NIHR HTA Programme

06 December 2012

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639

email: hta@hta.ac.uk
web: www.hta.ac.uk

Protocol for a systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of ablative therapy for men with localised prostate cancer (HTA no: 10/136/01)

1. Background

1.1 Description of the underlying health problem

Prostate cancer is the commonest cancer diagnosed in men in the UK and is the second commonest cause of cancer deaths.[1] It also incurs significant economic costs, costing the NHS in excess of £200 million annually.[1-3] In clinical practice three factors are considered in decision making concerning the mode of treatment for an individual with localised prostate cancer: firstly his life-expectancy according to chronological age and co-morbidities; secondly the tumour characteristics such as PSA level, stage of disease and histological pattern (Gleason score) which can be used for risk stratification to predict behaviour using nomograms; and thirdly patient preference balancing cure rate and potential adverse effects. The majority of men present with early, localised disease (see Table 1 for study definition) which is amenable to radical (curative) treatment by way of either surgery or radiotherapy. Indeed, there is evidence to indicate that the use of radical treatment for early, localised prostate cancer is increasing.[4] However, given that a large proportion of men with early, localised disease will not develop progressive disease, it is possible that the harms of this highly invasive treatment strategy may outweigh the benefits for some men. Radical prostatectomy or external beam radiotherapy are associated with significant adverse effects such as urinary incontinence, sexual dysfunction and bowel problems. It has been estimated that more than 40% of men with early localised prostate cancer have been over-treated with radical treatment,[5] and this has important repercussions for the men concerned and for the NHS. An alternative management strategy is active surveillance, whereby radical treatment is deferred until disease progression, or the cancer becomes more aggressive (e.g. higher Gleason grade) as identified by serial PSA testing and repeat prostate biopsies. Nevertheless, such a conservative approach risks disease progression to a stage where cure by radical treatment is no longer possible; involves repeated use of biopies with associated patient discomfort and clinical costs; and it is associated with patient anxiety in living with a cancer which is essentially untreated. Minimally invasive ablative therapies such as brachytherapy or cryotherapy have been proposed as a means of bridging the gap between radical treatments and active surveillance. These targeted therapies destroy the cancer in specific areas (foci) of the prostate in a minimally invasive manner whilst simultaneously minimising damage to adjacent structures such as urinary sphincter, urethra, bladder, rectum and nerves for erectile function, hence potentially reducing the risk of adverse effects.

In addition, ablative therapies have also been used in treating men with local relapse after radical external beam radiotherapy. Although radical external beam radiotherapy is considered a curative treatment option for localised prostate cancer, a relatively high proportion of men estimated at approximately 30%[6] will develop recurrent disease signalled by a rising PSA and a positive re-biopsy. This recurrence rate is, to some extent, inflated by the higher proportion of men being treated for more advanced disease compared with radical prostatectomy. If left untreated, at least 75% of these men will develop localised prostate cancer recurrence within 5 years[7] and hence require further treatment, although the timing of second-line treatment remains controversial. Subsequent treatment options include palliative hormonal therapy, and potentially curative salvage procedures. The currently recommended option, salvage prostatectomy, carries a high risk of morbidity including urinary incontinence and rectal injury.

1.2 Description of the interventions

1.2.1 Ablative therapies

Ablative therapies involve the localised application of various types of energy to targeted areas of the prostate using thin probes administered either percutaneously through the perineum, transurethrally or transrectally. Various imaging modalities such as transrectal ultrasound scan and/or MRI scan are employed to guide the delivery of treatment to targeted areas of the prostate and to monitor the effects of treatment in real-time, so that the treatment remains confined to the areas of known cancer to spare adjacent normal tissues. Whilst primarily undertaken using general anaesthetic, such minimally invasive procedures may also be performed under local anaesthetic or sedation in the outpatient setting. Other advantages include the ability to repeat the ablative procedure if required, and if the procedure fails to achieve cancer control, then salvage treatment by way of surgery or radiotherapy can be undertaken. The ablative technologies considered in this review are: (1) brachytherapy; (2) cryotherapy; (3) high intensity focused-ultrasound (HIFU); (4) vascular-targeted photodynamic therapy (PDT); (5) transperineal radiofrequency interstitial tumour ablation (RITA) therapy; and (6) laser ablation therapy (encompassing procedures such as photothermal therapy, laser interstitial tumour therapy and laser photocoagulation).

1.2.1.1 Brachytherapy

Interstitial brachytherapy involves the ultrasound and template-guided insertion of radioactive seeds into the prostate gland. It is an established curative treatment option for low risk, early-stage prostate cancer.[8,9] Due to its more localised effects of radiation, the procedure offers the potential advantage of delivering a higher radiation dose to the prostate than would be possible with conventional external beam radiotherapy. Brachytherapy is thought to be at least equivalent to the other curative treatment

options for localised prostate cancer in terms of cancer control.[9-11] There are various brachytherapy protocols, each with subtle differences in technique, including variations in radiation dosages and scheduling. It can be used either singly or in combination with external beam radiotherapy (especially IMRT). Two types of radioactive implants are available: permanent seeds (with either Iodine [I]-125 or Palladium [Pd]-103) or temporary implants (Iridium [Ir]-192). The recommended prescription doses for permanent seed brachytherapy (as monotherapy) are 145 Gy for I–125 and 120-125 Gy for Pd–103.[10] For temporary brachytherapy, the radiation dose is delivered at a higher dose rate than for a permanent implant, because the implant can be removed after the treatment session. As such, temporary brachytherapy is termed high dose rate brachytherapy. High dose rate brachytherapy is commonly delivered in 2 or more fractions of 810 Gy or more. The commonest adverse effects associated with brachytherapy include urinary, bowel and sexual dysfunction. Since it was first introduced, brachytherapy has been used to treat the entire prostate gland. However, the ability to target discrete lesions within the prostate by virtue of improved imaging techniques has made it possible to use brachytherapy as an intra-prostatic targeted treatment option for early, localised prostate cancer.[12]

1.2.1.2 Cryotherapy

Cryotherapy is the ablation of tissue using localised application of extreme cold. It achieves tissue destruction by 3 processes: (1) direct cell damage from the freeze-thaw cycle; (2) coagulative necrosis within a few days after treatment; and (3) apoptosis. The efficiency of tissue ablation is influenced by various factors, including velocity of cooling and thawing, nadir temperature, duration of freezing, number of freeze-thaw cycles, and presence of large blood vessels which can act as heat sinks. A minimum freezing cycle of -40°C for 3 minutes is required for tumour eradication.[13] The procedure involves the placement of needle probes transperineally using a template under transrectal ultrasound guidance. The probes are then cooled to generate an iceball within the prostate. Cryotherapy has been in use for prostate cancer whole gland treatment for more than 20 years but the technology has evolved considerably recently. Transrectal ultrasound guidance and urethral warmers were introduced resulting in more accurate probe placement and enabling monitoring of the iceball in real-time, whilst the urethral warmers decreased the risk of urethral sloughing.[14] Current third-generation devices utilise probes in which pressurised gas is used to freeze (argon gas) and thaw (helium gas). This enables use of finer calibre probes, which further enhance precision of probe placement and improve efficiency of tumour cell killing whilst reducing damage to surrounding structures.[15] The main adverse effects of cryotherapy are erectile dysfunction, urinary incontinence, urethral sloughing, rectal injury and recto-urethral fistula formation.[16]

1.2.1.3 High intensity focused-ultrasound

HIFU uses high-energy ultrasound waves (0.8-3.5MHz) focused to a specific point within the target organ in order to ablate tissue. Cellular damage occurs by two mechanisms: conversion of mechanical energy into heat and a process termed inertial cavitation. Once tissue temperature exceeds 56°C, irreversible cell death occurs from coagulative necrosis. Inertial cavitation results from the alternating cycles of compression and rarefaction of the sound waves. At the time of rarefaction, gas can be drawn out of solution to form bubbles, which then collapse rapidly, causing acoustic shock-waves which induce mechanical stress. The procedure involves the placement of an ultrasound probe transrectally. HIFU is also able to deliver its ablative energy more precisely than cryotherapy, with minimal effect on surrounding tissues outside the target zone. However, unlike cryotherapy, there is no 'ice-ball' equivalent, and hence it can be difficult to monitor the ablative effects of HIFU during treatment, although the process is guided by ultrasound. To minimise the thermal effects on the rectal wall, the rectum is irrigated with degassed, cooled water, which also eliminates acoustic interference between the transducer and the rectal mucosa. HIFU has been widely used in Europe for whole gland therapy and two systems are currently marketed. Both work by generating and focusing high-energy ultrasound waves at the target to generate temperatures above 60°C. The major adverse effects of HIFU include acute urinary retention, erectile dysfunction, urethral stricture, recto-urethral fistula and pelvic pain.[17] Disadvantages of HIFU include difficulty in achieving complete ablation of the prostate, especially in glands larger than 40 ml, and targeting cancers in the anterior zone of the prostate.[18]

