carried out on the samples with approval from the Research Ethics Committee. If such approval is gained the Ethics Committee may insist on those future researchers seeking your permission if the committee considers that the study is likely to substantially affect your interests.

#### **26. Will any genetic tests be done?**

No genetic studies will be carried out.

#### **27. What will happen to the results of the research study?**

The results of the study will be analysed and presented as publications for medical journals and at scientific meetings around the world. There will be no identifiable data in these publications. A summary of these results will be available for you and copies of full publications will also be available if you wish to have them.

#### **28. Who is organising and funding the research?**

The University College London Hospitals NHS Trust is sponsoring the study and are responsible for making sure it runs according to best research practice and relevant laws of the United Kingdom.

The study is funded by charity organisations.

**29. Who has reviewed the study?**

This study was given a favourable ethical opinion for conduct in the NHS by the UCLH Research Ethics Committee A.

A copy of this Information Sheet will be given to you and if you decide to participate, a copy of the signed consent form will also be given. Please feel free to ask any questions to the Research Staff. Many thanks for taking the time to read this Information Sheet and considering taking part in our Study.

Contact Details

Mr Hashim Uddin Ahmed  
Clinical Research Fellow  
Tel: 07980 551 297  
E-mail: hashim\_uddin\_ahmed@hotmail.com

Mr Mark Emberton  
Reader in Interventional Oncology  
Consultant Urological Surgeon  
Tel: 020 7380 9194

## 12.2 Appendix 2: Sample Informed Consent

### CONSENT FORM

Title of project:

*High Intensity Focused Ultrasound Focal Ablation of Localised Prostate Cancer*

Name of Chief Investigator: Mr Mark Emberton

Please tick box

1. I confirm that I have read and understood the information sheet dated 10<sup>th</sup> February 2007 (version 1) for the above study and have had the opportunity to ask questions.
2. *I confirm that I have had sufficient time to consider whether or not I want to be included in the study.*
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from University College London Hospitals NHS Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
5. I agree for my GP and other doctors (who are actively involved in my care at this hospital or others) to be informed of my participation in this study.
6. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status
7. I agree to take part in the above study.

Original with hospital notes, 1 copy for Patient, 1 copy for study documentation

***Continued on next page***



**12.3 Appendix 3: Patient Questionnaires**

**12.4 Appendix 4: Case Report Form (CRF)**

**12.5 Appendix 5: World Medical Association Declaration of Helsinki**

**12.6 Appendix 6: Research Governance Framework (version 2)**

**12.7 Appendix 7: Sonablate® 500 User Guide**

## 12.8 Appendix 8: Sonablate® 500 Liability Insurance

12<sup>th</sup> January 2007

Our Ref: AJW/IMAG/UKHIFU  
Your Ref: N/A

### 1.5. TO WHOM IT MAY CONCERN

Dear Sirs

### RE: IMAGING EQUIPMENT LTD & UKHIFU LTD

We act as Insurance Brokers for the above clients and would confirm their insurance as follows:

#### 1.6. Employers Liability

Insurance Company: Chubb Insurance Company Of Europe S.A  
Policy Number: 79804271  
Limit of Indemnity: £10,000,000 any one occurrence unlimited  
During the period of insurance  
Expiry Date: 12<sup>th</sup> January 2008

#### 1.7. Public/Products Liability

Insurance Company: Chubb Insurance Company Of Europe S.A  
Policy Number: 79804271  
Limit of Indemnity: £2,000,000 any one occurrence but in respect  
Of products liability claims made basis in the  
aggregate  
Expiry Date: 12<sup>th</sup> January 2008

#### 1.8. Excess Public/Products Liability

Insurance Company: Illium Managing Agency Limited (syndicate 4040)  
Policy Number: 664/42839A06  
Limit of Indemnity: £3,000,000 in excess of primary £2,000,000  
Expiry Date: 12<sup>th</sup> January 2008

We confirm that the premium for the current period has been paid. We trust this is the information you require, however should you have any further queries please do not hesitate to contact us.

Yours faithfully

ALEX WILLIS

### 2. Account Executive

### 3. CLARKE ROXBURGH INSURANCE BROKERS LIMITED

alex.willis@clarkeroxburgh.co.uk

Clarke Roxburgh  
Insurance Brokers Ltd

36 Greenhill Street  
STRATFORD UPON  
AVON  
Warwickshire  
CV37 6LE

Tel: 01789 415142  
Fax: 01789 294278  
www.clarkeroxburgh.co.uk

Registered in England  
Number 1428872

Clarke Roxburgh Insurance  
Brokers Ltd is Authorised and  
Regulated by the Financial  
Services Authority (310320)