1.2.1.4 Vascular-targeted photodynamic therapy

PDT is a technology which achieves destruction of targeted tissues using a light-sensitive agent (photosensitiser) and laser light of a specific wavelength in the presence of oxygen. The photosensitiser absorbs light of specific wavelength and transfers the energy to adjacent oxygen molecules, to create reactive oxygen species that trigger cell destruction.[19] To treat prostate cancer, the photosensitiser (Tookad® [WST09 and WST11, Steba Biotech, The Netherlands]), is administered intravenously and accumulates preferentially in the tumour blood vessels. The photosensitiser is activated by laser light of specific wavelength which is delivered transperineally using optical fibres. Alternative photosensitisers are also under investigation. Complications of vascular-targeted PDT include phototoxicity, skin photosensitisation, erectile dysfunction, urethral damage and recto-urethral fistula formation.[18]

1.2.1.5 Radiofrequency interstitial tumour ablation

RITA is a procedure that utilises low-level radiofrequency energy (approximately 460 kHz) to heat and ablate tissue in a focussed manner. Tissue destruction is achieved by coagulative necrosis resulting from heating tissues to 100°C for 5 minutes. The procedure has been shown to be effective

and safe in the treatment of primary and secondary liver tumours[20] and in renal cancer as an alternative to nephron-sparing surgery.[21] For the treatment of localised prostate cancer, the radiofrequency energy is delivered through needle probes which are inserted transperineally into the prostate and treatment is conducted under transrectal ultrasound guidance. Temperature in the rectal wall is monitored and both the urethra and rectum are irrigated with cooling solutions to avoid heat damage. The procedure is conducted under sedation on an outpatient basis. Patients are usually catheterised urethrally for a day. Adverse effects include frank haematuria, bladder spasms and dysuria, all of which appear to be transient.[22]

1.2.1.6 Laser ablation therapy

Laser ablation is a generic term implying thermal destruction of tissue by laser energy. It encompasses a number of technologies that have been used to treat prostate cancer and are therefore relevant to this review including photothermal therapy, laser interstitial tumour therapy and laser interstitial photocoagulation. Tissue destruction occurs by local coagulative necrosis, with temperatures ranging from 42°C to more than 60°C. However, laser energy has a localised effect, resulting in minimal damage outside the targeted ablation zone. Experience with laser ablation for solid tumours comes from the focal treatment of liver metastases from colorectal cancer.[23] The Nd-YAG laser, with a wavelength of 1064 nm was initially used for prostate cancer ablation but it is being superseded by more compact and less expensive infrared diode lasers (wavelength 800–980 nm). The laser is delivered transperineally through flexible quartz fibres within a flexible fibreoptic device which also allows the use of water-cooled laser application sheaths which prevent overheating close to the fibre tip.[24] Targeting of the lesion and real time-monitoring of the ablation can be performed using either magnetic resonance (MR) thermometry or contrast-enhanced ultrasound. The use of MR thermometry is particularly advantageous as it allows for individually adjusted heat dosing application, thereby ensuring adequate tumour ablation whilst simultaneously avoiding damage to adjacent normal tissues. Reported adverse effects include transient perineal discomfort and haematuria.[25] Laser ablation therapy has the theoretical advantages of accurate, predictable and reproducible delivery of energy. Real-time monitoring by either MR or contrast-enhanced ultrasound is also more easily performed.

1.2.2 Comparator interventions

1.2.2.1 Radical prostatectomy

The surgical treatment of localised prostate cancer is radical prostatectomy. It involves removing the prostate together with its surrounding thin layers of connective tissue and seminal vesicles, with or without ilio-obturator lymph node dissection depending on tumour grade and PSA level. The aims of the operation are: (1) to achieve cancer clearance; (2) to minimise perioperative morbidity; and (3) to preserve continence and sexual function. There are three main approaches to radical prostatectomy,

namely open, laparoscopic and robotic-assisted. Open radical prostatectomy can be accomplished either through the retropubic route (i.e. radical retropubic prostatectomy, or RRP) or through the perineal route (i.e. radical transperineal prostatectomy, or RPP). RRP using the nerve-sparing technique has long been regarded as the 'gold standard' of radical prostatectomy[26] and the technique continues to develop and evolve. RPP is considered a less invasive method of prostatectomy[27] and the technique has been further modified to optimise outcomes .[28] Over the past decade, advancements in minimally invasive surgery have seen the development of laparoscopic radical prostatectomy (or LRP) in order to minimise morbidity and improve functional outcomes. LRP, first described in 1998,[29] can be performed either transperitoneally[30] or extra-peritoneally.[31] More recently, technological advancements in robotics have enabled the development of robotic-assisted laparoscopic radical prostatectomy (RALRP) as an alternative to conventional LRP.[32]

1.2.2.2 Radical external beam radiotherapy (EBRT)

One of the main non-surgical treatment options in terms of curative intent for early prostate cancer is radical radiotherapy. It involves the administration of multiple doses of photon radiation from an external source over a period of several weeks. There are several different types of EBRT. Conformal radiotherapy (or 3D-CRT) [33] uses three dimensional planning systems which deliver a geometrically-shaped radiation beam in order to maximise radiation dosage delivered to the prostate, whilst at the same time minimising unwanted effects on adjacent healthy tissues and organs. Intensity modulated radiation therapy (or IMRT)[34] represents an advanced version of 3DCRT, which uses intensity-modulated beams (i.e. beams that deliver more than two intensity levels for a single beam direction and a single source position in space). IMRT provides the precise adjusted dose of radiation to target organs with less irradiation of healthy tissues compared to 3DCRT. Proton beam radiation therapy (or PBT) [35] is a form of EBRT in which protons rather than photons are delivered in a conformal manner to the prostate. PBT has the potential to improve the therapeutic ratio of prostate radiation by allowing for an increase in dose without a substantial increase in side effects. There are variations in each EBRT treatment modality, in terms of radiation dose, treatment schedules and whether the treatment is combined with hormonal therapy or otherwise, either in a neo-adjuvant or adjuvant fashion, or combined with other EBRT modalities (e.g. PBT may be combined with 3D-CRT). External beam radiotherapy is also being increasingly used in combination with high-dose-rate brachytherapy boost.[36,37]

1.2.2.3 Active surveillance

The policy of active surveillance for low-grade localised prostate cancer is based on the premise that such cancers are unlikely to become clinically significant in a rapid time frame, and it involves an active decision not to treat the patient immediately. Trends in population-based cohort studies on the

incidence and mortality rates of prostate cancer detected by PSA screening[38] and in retrospective cohort studies of men with clinically localised prostate cancer identified in the pre-PSA era[39] appear to support such an assertion. An active surveillance policy usually involves structured programs with serial PSA monitoring, regular digital rectal examination and repeat prostatic biopsies.[8] The rise in PSA level (considered as a surrogate marker of disease progression) or upgrading of cancer at repeat biopsy triggers curative intervention, such as radical treatment or androgen deprivation therapy. However, there is no consensus on the actual definition of disease progression (e.g. level or rate of PSA rise, or degree of disease upgrading).

Watchful waiting is a different strategy (and will not be considered here) whereby the decision is made at the outset that curative treatment is inappropriate for the patient, with the decision usually being based on a short life expectancy (e.g. elderly patients) or significant co-morbidities. The patient is monitored for signs of symptomatic or clinical progression, which triggers palliative treatment, which includes hormonal therapy or symptomatic treatment (e.g. analgesia for pain, or alleviation of bladder outflow obstruction through transurethral resection of prostate).

1.2.3 Summary of existing evidence evaluating the benefit of ablative therapies

HIFU[40] and cryotherapy[41,42] were both the subject of NICE Interventional Procedure Guidance issued in 2005 concerning their use as primary therapy for men with localised prostate cancer, and as salvage procedures for men with locally recurrent disease. Although they have been approved for use on the basis of safety and short-term efficacy, the guidance documents emphasised the lack of evidence on effects on quality of life and long term survival. In 2008, the evidence was updated with similar conclusions and included in NICE guidance for the diagnosis and treatment of prostate cancer. This guidance review stated that the overall quality of evidence was poor with short follow-up and hence concluded that the evidence for HIFU and cryotherapy is limited with poor quality data on cancer-specific outcome and overall survival. The guidance therefore did not recommend the routine use of either procedure for the treatment of localised prostate cancer. In contrast, the most recent EAU guidance[43] for the treatment of localised prostate cancer suggests that cryotherapy is a viable treatment option, although HIFU was still at the innovative, experimental stage. All other ablative therapies were termed “innovative” with no evidence base.

Up to the present time, several health technology assessment (HTA) reports have summarised various aspects of the evidence for effectiveness of newer ablative procedures. There have however been relatively few systematic reviews that have encompassed all ablative procedures and compared the findings to current management options for localised prostate cancer in the NHS. The most recent

review[44] found few relevant studies and restricted formal economic modelling to the role of brachytherapy, three-dimensional conformal radiotherapy and cryotherapy.

The most recent comprehensive systematic review of treatment options for localised prostate cancer was performed by the Institute for Clinical and Economic Review from a USA perspective.[45] The review summarised three separate reviews undertaken by the Institute.[46-48] In the review, comparative studies (randomised or non-randomised) were identified for all treatments of localised prostate cancer (including active surveillance). The review illustrated that comparative studies involving active surveillance, radical prostatectomy and radiotherapy have been published but none compared these modalities to HIFU, cryotherapy or brachytherapy. The review reported that comparison of effectiveness between different therapies was challenging because of the lack of head-to-head trials. Nonetheless, the review did conclude that radiation therapy has a higher rate of short and long-term bowel side effects than surgery and that, conversely, surgery has higher risks of urinary incontinence and sexual dysfunction. The report did not attempt to meta-analyse the difference in effectiveness between treatment modalities but simply tabulated all the data and made general observations. Regarding newer ablative technologies the review only commented on brachytherapy and PDT.

Specific ablative therapies have undergone individual HTAs from different international agencies. HIFU has undergone two HTAs from Canada[49] and Belgium.[50] Similarly cryotherapy has undergone two HTAs from Australia[51] and Canada.[52] The reports found only case series were available and concluded that no firm conclusions can be made on the effectiveness of the treatments. None of these reviews formally considered an indirect comparison network analysis to compare the role of differing ablative procedures to current practice which is a major deficiency given the increasing experience with this type of analysis.

1.3 Summary

In summary, the strength of the evidence provided by the systematic reviews is limited by the variation in characteristics of the primary studies and in the quality of the methods and reporting of the systematic reviews themselves. As a result, the conclusions of these reviews were often inconsistent. There is a need to perform a comprehensive comparative review of ablative therapies using cross-design research synthesis methodology and to take a UK NHS perspective.

2 AIMS AND OBJECTIVES

The study aims to systematically review and meta-analyse evidence on clinical effectiveness and harms and then use these data to model cost-effectiveness of ablative therapies including those

recently developed for localised prostate cancer within the United Kingdom (UK) National Health Service (NHS). The specific objectives of the study are to:

1. Develop clinical care pathways for treatment of localised prostate cancer in a UK NHS context (objective 1)
2. Review systematically the evidence of the clinical effectiveness and safety of each ablative therapy concerning:
    a. Primary treatment of localised low/intermediate risk prostate cancer compared with active surveillance, radical prostatectomy and external beam radiotherapy (objective 2a)
    b. Primary treatment of localised high risk prostate cancer compared with radical prostatectomy and external beam radiotherapy (objective 2b)
    c. Salvage treatment for local prostate cancer relapse after external beam radiotherapy compared with salvage radical prostatectomy (objective 2c)
3. Determine which therapies are most likely to be efficient for implementation into the UK NHS (objective 3)
4. Identify and prioritise future research needs (objective 4)

3. RESEARCH METHODS

3.1 Development of care pathway for patients with localised prostate cancer (objective 1)

The study will be based upon a detailed protocol developed over the first three months of the project mapping out care pathways, identifying key outcome measures and resource use. Our research group have recently published care pathways for the treatment of prostate cancer[53] developed by an international collaboration of health professional experts, methodologists and patients. These care pathways will be developed in an iterative fashion following discussion between the methodologists and the local health care professional work team. They will then be shared with the wider research team and the expert panel (see Section 3.4) so that errors and inconsistencies can be identified and also to identify substantial variations in practice in management for specific strategies e.g. the organisation of surveillance may differ substantially between localities.

The care pathways developed will provide the conceptual structure for the economic model and will be converted into a mathematical model as described in Section 3.3 below. Core datasets will then be developed for the systematic review of relative effectiveness, epidemiological/natural history data, resources, costs and utilities (for health states and the outcomes and processes of care). This approach will ensure that the work conducted in the other elements of the project will generate the parameter

estimates required for the economic model. An example of a care pathway for cryotherapy ablation is given in Appendix 1.

3.2 Systematic reviews of the safety and effectiveness of ablative procedures versus alternative procedures (objectives 2a-c)

The overarching structure of each of the proposed systematic reviews is to consider evidence from all randomised comparative designs (or non-randomised comparative designs if none available) and this will be supplemented by case series for the ablative procedures only should no comparative studies be identified. Taking such an approach will enable a network analysis of the available data to be undertaken.

3.2.1 Inclusion criteria

The inclusion criteria for types of studies, participants and outcome measures will be the same for the two reviews addressing objectives 2a and 2b. However, the comparator treatments will differ. For objective 2c, the participants will also differ. As the research progresses it may be more appropriate to consider the research as one large review with three sub-questions or as two reviews with one focusing on management of localised disease and the other focusing on salvage treatment for local recurrence. This decision will be influenced by the availability of detailed clinical cancer T-stage in included study reports (see types of patients section below).

Types of studies

For all three reviews, we shall consider evidence from randomised controlled trials, non-randomised comparative studies (if no RCT evidence is identified) and case series (greater than 10 participants) for only the ablative procedures, the latter primarily because of the lack of comparative data found during the scoping reviews. Should comparative studies of the ablative procedures be identified, consideration will be given to removing case series from the reviews. Studies comparing only multiple treatments of the same non-ablative therapy within the same comparative study (e.g. comparing different dosages of radiotherapy or studies comparing open versus laparoscopic prostatectomy) will be excluded. We will not include conference abstracts or non-English language reports (except if included study is an RCT incorporating an ablative procedure comparison where no language restriction will be applied).

Types of participants

Studies describing treatment of men with localised prostate cancer, defined as cancer confined to the prostate gland, will be included. The eligible patients will have clinical stage T1 or T2 disease at presentation (not pathological staging) stratified into localised low/intermediate risk and localised

high risk of progression based upon the criteria shown in (Table 1).[54] The patient risk of recurrent disease criteria are the same for primary or salvage treatment. For studies with mixed clinical stage patients (i.e. T1 to T4), the study will be included if greater than 80% of the patients are stage T1 or T2. Additionally, for the salvage therapy review (objective 2c) the patients must have received EBRT prior to salvage therapy being considered. Studies of men with locally advanced prostate cancer (considered as stage T3/T4) will be excluded.

Table 1: Risk stratification for men with localised prostate cancer

Group	**PSA (ng/ml)**		**Gleason Score (0 – 10)**		**Clinical Stage**
Low risk	< 10	**And**	≤ 6	**and**	T1 – T2a
Intermediate risk	10 – 20	**Or**	7	**or**	T2b – T2c
High risk	> 20	**Or**	8 – 10	**and**	T2c or lower

Whilst the systematic reviews of primary treatment of localised low/intermediate/high risk prostate cancer (objectives 2a and 2b) and salvage therapy (objective 2c) relate to subsets of T1 and T2 disease, we will include any studies that report comparative data on T1 and/or T2 disease. This reflects the observation during scoping (and our experience of conducting such reviews in prostate cancer) that many studies do not report outcomes by the sub-stages of T1 or T2 disease

Types of interventions and comparators

For the primary therapy systematic review on low/intermediate risk localised prostate cancer (objective 2a), the ablative therapies being considered are cryotherapy, HIFU, PDT, RITA, laser ablation and brachytherapy. The comparators will be active surveillance, radical prostatectomy and EBRT.

For the primary therapy systematic review on high risk localised prostate cancer (objective 2b), the ablative therapies being considered are cryotherapy, HIFU, PDT, RITA, laser ablation and brachytherapy. The comparators will be radical prostatectomy and EBRT.

For the salvage therapy systematic review (objective 2c), the ablative therapies being considered are cryotherapy and HIFU. The comparator will be radical prostatectomy.

Descriptions of all interventions and comparators are as given in section 1.2.

Types of outcomes

The outcomes to be considered in the review can be categorised as follows:

Cancer related

- Biochemical (PSA) recurrence [55] (primary cancer related outcome)
- Disease free survival – defined as absence of clinically detectable disease in surviving patient
- Overall survival
- Further prostate cancer treatment

Adverse effects

- Sexual (penile erection) function – defined by validated score (such as the International Index of Erectile Function, IIEF-5) or as defined by the trialists
- Urinary continence – defined such as ≤1 thin pad per day and/or validated symptom score (such as the International Consultation on Incontinence Modular Questionnaire, ICIQ-UI) or as defined by the trialists

Quality of life

Generic and disease-specific quality of life – validated quality of life score (such as the SF-36)

Procedural

Procedure time

Length of hospital stay (if applicable)

Abandonment

Procedural complications and early death

Including but not restricted to, urethral sloughing, recto-urethral fistula formation, urethral stricture formation, acute urinary retention, dysuria, pelvic pain, rectal injury, perioperative death, and peri-procedural death and Clavien score.

3.2.2 Search strategy for identification of published reports of studies

Comprehensive electronic searches will be conducted to identify reports of published studies. Highly sensitive search strategies will be designed, including appropriate subject headings and text word terms, interventions under consideration and included study designs. Given the anticipated large number of studies requiring full paper assessment, only English language reports will be included with the exception of RCT evidence that involves an ablative procedure where no language restriction will be applied. Searches will not be restricted by year of publication. Medline, Medline in Process, Embase, CINAHL, Biosis, Science Citation Index, Cochrane Controlled Trials Register (CENTRAL),

Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Review of Effectiveness (DARE) and the HTA databases will be searched. Reference lists of all included studies will be scanned and our expert panel will be asked for details of additional reports. A draft MEDLINE and EMBASE search strategy for clinical effectiveness is detailed in Appendix 2.

3.2.3 Identification of other relevant information, including unpublished data

Ongoing studies will be found from WHO International Clinical Trials Registry, EU Clinical Trial register, Current Controlled Trials, Clinical Trials and NIHR Portfolio. Websites of manufacturers, professional organisations, HTA organisations and regulatory bodies will be checked for additional reports.

3.2.4 Assessment of study risk of bias

Our previous experience has demonstrated that multiple quality assessment tools are required for this type of systematic review. Two reviewers will independently assess quality of all included studies, using one of three separate checklists depending on study design. The standard Cochrane Collaboration risk of bias tool will be used to assess the risk of bias in randomised studies and the risk of bias tool recommended by the Cochrane Non-Randomised Studies Methods Group will be used for non-randomised comparative studies.[56] The expert panel will *a priori* identify the main confounders (by outcome) for non-randomised comparative studies and imbalance in any of the confounders (e.g. pathological cancer T-stage rates differ between comparative groups) will reflect a study at high risk of bias. We developed a case series tool for assessing risk of bias through our partnership in the Review Body for Interventional Procedures for the National Institute for Health and Clinical Excellence (NICE). The case series tool rates bias and generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of the analysis. In general, the risk of bias assessment will be used in a sensitivity meta-analysis. Discrepancies will be resolved by discussion or by a third party.

3.2.5 Data extraction

Two reviewers will independently screen titles and abstracts of all identified citations. Full text copies of all potentially relevant reports will be obtained and independently assessed by two reviewers to determine whether they meet the pre-defined inclusion criteria. Any disagreements will be resolved by consensus or arbitration by a third person. A data extraction form will be developed to collect information on study design, characteristics of participants, characteristics of interventions, and outcome measures. For studies reporting adverse events, two surgeons will categorise each complication using the Clavien – Dindo Classification of Surgical Complications with a third surgeon acting as arbiter in cases of disagreement about classification.

3.2.6 Data analysis

For all systematic reviews, data from each procedure and population group will be tabulated and summarised in a form appropriate for the model. Crude event rates (and 95% confidence intervals calculated by using binominal distribution approximation) for each of the intervention categories will be tabulated by summing across studies for outcomes, and also according to study design (RCT, non-randomised comparative studies, case series) to facilitate qualitative assessment of potential heterogeneity of event rates across different study designs. Where necessary we will adopt an indirect comparison (cross design) approach to allow inclusion of non-randomised comparative data and case series.[57] Reasons for clinical heterogeneity between studies will be explored, including differences in populations studied, outcome assessment, and risk of bias. We will examine statistical heterogeneity between and within studies using a Bayesian hierarchical random effects model enabling use of all available evidence.[58] Differences between interventions will be assessed by the corresponding odds ratio and 95% credible interval. WinBUGS software version 14 will be used to produce the Bayesian meta-analysis models.[59]

3.3 Economic evaluation (objective 3)

The scoping review illustrated that few economic evaluations have been conducted that compare any of the target interventions against each other or against standard therapies. No economic evaluation was identified that compared all the intervention from the UK perspective. Given this absence of evidence we propose to conduct a cost-utility analysis where results will be presented in terms of incremental costs per quality adjusted life year (QALY). This analysis will be based on an economic evaluation model as described below.

3.3.1 Model structure

We will construct a discrete event simulation model to estimate the costs, long-term effects and relative efficiency of the alternative interventions. Model structure will be informed by our current modelling strategy comparing robotic with laparoscopic prostatectomy which has been completed as part of an NIHR HTA funded study (09 14 02). A discrete event simulation model specifically models the processes involved in disease progression, primary treatment, and complications arising from treatment and/or endogenous disease state. These processes are simulated probabilistically, drawing random deviates from known distributions of events. Events are explicitly mapped through care pathways, and are linked by logical and mathematical relationships. The model will capture the side effects of management such as erectile dysfunction and incontinence, which can occur after treatment. It will also reflect potential requirements for salvage therapy and the consequences of development of recurrent local and metastatic disease including death. The time horizon for estimation of cumulative

costs and QALYs will be 10 years in the base case analysis as this represents the time period over which the most reliable data used to inform model parameters is expected to be available. The discrete event simulation model derives its parameters from the odds ratios that result from pre-existing studies, and the event rates and meta-analyses proposed in this study. All uncertainty surrounding estimates of input parameters will be informed by appropriate distributions calculated from meta-analysis (e.g. length of stay) or from expert opinion (e.g. equipment lifetime and reuse). We will employ sensitivity analysis to investigate the impact of uncertainty in model parameters using Latin hypercube sampling and partial correlation. This technique identifies the relative importance of each model parameter for each outcome, potentially highlighting gaps in our knowledge and priorities for future research. Modelling will conform with recommendations for best practice including those developed for economic evaluation models.[60] The economic perspective will be that of the UK NHS and costs and effects will be discounted in the base case at 3.5%.[61]

Some of the technologies compared will have a finite lifetime (e.g. items of surgical equipment) estimates on equipment life used in the model will be based upon information from manufacturer and clinical expert opinion.

3.3.2 Derivation of cost data

Information on the precise description of the resources required for each intervention is unlikely to be obtained from identified studies. The most appropriate sources for these data will be centres currently providing the target interventions. With the help of relevant members of the expert group, we will seek information from NHS centres on the quantity and configuration of resources required to provide each intervention. This will be supplemented by advice from other members of the expert advisory panel and information from the systematic review such as information on operation times and length of stay. Unit costs will be taken from appropriate routine sources e.g. British National Formulary for drugs, NHS centres and from equipment manufacturers. NHS reference costs

3.3.3 Derivation of utilities

For the cost utility analysis effects/benefits will be estimated in QALYs. For each health state a health state utility will be defined. We anticipate that the utilities incorporated into the existing model defined above will provide the majority of data required. These data have been derived using rigorous methodology but we will update our structured search of the literature to identify more up to date or relevant data. This structured economic literature review will also seek to identify utility data for health states not currently identified within the existing model. The estimates used within the model will be based upon the best available data, ideally derived using EQ-5D or similar (SF-36).[61-65] If data

specific to our study question are not available , we will explore the adaptation of utility values derived from different patient populations.

3.3.4 Epidemiological and relative effectiveness data

The main source of evidence to inform the probabilities required for the model will be the systematic reviews and meta-analyses (Section 3.3). It is unlikely that sufficient data to inform all probabilities will be derived from these sources. Additional focused searches will be conducted as necessary to identify the best available evidence relevant to the UK NHS for probabilities not available from other sources.

3.3.5 Estimation of relative efficiency

The results of the economic model will be presented as a cost-utility analysis (CUA). In the CUA, mean costs, mean QALYs, incremental costs and QALYs, which capture men's preferences for changes in health outcomes, and the incremental cost per QALY gained.

3.3.6 Uncertainty

Deterministic sensitivity analyses will be carried out to test for the effect of assumptions and variability.[66] A probabilistic sensitivity analysis will also be undertaken allowing presentation of results in a series of cost-effectiveness acceptability curves (CEAC). Estimates of costs and QALYs will be calculated as the expectation over the joint distribution of the parameters. Relevant distributions will be informed by the systematic reviews and meta-analyses, or expert opinion according to best practice.[67]

3.3.7 Liaison with manufacturers

We will contact the manufactures of the ablative therapies to contribute data concerning current capital, maintenance, instrument, and training costs together with current and projected future sales of the devices. These data will be needed to model the longer term impact of introduction of the device to the UK NHS. This will be facilitated by members of the expert group experienced in clinical use of the technologies.

3.3.8 Identification of future research needs (objective 4)

An extension of probabilistic sensitivity analysis is a value of information analysis.[68] We will conduct an expected value of perfect information (EVPI) and expected value of removing uncertainty surrounding specific parameters or groups of parameters (expected value of partial perfect information) to identify more precise and reliable estimates of parameters for use in subsequent economic evaluations.

3.4 Advisory Panel of Experts

An advisory panel of experts comprising the applicants, international leaders in ablative therapies and representatives from a patient organisation (UCAN – www.ucanhelp.org.uk) and professional societies (British Association of Urological Surgeons and European Association of Urology) will be convened at the start of the project. This expert panel will advise on the content of the protocol, provide guidance on the clinical pathways and assist in the interpretation of the evidence from the systematic reviews. The panel will meet twice during the study. Panel members include:.Damian Greene is Professor and lead clinician for urology at Sunderland Royal Hospital. He regularly undertakes cryotherapy of the prostate and is Chairman of EUCAP, the European Cryosurgery database; he is also a member of the International Consensus Panel for Focal Therapy in Prostate Cancer. Roger Kockelbergh, Consultant Urological Surgeon and Clinical Director, University Hospitals of Leicester, UK will advise on implementation pathways in the UK NHS with added expertise in his role as representative of the Section of Oncology, British Association of Urological Surgeons. John Gaunt will provide patient insights and perspectives (see section 5 for details). Ian Pedley, Consultant Clinical Oncologist, Northern Centre for Cancer Care, Freeman Hospital, Newcastle will provide expert oncological advice and share his experience of using EBRT and brachytherapy. Mark Emberton is Professor of Interventional Oncology, Division of Surgery and Interventional Science at University College London, and Clinical Director, Clinical Effectiveness Unit at the Royal College of Surgeons of England. He is an international expert on focal therapy for prostate cancer, especially on HIFU, and he is a member of the International Consensus Panel for Focal Therapy in Prostate Cancer. He will provide clinical and methodological expertise on focal therapy and HIFU.

3.5 Ethical arrangements

It is envisaged that only secondary data sources will be used in this project and ethical approval is not required. If previously collected primary datasets are subsequently used to estimate some parameters in the economic model, the relevant Ethics Committee will be informed to confirm that the data can be used for research purposes. The Universities of Aberdeen and Newcastle both conform to recognised high standards of research governance and abide by the 1998 Data Protection Act.

3.6 Management of the project

We propose to make use of a two level group structure to manage the project. The first level is the project steering group comprised of all co-applicants which will be responsible for strategic leadership and to ensure the project is delivering in a timely manner. The project steering group will teleconference or meet on a monthly basis. The day to day running of the project will be the

responsibility of co-PIs Ramsay and Lam in Aberdeen, and Professor Vale in Newcastle. This reflects the clear division of responsibilities between Aberdeen (systematic reviews and surgical expertise) and Newcastle (modelling and economic evaluation). Together with the senior and junior staff at both institutions, they will form the project management group. To provide continuity in clinical support to the economic group, Professor Rob Pickard in Newcastle will provide clinical expertise liaison to the economic team. The project management group will meet at least twice-monthly to address any concerns and discuss progress. This structure has worked successfully on previous reviews for the HTA programme (e.g. HTA no:04/38 and 09/14).

4. PROJECT TIME TABLE AND MILESTONES

Month	Task
1-3	Develop protocol, care pathways, develop and run literature searches, develop tools for data abstraction and quality assessment
3	First Expert panel convened
3-10	Systematic reviews – primary treatment (data abstraction completed)
3-10	Systematic review – salvage treatment (data abstraction completed)
11	Second Expert panel convened
10-12	Statistical analysis
3-14	Economic modelling
12-14	Report writing

5. SERVICE USERS

This project is supported by the **U**rological **Can**cer (UCAN) charity (letter of support available on request). The charity has nominated a representative to participate in the project and to take part in the advisory panel meetings. The representative is John Gaunt who chairs the UCAN research steering committee.

6. REFERENCES

1 *Cancer incidence and mortality in the United Kingdom and constituent countries, 2006-08 [document on the Internet]*. London: Office for National Statistics; 2011 [accessed May 2012]. URL:http://www.ons.gov.uk/ons/rel/cancer-unit/cancer-incidence-and-mortality/2006-2008/cancer-incidence-and-mortality-in-the-uk--2006-2008.pdf.

2 *Prescription Cost Analysis England - 2011 [webpage on the Internet]*. NHS Information Centre; 2012 [accessed May 2012]. URL:

http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-england--2011.

3 Chamberlain J, Melia J, Moss S, Brown J. The diagnosis, management, treatment and costs of prostate cancer in England and Wales. *Health Technol Assess* 2001;**1**(3).

4 Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. *J Urol* 2007;**178**:14-9.

5 Shao YH, Albertsen PC, Roberts CB, Lin Y, Mehta AR, Stein MN et al. Risk profiles and treatment patterns among men diagnosed as having prostate cancer and a prostate-specific antigen level below 4.0 ng/ml. *Arch Intern Med* 2010;**170**:1256-61.

6 Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010;**28**:1106-11.

7 Lee WR, Hanks GE, Hanlon A. Increasing prostate-specific antigen profile following definitive radiation therapy for localized prostate cancer: clinical observations. *J Clin Oncol* 1997;**15**:230-8.

8 *Prostate cancer: diagnosis and treatment; full guidance. CG58 [document on the Internet]*. London: National Insititute for Health and Clinical Excellence; 2008 [accessed May 2012]. URL: http://www.nice.org.uk/nicemedia/pdf/CG58FullGuideline.pdf.

9 *Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer [document on the Internet] Health Care Bulletin No 13.* US Department of Health and Human Services: Agency for Healthcare Research and Quality; 2008 [accessed May 2012]. URL: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=79.

10 *Comparative evaluation of radiation treatments for clinically localized prostate cancer: an update [document on the Internet]*. US Department of Health and Human Services: Agency for Healthcare Research and Quality; 2010 [accessed May 2012]. URL:http://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=69&bc=BAAgAAAAAAAA&.

11 Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol* 2009;**27**:607-12.

12 Eggener SE, Scardino PT, Carroll PR, Zelefsky MJ, Sartor O, Hricak H et al. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. *J Urol* 2007;**178**:2260-7.

13 Hoffmann NE, Bischof JC. The cryobiology of cryosurgical injury. *Urology* 2002;**60**:40-9.

14 Cohen JK, Miller RJ, Shuman BA. Urethral warming catheter for use during cryoablation of the prostate. *Urology* 1995;**45**:861-4.

15 Hubosky SG, Fabrizio MD, Schellhammer PF, Barone BB, Tepera CM, Given RW. Single center experience with third-generation cryosurgery for management of organ-confined prostate cancer: critical evaluation of short-term outcomes, complications, and patient quality of life. *J Endourol* 2007;**21**:1521-31.

16 Merrick GS, Wallner KE, Butler WM. Prostate cryotherapy: more questions than answers. *Urology* 2005;**66**:9-15.

17 Thuroff S, Chaussy C, Vallancien G, Wieland W, Kiel HJ, Le DA et al. High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. *J Endourol* 2003;**17**:673-7.

18 Marberger M, Carroll PR, Zelefsky MJ, Coleman JA, Hricak H, Scardino PT et al. New treatments for localized prostate cancer. *Urology* 2008;**72**:36-43.

19 Brown SB, Brown EA, Walker I. The present and future role of photodynamic therapy in cancer treatment. *Lancet Oncol* 2004;**5**:497-508.

20 Raut CP, Izzo F, Marra P, Ellis LM, Vauthey JN, Cremona F et al. Significant long-term survival after radiofrequency ablation of unresectable hepatocellular carcinoma in patients with cirrhosis. *Ann Surg Oncol* 2005;**12**:616-28.

21 Corwin TS, Lindberg G, Traxer O, Gettman MT, Smith TG, Pearle MS et al. Laparoscopic radiofrequency thermal ablation of renal tissue with and without hilar occlusion. *J Urol* 2001;**166**:281-4.

22 Shariat SF, Raptidis G, Masatoschi M, Bergamaschi F, Slawin KM. Pilot study of radiofrequency interstitial tumor ablation (RITA) for the treatment of radio-recurrent prostate cancer. *Prostate* 2005;**65**:260-7.

23 Vogl TJ, Straub R, Eichler K, Sollner O, Mack MG. Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy--local tumor control rate and survival data. *Radiology* 2004;**230**:450-8.

24 McNichols RJ, Gowda A, Kangasniemi M, Bankson JA, Price RE, Hazle JD. MR thermometry-based feedback control of laser interstitial thermal therapy at 980 nm. *Lasers Surg Med* 2004;**34**:48-55.

25 Lindner U, Lawrentschuk N, Trachtenberg J. Focal laser ablation for localized prostate cancer. *J Endourol* 2010;**24**:791-7.

26 Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. *Prostate* 1983;**4**:473-85.

27 Frazier HA, Robertson JE, Paulson DF. Radical prostatectomy: the pros and cons of the perineal versus retropubic approach. *J Urol* 1992;**147**:t-90.

28 Harris MJ. Radical perineal prostatectomy: cost efficient, outcome effective, minimally invasive prostate cancer management. *Eur Urol* 2003;**44**:303-8.

29 Guillonneau B, Vallancien G. Laparoscopic radical prostatectomy: initial experience and preliminary assessment after 65 operations. *Prostate* 1999;**39**:71-5.

30 Guillonneau B, Vallancien G. Laparoscopic radical prostatectomy: the Montsouris technique. *J Urol* 2000;**163**:1643-9.

31 Bollens R, Vanden Bossche M, Roumeguere T, Damoun A, Ekane S, Hoffmann P et al. Extraperitoneal laparoscopic radical prostatectomy. Results after 50 cases. *Eur Urol* 2001;**40**:65-9.

32 Menon M, Tewari A, Peabody JO, Shrivastava A, Kaul S, Bhandari A et al. Vattikuti Institute prostatectomy, a technique of robotic radical prostatectomy for management of localized carcinoma of the prostate: experience of over 1100 cases. *Urol Clin North Am* 2004;**31**:701-17.

33 Morris DE, Emami B, Mauch PM, Konski AA, Tao ML, Ng AK et al. Evidence-based review of three-dimensional conformal radiotherapy for localized prostate cancer: an ASTRO outcomes initiative. *Int J Radiat Oncol Biol Phys* 2005;**62**:3-19.

34 Hummel S, Simpson EL, Hemingway P, Stevenson MD, Rees A. Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(47).

35 Allen AM, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, Cengel K et al. An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee. *Radiother Oncol* 2012;**103**:8-11.

36 Martinez AA, Gonzalez J, Ye H, Ghilezan M, Shetty S, Kernen K et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;**79**:363-70.

37 *High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. Interventional Procedure Guidnace IPG 174 [website on the Internet]*. London: National Institute for Health and Clinical Excellence; 2012 [accessed May 2012]. URL: http://guidance.nice.org.uk/IPG174.

38 Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;**101**:374-83.

39 Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005;**293**:2095-101.

40 *High intensity focused ultrasound for prostate cancer. Interventional Procedure Guidance IPG 118 [webpage on the Internet]*. London: National Institute for Health and Clinical Excellence; 2005 [accessed May 2012]. URL:http://guidance.nice.org.uk/IPG118.

41 *Cryotherapy as a primary treatment for prostate cancer. Interventional Procedure Guidance IPG 145 [website on the Internet]*. London: National Institute for Health and Clinical Excellence; 2005 [accessed May 2012]. URL:http://guidance.nice.org.uk/IPG145.

42 *Cryotherapy for recurrent prostate cancer. Interventional Procedure Guidance IPG 119 [website on the Internet]*. London: National Institute for Health and Clinical Excellence; 2005 [accessed May 2012]. URL:http://guidance.nice.org.uk/IPG119.

43 Heidenreich A, Bolla,M, Joniau S, Mason,MD, Matveev,VB, Mottet N et al. *Guidelines on prostate cancer [document on the Internet[*. European Association of Urology; 2012 [accessed May 2012]. URL:http://www.uroweb.org/?id=217&tyid=1.

44 Hummel S, Paisley S, Morgan A, Currie E, Brewer N. Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review. *Health Technol Assess* 2003;**7**(33).

45 Ollendorf DA, Hayes,JH, McMahon,PM, Kuba,M, Pearson,SD. *Management options for low-risk prostate cancer: a report on comparative effectiveness and value [document on the Internet]*. Boston, MA: Institute for Clinical and Economic Review; 2009 [accessed May 2012]. URL: http://www.icer-review.org/index.php/mgmtoptionlrpc.html.

46 Pearson SD, Lapado,J, Prosser,L. *Intensity modulated radiation therapy (IMRT) for localiized prostate cancer [document on the Internet]*. Boston, MA: Institute for Clinical and Economic Review; 2007 [accessed May 2012]. URL:http://www.icer-review.org/index.php/imrt.html.

47 Ollendorf DA, Hayes,JH, McMahon,E, Pearson,SD. *Brachytherapy and proton beam therapy for treatment of clinically localized, low-risk prostate cancer [document on the Internet]*. Boston, MA: Institute for Clinical and Economic Review; 2008 [accessed May 2012]. URL:http://www.icer-review.org/index.php/bt-pbt.html.

48 Ollendorf DA, Hayes,JH, McMahon,E, Pearson,SD. *Active surveillance and radical prostatectomy for the management of low-risk, clinically localized prostate cancer [document on the Internet]*. Boston, MA: Institute for Clinical and Economic Review; 2009 [accessed May 2012]. URL:http://www.icer-review.org/index.php/as-rp.html.

49 *High-intensity focused ultrasound for prostate cancer [document in the Internet]*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009 [accessed May 2012]. URL:http://www.cadth.ca/media/pdf/htis/High%20Intensity%20Frequency%20Ultrasound%20final.pdf.

50 *Rapid assessment of a selection of new treatments for prostate cancer and benign prostate hypertrophy. [document on the Internet]*. Brussels: Belgian Health Care Knowledge Centre (KCE); 2008 [accessed May 2012]. URL:https://kce.fgov.be/publication/report/rapid-assessment-of-a-selection-of-new-treatments-for-prostate-cancer-and-benign-.

51 *Cryotherapy for recurrent prostate cancer and renal cancer. Application 1124 [document on the Internet]*. Canberra: Medical Services Advisory Committee, Australian Government Department of Health and Ageing; 2009 [accessed May 2012]. URL:http://www.msac.gov.au/internet/msac/publishing.nsf/Content/BAE45713D7D0FDEBCA257817001CB46D/$File/1124_MSAC_Assessment_Report.pdf.

52 *Cryosurgery for non-metastatic prostate cancer: clinical and cost effectiveness [document on the Internet[*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008 [accessed May 2012]. URL:http://www.cadth.ca/media/pdf/htis/Cryosurgery%20for%20Non-Metastatic%20Prostate%20Cancer%20Clinical%20and%20Cost%20Effectiveness.pdf.

53 MacLennan S, MacLennan S, Imamura M, Omar M, Vale L, Lam T et al. Urological cancer care pathways: development and use in the context of systematic reviews and clinical practice guidelines. *World J Urol* 2011;**29**:291-301.

54 *Prostate Cancer Nomograms [website on the Internet]*. New York: Memorial Sloan-Kettering Cancer Center; 2009 [accessed May 2012]. URL: http://www.mskcc.org/mskcc/html/10088.cfm.

55 De la Rosette J, Ahmed H, Barentsz J, Johansen TB, Brausi M, Emberton M et al. Focal therapy in prostate cancer-report from a consensus panel. *J Endourol* 2010;**24**:775-80.

56 Higgins JP, Altman,D, Sterne,J, Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. *Assessing risk of bias in included studies. Chapter 8 [document on the Internet]*. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0

[updated March 2011].The Cochrane Collaboration; 2011 [accessed May 2012]. URL:http://www.cochrane-handbook.org/.

57 Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res* 2001;**10**:277-303.

58 Prevost TC, Abrams KR, Jones DR. Hierarchical models in generalized synthesis of evidence: an example based on studies of breast cancer screening. *Stats Med* 2000;**19**:3359-76.

59 Spiegelhalter D, Thomas A, Best N. *WinBUGS: Bayesian inference using Gibbs sampling. User manual, version 1.4.* Cambridge: MRC Biostatistics Unit; 2003.

60 Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36).

61 National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal [document on the Internet]*. London: National Institute for Health and Clinical Excellence; 2008 [accessed May 2012] URL: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf.

62 Albertsen PC, Nease RF, Jr., Potosky AL. Assessment of patient preferences among men with prostate cancer. *J Urol* 1998;**159**:158-63.

63 Smith DS, Krygiel J, Nease RF, Jr., Sumner W, Catalona WJ. Patient preferences for outcomes associated with surgical management of prostate cancer. *J Urol* 2002;**167**:2117-22.

64 Krahn M, Ritvo P, Irvine J, Tomlinson G, Bremner KE, Bezjak A et al. Patient and community preferences for outcomes in prostate cancer: implications for clinical policy. *Med Care* 2003;**41**:153-64.

65 Dale W, Basu A, Elstein A, Meltzer D. Predicting utility ratings for joint health States from single health States in prostate cancer: empirical testing of 3 alternative theories. *Med Decis Making* 2008;**28**:102-12.

66 Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;**17**:479-500.

67 Briggs AH. *Handling uncertainty in economic evaluations and presenting the results.* In: McGuire M, Drummond AM, McGuire A, editors. Economic evaluation in health care: merging theory with practice. Oxford: Oxford University Press; 2001.

68 Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999;**18**:341-64.

Appendix 1 - Example of a care pathway

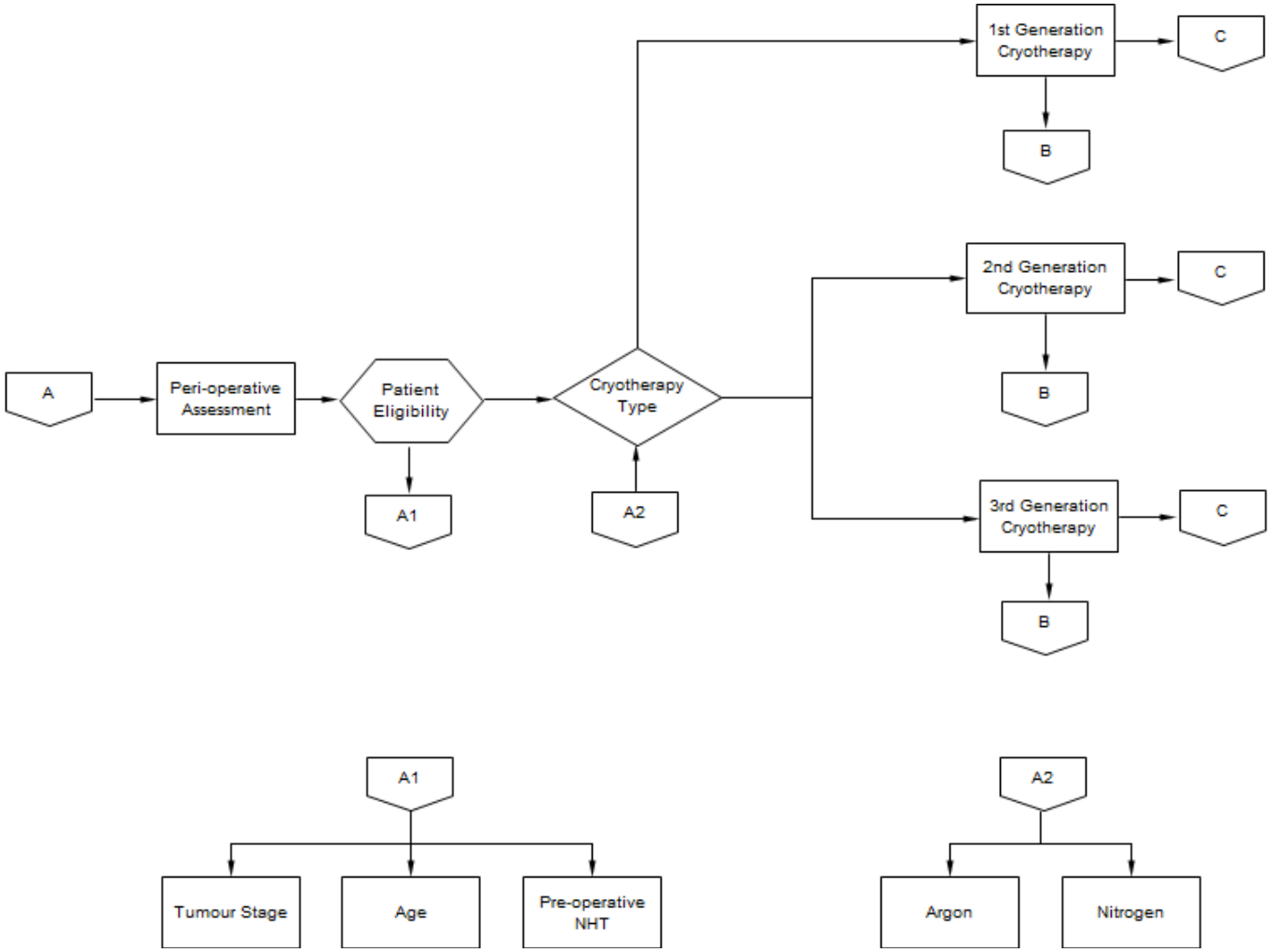

Figure 1. Care-pathway illustrating peri-operative assessment criteria. A choice of Cryotherapy techniques [Argon or Nitrogen] and advances in technology were identified from the literature. Suffix A, B and C provides links to subsequent sections of the care-pathway; section B describes Post-operative Complications (Figure 2), section C describes the processes involved in post-operative assessment (Figure 3.) and section D describes health related outcomes (Figure 4.).

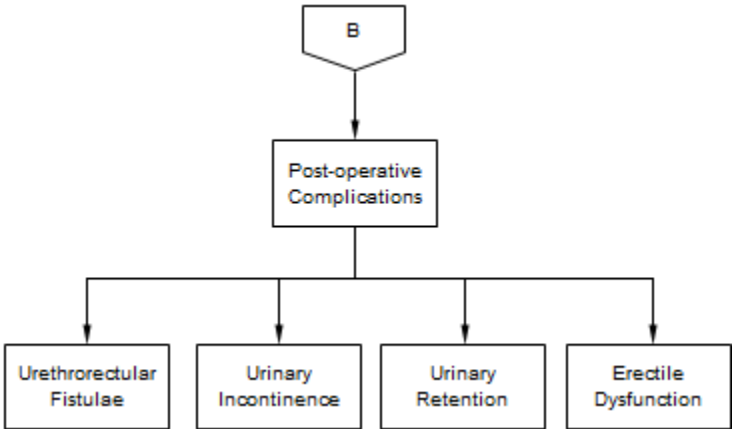

Figure 2. Potential post-operative complications identified thus far (not necessarily exhaustive).

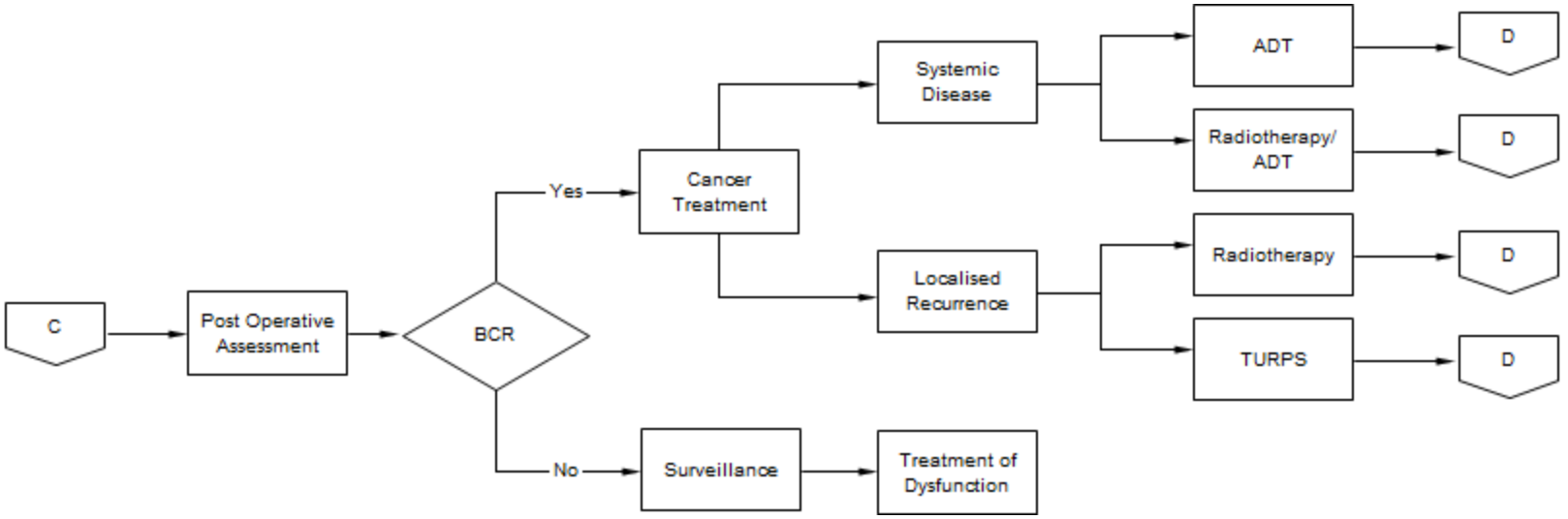

Figure 3. Post-operative assessment involves the evaluation of PSA levels. An individual is allocated to a particular treatment path consistent with the characteristics of the disease upon bio-chemical recurrence.

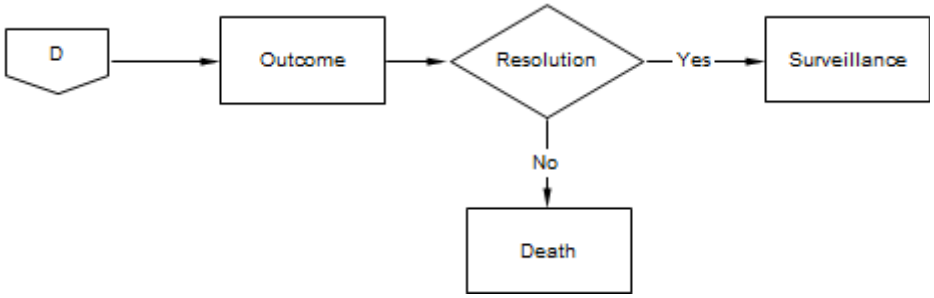

Figure 4. Health outcomes defines the success of further treatment for cancer.

Appendix 2

Clinical Effectiveness of Ablative Techniques and Comparators
MEDLINE and EMBASE

1. Prostatic Neoplasms/ use mesz
2. exp prostate cancer/ use emez
3. (prostat$ adj3 (neoplasm$ or cancer or carcinoma or tumo?r$ or malignan$)).tw.
4. or/1-3
5. ablation techniques/ use mesz
6. ablation therapy/ use emez
7. (ablation or ablative).ti.
8. brachytherapy/
9. interstitial radiation/ use emez
10. brachytherap$.tw.
11. (seed$ adj3 implant$).tw.
12. ((interstitial or intracavit$ or implant$ or surface) adj3 radio$).tw.
13. cryosurgery/
14. (cryotherap$ or cryoablat$ or cryosurg$).tw.
15. exp High-Intensity Focused Ultrasound Ablation/ use mesz
16. high intensity focused ultrasound/ use emez
17. (hifu or "high intensity focused ultrasound").tw.
18. Photochemotherapy/ use mesz
19. photodynamic therapy/ use emez
20. (photodynamic adj3 (therap$ or treat$)).tw.
21. (photosensitiv$ or phototherm$).tw.

22. exp Light Coagulation/

23. (laser adj3 (photocoagulat$ or coagulat$ or therap$ or treat$)).tw.

24. laser surgery/

25. laser coagulation/ use emez

26. (laser adj3 (ablat$ or interstitial tumo?r)).tw.

27. radiofrequency interstitial tumo?r ablat$.tw.

28. rita.tw.

29. catheter ablation/

30. ((focal or focus$) adj3 (therap$ or treat$)).tw.

31. hemi?ablat$.tw.

32. or/5-31

33. 4 and 32

34. (external beam adj3 (radiotherapy or radiation)).tw.

35. ebrt.tw.

36. Radiotherapy, Conformal/ use mesz

37. extrenal beam radiotherapy/ use emez

38. ((active or expectant or conservative) adj3 (management or surveillance or treatment)).tw.

39. watchful waiting.tw.

40. Watchful Waiting/

41. conservative treatment/ use emez

42. or/34-41

43. 4 and 42

44. exp clinical trial/ use emez

45. randomized controlled trial.pt.

46. controlled clinical trial.pt.

47. randomization/ use emez

48. randomi?ed.ab.

49. randomly.ab.

50. trial.ab.

51. groups.ab.

52. or/44-51

53. exp animals/ not humans/

54. 52 not 53

55. 33 and 54

56. 43 and 54

57. 55 or 56

58. comparative study/ use mesz

59. controlled study/ use emez

60. (compare$ or compara$).tw. use emez

61. or/58-60

62. 61 and (33 or 43)

63. 62 not 53

64. 63 not 57

65. limit 64 to english

66. follow-up studies/ use mesz

67. time factors/ use mesz

68. Treatment outcome/ use emez

69. major clinical study/ use emez

70. (preoperat$ or pre operat$).mp. use mesz

71. (chang$ or evaluat$ or reviewed or baseline).tw.

72. (prospective$ or retrospective$).tw. use mesz

73. (cohort$ or case series).tw. use mesz

74. or/66-73

75. case report/ use emez

76. case reports.pt.

77. 74 not (75 or 76)

78. 77 not 53

79. 33 and 78

80. 79 not (57 or 65)

81. limit 80 to english

82. 57 or 65 or 81

83. 82 not conference abstract.pt.

84. 83 not (letter or editorial or review or comment or notes or short surveys).pt.

85. remove duplicates from 84